Journal of Mental Health Issues and Behavior
Vol: 05, No. 01, Jan-June 2025
ISSN: 2799-1261, DOI: 10.55529/jmhib.51.12.22

Research Paper

Fentanyl abuse and its implication on health and society

Priyanka De[1*], Anuvhab Mondal[2], Ayush Bhattacharya[3], Nilratan Pal[4]
[1*]Assistant Professor Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), 30, Park Street, Kolkata 700016, India.
[2,3,4]Professor Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), 30, Park Street, Kolkata 700016, India.

Article Info

Article History:
Received: 31 January 2025
Revised: 08 April 2025
Accepted: 15 April 2025
Published: 30 May 2025

Keywords:
Fentanyl
Opioids
Drug Abuse
Systemic Effect
Neurotoxicity

ABSTRACT

Fentanyl, a potent synthetic opioid developed in 1960, initially offered a breakthrough in pain management with its high potency and favorable safety profile. However, escalating cases of its misuse has resulted in alarming rates of overdose deaths, particularly in North America and Europe. This comprehensive review examines the multifaceted impact of fentanyl on various physiological systems. Tracing its timeline from a medical breakthrough to an illicit substance, the paper explores neurological, cardiovascular, renal, reproductive, respiratory, thermoregulatory, and immunological effects of fentanyl. The rise of more potent analogues further complicates the crisis. The neurological implications encompass altered cognition, neuropsychological effects, and neuro inflammation. The review also delves into the intricate connections between fentanyl and the immune system, introducing the concept of vaccination as a treatment strategy for overdose. The urgent need for a collaborative effort from the medical, legal, and public health sectors to address fentanyl's devastating consequences is emphasized, stressing the importance of a better understanding of its systemic effects for effective harm-reduction strategies and combating this escalating epidemic.

Corresponding Author:
Dr. Priyanka De
Assistant Professor, Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), 30, Park Street, Kolkata 700016, India.
Email: priyankade@sxccal.edu

1. INTRODUCTION

Fentanyl, created in 1960 by Paul Janssen, was considered a ground-breaking substance, with a potency far beyond that of morphine, a naturally occurring opioid, and a significantly higher safety margin than other pharmaceutically produced synthetic opioids like dextromoramide, meperidine, and phenoperidine. The World Health Organization (WHO) list of essential medicines includes four opioid analgesics, namely, fentanyl, codeine, methadone, and morphine. According to preliminary estimates, there were more than 60,000 drug overdose deaths in the United States in 2016. Alarming epidemiological and forensic medicine findings, mostly from the last 20 years, indicate a sharp rise in fentanyl use, especially in North America and Europe. Fentanyl, sometimes known as 'fake heroin', is mostly obtained from the 'recreational drug market' and is frequently combined with heroin or added to cocaine products in order to improve the drug's strength at a low cost. It can be sold along with pills containing oxycodone, hydrocodone, or alprazolam. Since the abuse of opioids has terrible consequences for patients, their families, and society, there is an urgent need for novel, efficient harm-reduction techniques in view of the fentanyl crisis. An in-depth understanding of the prolonged and painful symptoms of the withdrawal effect of fentanyl is urgently needed, given the rapid rise in addiction and overdose cases caused by illicit use [1]. Most of the surveys and data are primarily focused on fentanyl-related issues in the Western world and very little statistical data are available from China and India, which are home to the greatest unlicensed fentanyl production and unrestricted fentanyl marketing. This paper primarily focuses on the physiological consequences of fentanyl abuse, raising public awareness of the issue.

2. RELATED WORK

Fentanyl, with potency that is frequently stated to be 50X or 100X greater than that of heroin and morphine, respectively, is an opioid drug applied for the treatment of pain. The U.S. FDA approved this drug as an intravenous anaesthesia agent in 1972. Fentanyl patches have been widely used since 1990s to treat chronic pain associated with all types of cancer, as well as acute pain associated with many non-cancerous conditions. Before the development of fentanyl (pre-fentanyl years), which lasted from 1953 to 1960, there was a unique historical epoch, that began with Paul Janssen, founding his pharmaceutical company in 1953, and creating strong, effective and fast-working analgesics. Fentanyl was first utilized as a pain-relieving medication administered through intravenous means in various Western European nations in 1963. During 1960s and 1970s, scientists endeavoured to create a novel form of complete intravenous anaesthesia by combining Fentanyl with various intravenous tranquilisers, sedatives, and amnestic [1]. The timeline of major fentanyl related events in US history is provided in Figure 1.

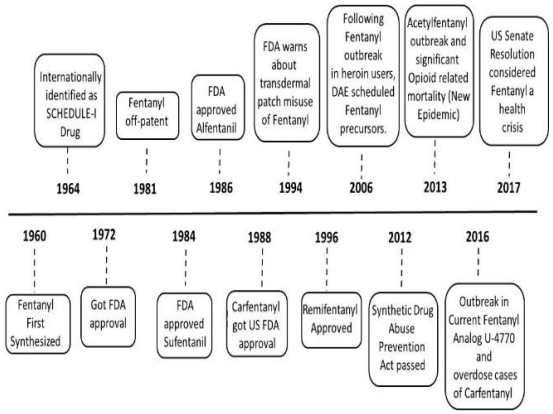

Figure 1. Timeline of Major Fentanyl Events in US History

Tragically, there is rising concern in drug adulteration cases and drug overdose mortality [2]. The quick augmentation in fentanyl drug-induced mortality rate is called 'fentanyl epidemic'. Huge mortality cases were observed in USA as a result of mixing fentanyl with other drugs, including cocaine and heroin.

China has become the largest producer of illicit fentanyl accounting for 70% of the world's illicit fentanyl production. Due to insufficient drug control and legislative execution, fentanