A HOLISTIC REVIEW OF FENTANYL USE AND ITS IMPACT ON PUBLIC HEALTH

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Fentanil kullanımının bütünsel bir incelemesi ve bunun halk sağlığı üzerindeki etkisi

ÖZET

Fentanil, güçlü bir analjezik etki sağlamak üzere tasarlanmış sentetik bir opioiddir ve tıbbi kullanımı ağrı yönetimi ve anestezi gibi klinik bağlamlarda yaygın olarak yerleşmiştir. Fentanil kullanımı, kötüye kullanım ve yasadışı üretimin hızla yaygınlaşması nedeniyle kritik bir halk sağlığı sorunu haline geldi. Yasa dışı üretilen fentanil dağıtımındaki bu kalıcı artış, herhangi bir düşüş belirtisi göstermiyor; bu durum, aşırı dozdan ölümlerdeki dramatik artış da dahil olmak üzere, halk sağlığı ve opioid kötüye kullanım eğilimleri üzerindeki etkisine ilişkin önemli endişeleri artırıyor. Ayrıca, sosyal veya ekonomik açıdan istikrarsız geçmişlere sahip bireyler ve zihinsel sağlık bozukluklarından muzdarip olanlar özellikle savunmasızdır; çünkü kaynaklara ve destek sistemlerine sınırlı erişim, stres ve olumsuzluklarla başa çıkma mekanizması olarak madde kullanımının artmasına neden olabilir. Bu nedenle, bu anlatı incelemesinin amacı fentanil hakkında bütünsel bir genel bakış sunmak, sentez sürecini, farmakolojisini ve klinik kullanımını, bağırsak mikrobiyomu ile ilişkisini, epidemiyolojiyi ve küresel dağılımını, kullanım kalıplarını ve motivasyonlarını ve aşırı doz tedavisini ele almaktır. Bu amaçla, fentanil ve türevlerine ilişkin mevcut ve ilgili kanıtlar dikkatli bir şekilde değerlendirilmiş ve özetlenmiştir.

Anahtar Kelimeler: fentanil kullanımı, bağırsak mikrobiyomu, epidemiyoloji, motivasyonlar, doz aşımı tedavisi

A holistic review of fentanyl use and its impact on public health

ABSTRACT

Fentanyl is a synthetic opioid that was engineered to provide a potent analgesic effect, with its medical utility widely established in clinical contexts such as pain management and anesthesia. Fentanyl use has become a critical public health issue due to diversion for misuse and to rapidly proliferation of illicit manufacturing. This persistent increase in illicitly manufactured fentanyl distribution shows no indication of decline, raising significant concerns regarding its impact on public health and opioid misuse trends, including a dramatic increase in overdose deaths. Moreover, individuals from socially or economically precarious backgrounds, as well as those suffering from mental health disorders, are particularly vulnerable, as limited access to resources and support systems can lead to increased substance use as a coping mechanism for stress and adversity. Therefore, the objective of this narrative review is to provide a holistic overview on fentanyl, addressing its synthesis process, pharmacology and clinical use, relationship with gut microbiome, epidemiology and global distribution, patterns of use and motivations, and overdose treatment. For this purpose, current and relevant evidence on fentanyl and its correlates has been conscientiously assessed and outlined.

Keywords: fentanyl use, gut microbiome, epidemiology, motivations, overdose treatment

INTRODUCTION

Opioids have been used for centuries to treat pain and invoke pleasure, remaining pivotal in medicine throughout history while continuing to play essential roles in several medical disciplines (1). Healthcare professionals should be informed about updated regulations governing opioids prescriptions, and unlike in previous practices, empirical prescribing of narcotics such as fentanyl may result in legal consequences, including the potential revocation of prescription privileges (2,3). Despite that, they have faced increased scrutiny due to the ongoing opioid crisis impacting the world, particularly in the United States, where the current opioid epidemic is one of the most severe current public health issues (4).

Fentanyl, a synthetic opioid with high affinity for μ-opioid receptors, was engineered to provide a potent analgesic effect, with its medical utility widely established in clinical contexts such as pain management and anesthesia. This drug is also subject to diversion for misuse, as fentanyl can be combined with heroin to enhance potency or be sold under the appearance of highly potent heroin; in this regard, when users believe they are purchasing heroin but instead receive fentanyl, it can frequently lead to fatal overdoses (5). The illicitly manufactured fentanyl (IMF) has proliferated rapidly, frequently displacing heroin in illegal drug markets across multiple regions in the United States (6). This persistent increase in IMF distribution shows no indication of decline, raising significant concerns regarding its impact on public health and opioid misuse trends, including a dramatic increase in overdose deaths (7,8). In this sense, the inability to precisely titrate doses among novice users represents a critical factor contributing to the observed increase in overdose incidents (9). For this reason, the recent escalation in overdose incidents underscores the alarming implications of young individuals constituting a key at-risk population for fentanyl use (10), as they often face significant life uncertainties and are influenced by motivations such as curiosity and the desire for novel experiences (11), which can drive them toward the consumption of this drug or its adulterated variants. Additionally, individuals from socially or economically precarious backgrounds are particularly vulnerable, as limited access to resources and support systems can lead to increased substance use as a coping mechanism for stress and adversity (12). Moreover, those suffering from mental health disorders, such as anxiety or depression, may also find themselves at heightened risk for fentanyl misuse, as they often seek relief from their psychological distress through substance use, further aggravating their conditions and contributing to a pattern of drug dependence (13).

Since fentanyl has become a critical public health issue, a comprehensive examination of the impact of this drug is essential for raising awareness and developing effective intervention strategies. Therefore, the objective of this narrative review is to provide a holistic overview on fentanyl, addressing its synthesis process, pharmacology and clinical use, relationship with gut microbiome, epidemiology and global distribution, patterns of use and motivations, and overdose treatment. For this purpose, current and relevant evidence on fentanyl and its correlates has been conscientiously assessed and outlined.

SYNTHESIS OF FENTANYL

Valdez et al. (14) explain the synthesis process of fentanyl, which encompasses several key chemical steps. Initially, 4-piperidone is reacted with (2-bromoethyl) benzene in the presence of a base, such as cesium carbonate, to facilitate nucleophilic substitution. This reaction forms a piperidine ring with an ethyl benzyl substituent. Following this, the resulting intermediate undergoes reductive amination with phenethylamine, which is essential for constructing the fentanyl structure. This step typically requires a reducing agent, such as sodium cyanoborohydride, to facilitate the reaction and ensure the formation of the desired amine product. The final step involves the introduction of the acyl group, achieved through acylation, often using an acyl chloride such as phenylacetyl chloride. This reaction modifies the amine, completing the synthesis of fentanyl. Optimization steps in this synthesis have demonstrated significant improvements in yield. For instance, during the alkylation phase, using (2-bromoethyl) benzene with cesium carbonate in dimethylformamide yielded 72% at 80 °C, which increased to 88% when acetonitrile was used as the solvent. The use of alternative reagents such as R-OMs showed yields of 62% in dimethylformamide and 83% in acetonitrile. The reductive amination steps highlighted sodium acetate borohydride as the most effective reducing agent, achieving a yield of 91% at room temperature with dichloromethane and acetic acid. When the temperature was increased to 80 °C, sodium cyanoborohydride and sodium borohydride produced yields of 86% and 84%, respectively. The acylation phase also proved efficient, with propanoyl anhydride and propanoyl chloride achieving yields of 94% and 95% in the presence of pyridine at room temperature.

PHARMACOLOGY OF FENTANYL AND CLINICAL USE

Fentanyl is a powerful synthetic opioid analogous to morphine, but with a higher analgesic effect (50 to 100 times stronger than morphine), which is attributed to its differential pharmacodynamics and pharmacokinetics (15). Clinical use of fentanyl was approved in the United States in 1968, and its most common application is as an analgesic for intraoperative procedures and for the management of chronic pain conditions (16). Clinicians may also prescribe fentanyl to patients who have developed opioid tolerance (17), and for surgical seizure therapy during electrocorticography (18).

As a lipophilic opioid, fentanyl acts as a μ-selective

opioid agonist with the ability to stimulate additional receptors of the opioid system, including the δ- and the κ-receptors. The stimulation of these receptors, especially the μ-receptors, is what explains its analgesic effects. Its exceptional potency and rapid onset of action, compared to morphine, are linked to its high lipid solubility, facilitating swift blood-brain barrier (BBB) penetration. Predominantly metabolized by CYP3A4 into inactive norfentanyl, fentanyl is prone to drug interactions, with agents like ritonavir and diltiazem increasing its plasma levels. P-glycoproteins at the BBB help limit central nervous system (CNS) accumulation of fentanyl, although genetic ABCB1 polymorphisms can increase its CNS retention, leading to enhanced effects such as respiratory depression (19).

In clinical practice, fentanyl is commonly delivered via intravenous, intramuscular, intranasal, intrathecal, oral, and transdermal routes. The side effects of fentanyl are comparable to those of other opioids, causing analgesia, anxiolysis, chest wall rigidity, constipation, dizziness, drowsiness, euphoria, impaired mental function, pruritus, nausea, vomiting, orthostatic hypotension, and respiratory depression (15,20). Interactions between fentanyl and other substances of abuse can lead to severe and unpredictable consequences. When combined with heroin or alcohol, fentanyl potentiates CNS depression, which can result in respiratory distress, coma, or death (21,22). Mixing the stimulant effects of cocaine with the depressant properties of fentanyl intensifies euphoria but also increases the risk of overdose. Amphetamines, such as dexamphetamine and methylphenidate, may enhance the euphoric effects of opioids and potentially reduce their sedative and depressant effects. However, opioid-amphetamine combinations, especially those involving fentanyl, may elevate the risk of serotonin syndrome (22).

Anomalous aspects of fentanyl pharmacology refer to its behavior in a manner that appears distinct from that observed with other widely used μ-receptor agonists, such as morphine and oxycodone (23). According to Kelly et al. (24), the anomalous pharmacological properties of fentanyl include the following: (i) *in vitro* and *in vivo* potency does not correlate with measurements of affinity or efficacy; (ii) the potential for the fentanyl molecule to orient in different ways within the orthosteric binding pocket of the μ-receptor; (iii) access to the orthosteric binding pocket via a lipophilic pathway; (iv) lower cross-tolerance to heroin *in vivo*; (v) induction of respiratory muscle rigidity; and (vi) reduced sensitivity to reversal by naloxone compared to other opioid agonists. The high lipid solubility of fentanyl causes very rapid movement of fentanyl from the periphery to the brain and produces higher effects compared to other opioids.

RELATIONSHIP BETWEEN GUT MICROBIOME AND FENTANYL

The gut microbiome and the brain communicate bidirectionally via the gut-brain axis, which in turn regulates an array of psychological and psychiatric processes (25), including emotions, behavior, and neuropsychiatric disorders (26,27). An imbalanced gut environment, known as gut dysbiosis, has been linked bidirectionally with anxiety, depression, and impairments in learning and memory (28). Furthermore, evidence indicates that the microbiota-gut-brain axis plays a significant role in regulating reward and motivation (29,30). Stressful experiences may adversely affect the dopaminergic reward system, alerting reward sensitivity and highlighting the necessity of this system for managing stress-related behaviors (31). In addition, substance use is often related to social self-isolation, which impairs social engagement in drug addicts, acts as an aversive stimulus, and promotes drug use to cope with this social stress (32).

Variations in gut microbial composition associated with opioid use differ across studies, largely influenced by factors such as the specific opioid, dosage, route of administration, and treatment duration. Microbiome analyses across these studies have shown that opioid consumption results in the increase of pathogenic bacteria, including genera like *Clostridium*, *Enterococcus, Flavobacterium, Fusobacterium*, *Rikenellaceae*, *Ruminococcus*, and *Sutterella*, alongside a reduction in beneficial probiotic bacteria, specifically *Lactobacillus* and *Bifidobacterium* (33-35). Bacteria from the *Lactobacillus* and *Clostridium* genera, involved in secondary bile acid deconjugation, decline with morphine treatment, a change linked to reduced bile salt deconjugation, compromised intestinal barrier function, and heightened inflammation (36).

The connection between gut health and opioid use is evident in the substantial impact that opioids have on gastrointestinal function, such as opioid-induced constipation. In fact, opioid consumption has been related to an imbalance in gut bacteria in humans (33,37,38). Interestingly, interactions between gut bacteria and the brain play a mediating role in the rewarding and reinforcing effects of fentanyl (39). These authors found that several bacterial groups were affected by the intravenous injection of fentanyl in rats, such that members of the phylum Verrucomicrobiota and the genera *Akkermansia* decreased in abundance after drug administration, while the genera *Prevotella* and *Ruminococcus* increased in abundance in the gut microbiome of the rats. Later, Hofford et al. (40) reported that the abundance of *Ruminococcus, Butyricicoccus, Lachnospiracae_unclassified*, and *Anaerotignum* were negatively correlated with fentanyl intake in rats. However, the mechanisms involved in the gut microbiome dysbiosis induces by fentanyl are not established in the above studies. More recently, Greenberg et al. (41) found β-diversity differences between the gut microbiome of

rats subjected to heroin self-administration. In addition, in the experimental rat group and at the phylum level, the relative abundance of Bacillota was increased during the self-administration phase. Deferribacterota was decreased in heroin whereas members of the superphylum Patescibacteria were increased in heroin at the extinction phase.

To address this aspect, Ren et al. (42) conducted an investigation to know the precise communication between the brain and the gut microbiome affected by the fentanyl self-administration, and to elucidate the role of gut microbiota on fentanyl reinforcement and reward. These authors depleted gut bacteria in adult male and female Sprague Dawley rats using an oral, non-absorbable antibiotic mixture and allowed the rats to intravenously self-administer fentanyl on an escalating schedule of reinforcement, finding that antibiotic treatment produced two effects: (i) a significant decrease in members of the Bacillota phylum and an increase in members of the Pseudomonadota, Mycoplasmatota and Verrucomicrobiota phyla; and (ii) increased fentanyl self-administration in males, but not females, at the lowest schedule of reinforcement. When they replenished microbial metabolites through short-chain fatty acid delivering to assess a potential mechanism in gut-brain communication, they observed that restoring metabolites decreased fentanyl self-administration in the gut bacteria-depleted rats.

Other studies have shown that prolonged exposure to opioid analgesics such as morphine or fentanyl disrupts the intestinal epithelial barrier and induces gut dysbiosis (43,44). Depletion of gut bacteria can prevent the development of tolerance to opioid-induced antinociception (i.e., response of the organism to potentially toxic stimuli), underscoring a pivotal role of the gut-brain axis in modulating opioid effects. However, the mechanisms underlying opioid-induced dysbiosis remain unclear. Mucchala et al. (45) found that host-produced antimicrobial peptides (AMPs) are essential for maintaining the integrity of the intestinal epithelial barrier by preventing pathogenic overgrowth in the enteric microbiota. These authors reported that chronic morphine or fentanyl exposure reduced the antimicrobial activity in the ileum, altering bacterial composition. Fecal analysis of morphine-treated mice revealed elevated levels of *Akkermansia muciniphila* and a shift in the relative abundance of Bacillota and Bacteroidota. Fecal microbial transplantation (FMT) in morphine-naïve mice or oral butyrate supplementation: (i) reinstated antimicrobial activity; (ii) restored the expression of the antimicrobial peptide Reg3γ; (iii) reduced intestinal permeability; and (iv) prevented antinociceptive tolerance in morphine-dependent mice. Enhanced epithelial barrier function through FMT or butyrate also prevented the overgrowth of mucin-degrading *A. muciniphila* in morphine-dependent mice. These findings suggest that impaired intestinal epithelial antimicrobial activity may underlie opioid-induced disruptions in the microbiota-gut-brain axis.

EPIDEMIOLOGY OF ILLICIT FENTANYL AND GLOBAL DISTRIBUTION TRENDS

Fentanyl is primarily sourced from two main ways in the recreational drug market: IMF, often mixed with heroin or stimulant drugs (e.g., amphetamines, cocaine, methamphetamines) to enhance potency, and the diversion of fentanyl-containing medications, which can be administered through various methods including intravenous use, insufflation, inhalation, oral, topical or transmucosal application, and rectal insertion (46). Fentanyl misuse remained relatively uncommon, predominantly limited to healthcare professionals with access, until more recent periods when a marked increase in overdose fatalities emerged due to the aforementioned clandestine production of illicit fentanyl, often combined with other substances (19). In fact, since the late 1970s, fentanyl and its analogs have been illicitly produced and distributed in United States as substitutes for heroin, contributing to a significant increase in overdose deaths associated with their use (47). Subsequently, during the summer of 2005, multiple cities reported outbreaks of fentanyl-related deaths among illicit drug users, driven by the presence of undeclared ingredients in these substances that heightened the risk; moreover, gender differences in fentanyl-related mortality were found to be influenced by age and marital status (48). Since that time, opioid-related mortality has steadily risen, with significant increases in fentanyl-related deaths indicating a troubling trend in several regions, including economically disadvantaged communities in the United States, Canada, and Australia (49,50). In this regard, although fentanyl has commonly been mixed with heroin, by 2021, stimulants became the most prevalent drug class in fentanyl-related overdoses across all US states, with the rise in deaths involving cocaine and methamphetamine reflecting a drug market dominated by illicit fentanyl that has normalized polysubstance use (51). In addition, this serious public health treat has extended to Europe, with a marked increase in cases beginning around 2015, primarily affecting Northern and Eastern countries, and eventually impacting the Mediterranean region (52-55). This alarming situation has highlighted the role of Asia, particularly China and India, the world's primary producers of fentanyl and its precursors (56).

PATTERNS OF FENTANYL USE AND MOTIVATIONS

In the context of the ongoing fentanyl epidemic, characterized by its alarming mortality rates, regional studies in the United States indicate a polarization of attitudes among users: some actively seek out fentanyl despite the associated risks, while others make concerted efforts to avoid it (21). Indeed, opinions vary on the appropriateness of fentanyl and mixtures of fentanyl with other drugs; its proponents praise fentanyl's high and potency in overcoming tolerance to heroin or opioid receptor blocking medications, while detractors highlight the significant risk

of overdose, adverse physiological reactions, and shorter duration of fentanyl compared to heroin as main concerns (57). It has been noted that young individuals who smoke have a higher tendency to consume fentanyl (10), underscoring that early age is a risk factor for the initiation of drug use, which is more likely to become an established habit if initiated early (11). In this sense, there is evidence of peripheral accumulation due to fentanyl consumption that may contribute to a profile more similar to that of a long-acting opioid in users exposed to the substance, with accumulation suggesting that people who regularly use adulterated forms of this drug are likely to continue being exposed to fentanyl for an extended period after its last use (6). Furthermore, the preference for fentanyl may also be attributed to the drug's increased prevalence in the supply, resulting in greater exposure and consumption among users (21), but also to socioeconomic inequalities, as marginalized individuals often turn to the drug as a means of coping with limited resources (12). This phenomenon is especially pronounced in the context of the ongoing opioid overdose crisis, notably escalating due to the proliferation of fentanyl and the rising prevalence of polydrug use (58), further exacerbated by the COVID-19 pandemic, underscoring and amplifying existing racial and economic disparities (59). Moreover, there was a significant increase in the volume of social media posts discussing alternatives to heroin, including fentanyl, during the COVID-19 pandemic, which may have contributed to a rise in its consumption (60). On the other hand, motivations for consuming fentanyl among drug users have been linked to both the intensity and the immediacy of the high, the cost-effectiveness associated with its potency, and the necessity to avoid withdrawal symptoms, all of which drive their willingness to purchase and use this drug or its adulterated variants (61,62). In addition, several psychological conditions such as anxiety, depression, and post-traumatic stress disorder have been associated with an increased risk of developing opioid addiction; regarding this, subjects who have experienced early life stress are particularly susceptible to opioid dependence, which highlights how adverse childhood experiences can significantly influence the likelihood of developing substance use disorders later in life (13).

TREATMENT OF FENTANYL OVERDOSE

Fentanyl treatments are the same of those prescribed for opioid use disorder and overdose, encompassing the medications approved by the Food and Drug Administration (FDA), such as buprenorphine, methadone, extended-release naltrexone, lofexidine, and naloxone (49,63). Compared to other opioid-related overdoses, illicit fentanyl-related overdoses seem to present distinctive symptoms, including dyskinesia, body and chest rigidity, and bradycardia or arrhythmias, which may complicate overdose management, particularly in terms of oxygen administration and naloxone doses (64).

Data on the effectiveness of buprenorphine or methadone for managing illicit fentanyl use remain limited. A retrospective study in Rhode Island found that six months of methadone maintenance therapy reduced mortality risk and fostered abstinence in fentanyl-exposed individuals, although relapse rates remained substantial (65). Buprenorphine, a μ-opioid receptor partial agonist and κ-opioid receptor antagonist, is widely applied in opioid use disorder treatment, offering additional anxiolytic and antidepressant effects, as well as showing promise in treating neonatal opioid withdrawal syndrome (66). A retrospective cohort study reported no significant differences in six-month retention and opioid abstinence rates between subjects initially testing positive for fentanyl or heroin prior to beginning buprenorphine treatment, suggesting that buprenorphine could be effective for addressing fentanyl exposure (67).

Lofexidine, a central α-2 adrenergic receptor agonist, was the first non-opioid drug approved by the United States FDA specifically for opioid withdrawal treatment (63). It alleviates withdrawal symptoms without addressing drug craving (68). Naloxone, a μ-opioid receptor antagonist, is employed to treat fentanyl-related overdose across all administration routes. Nevertheless, its effectiveness can vary, and dosing must be carefully managed, as multiple doses are often required due to the potency of fentanyl and its rapid onset of respiratory depression (46). Research has shown that extended-release naltrexone is as safe and effective as a buprenorphine-naloxone combination in promoting abstinence and retention once treatment begins, although fewer individuals successfully initiated therapy with naltrexone (69,70). A systematic review identified a low incidence of mortality or serious adverse episodes from prehospital naloxone supply for opioid overdoses, although most cases involved heroin rather than fentanyl (71). In addition, a survey of 316 street-recruited opioid users in Baltimore revealed that while most participants recognized the risks of fentanyl-adulterated heroin and overdose, few routinely carried naloxone (72). Early adoption and distribution of take-home naloxone kits have been shown to effectively reduce opioid overdose fatalities. Thus, to mitigate the adverse effects and overdose rated derived from fentanyl use, harm reduction strategies are essential, including safe injection sites, expanded opioid agonist treatments, and overdose prevention training (e.g., carrying naloxone, avoiding solo drug use, and providing higher or repeated naloxone doses) (49,73).

There is a pressing need for more powerful and longer-acting opioid receptor antagonists to mitigate fentanyl-related overdose fatalities (49). Nalmefene has emerged as a generally well-tolerated option for individuals with alcohol dependence (74). Furthermore, novel, selective, and potent μ-opioid receptor antagonists, such as NAQ (17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[isoquinoline-3-carboxamido] morphinan) and NAN (17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-

[indole-7-carboxamido] morphinan), have demonstrated a reduced potential for opioid dependence, tolerance, and withdrawal signs, making them promising candidates for the treatment of opioid use disorder (75). Additionally, chronic administration of the anticonvulsant carbamazepine has been shown to enhance fentanyl clearance and to lower plasma concentrations in neurosurgical patients, potentially diminishing the effects of the drug (76).

Previous research has shown that vaccines incorporating fentanyl hapten conjugated to either tetanus toxoid or keyhole limpet hemocyanin as carrier proteins can significantly reduce the biodistribution of fentanyl to the brain. Immunization with these vaccines attenuated both the antinociceptive effects and respiratory depression associated with fentanyl in rodent models (77,78). In addition, the conjugate vaccine prompted the endogenous production of antibodies with high affinity for various fentanyl analogs (77), and was effective in diminishing the reinforcing effects of fentanyl (79). A recent study isolated and purified monoclonal antibodies (mAbs) from mice that had been vaccinated, revealing that the 6A4 mAb effectively prevented acute fentanyl lethality and reversed the antinociceptive effects of both fentanyl and carfentanil, showing efficacy comparable to naloxone (80). These findings indicate that immunopharmacotherapies, including active vaccinacion or a combination with passive mAb, represents promising treatment strategies to combat the ongoing opioid crisis. Moreover, accumulating evidence points to dysbiosis of the gut microbiome as a contributing factor in the pathophysiology of drug addiction. Thus, manipulating gut microbiome composition or its metabolites may provide new insights on novel adjunct therapies for opioid addiction in the future.

DISCUSSION AND CONCLUSIONS

The fentanyl crisis highlights the complexities of its sourcing in the recreational drug market, primarily through IMF. This pathway has exacerbated overdose risks, particularly as users may be unaware of fentanyl's potency when combined with heroin or stimulants. As an illicit adulterant, fentanyl constitutes an exceptionally dangerous substance with high abuse potential and life-threatening effects (81). A characteristic manifestation of its use, known as the "fentanyl fold", involves a pronounced loss of muscle control, causing users to bend over in unusual, involuntary positions. This phenomenon may arguably reflect the potential lethality of this drug, as it can be attributed to a rapid onset of rigidity in critical muscle groups, including those involved in respiration. In fact, evidence suggests that the sudden chest wall rigidity may represent an underestimated factor in fentanyl-related deaths (82), as it imposes a significant, immediate increase in the mechanical load required to breathe, critically disrupting blood gas homeostasis and impacting overall metabolic function (83). Historically confined to healthcare professionals, fentanyl misuse has become common, contributing to rising mortality rates, especially in economically disadvantaged communities. The troubling trend of increasing polysubstance use, alongside the international production, underscores the urgent need for targeted public health interventions.

Reviewed studies reveal a dichotomy in user behavior and perception, with some individuals actively seeking this powerful opioid while others attempt to evade its dangers. Without a doubt, fentanyl is a drug that warrants consideration due to the nature of its effects; despite its significant potential in various fields of medicine, recreational use of this substance carries greater risks than those associated with other drugs. Young and socioeconomically marginalized populations emerge from this perspective as high-risk groups facing a growing prevalence of fentanyl in the drug market, reflecting broader socioeconomic disparities. The interplay between drug accessibility and user motivations underscores the urgent need for educational efforts to mitigate the impact of this potent opioid on society. In this regard, these motivations are influenced not only by powerful positive reinforcement but also by components linked to negative reinforcement that may exceed those found in other substances with a high potential for addiction.

It is evident that synthesizing fentanyl can be challenging, as it requires components that are difficult to obtain, precise instruments, and in-depth knowledge of the subject matter. In this respect, a skilled drug cook, along with appropriate resources, is necessary to generate this drug and subsequently make it profitable in the market. Indeed, a fentanyl cook must possess a unique mixture of specialized competences to effectively operate; first, a strong understanding of organic chemistry, as it enables the manipulation and synthesis of compounds with precision, and second, proficiency in handling hazardous materials. Minor deviations in formulation or procedural steps can result in products that are ineffective or potentially lethal, although the latter is not something that matters in high extent to the majority of clandestine organizations. These organizations, in fact, prioritize the identification of alternative supply sources, relationships with distributors, and innovative production methods that allow them to obtain the greatest economic benefit. Not everyone has the capacity or possibility to undertake such an enterprise, but many have attempted to embark on this endeavor, with variable success; however, illicit organizations from different parts of the world are increasingly engaging in this practice, finding a significant profit niche in adulterating other drugs with fentanyl and thereby fueling a wave of mass addiction that is fully reflected in the ongoing epidemic being experienced worldwide.

Research on opioid addiction treatment focuses on developing more effective therapies. Although current pharmacological treatments can be beneficial (84), many patients struggle to maintain abstinence (85). Thus, new ap-

proaches are needed that address not only abstinence but also cravings, sleep quality, and psychiatric comorbidities (85,86). Non-pharmacological treatments are still being tested but show great potential as complementary therapies, encompassing a wide range of initiatives, including community interventions, educational prevention programs, psychotherapy, integrative practices like yoga and mindfulness, coping skills counseling, group meetings, as well as neuromodulation techniques, such as magnetic, ultrasound, and deep brain stimulation (85,87-92). Additionally, emerging strategies for addressing fentanyl addiction may benefit from the incorporation of healthy lifestyle habits as adjunct therapies. Dietary interventions could play a pivotal role, particularly in regulating the composition and function of the gut microbiome, which has been increasingly recognized for its influence on the global host health (93). Furthermore, treatments with psychobiotics have shown promise in alleviating adverse mental states (94). These innovative therapies highlight the need for a holistic approach to addiction treatment, where lifestyle modifications, including nutrition and gut health, can synergistically enhance recovery outcomes for individuals with substance dependence.

In conclusion, the complexity of the fentanyl crisis is underscored by several factors, including addiction, chronic pain management, market availability, mental health considerations, pharmacological effects, socioeconomic disparities, the influence of prescription practices, and contextual circumstances such as the COVID-19 pandemic (12,13,21,46,59). This last factor highlights that the COVID-19 pandemic not only inflicted severe harm on vulnerable groups such as older adults (95), but also served as a catalyst for increased drug consumption, particularly through dynamics that fostered substance use in vulnerable populations. Consequently, the rise of fentanyl-related overdoses, due mainly to its misuse and to the normalization of polydrug use, emphasizes the critical need for targeted interventions that address both individual and systemic factors. Understanding the social dynamics that drive fentanyl consumption, alongside its implications on public health, can inform policies aimed at reducing the burden of opioid addiction. Furthermore, it is essential to tackle the illegal distribution of substances, as the proliferation of illicitly manufactured fentanyl poses significant challenges to both prevention and treatment efforts.

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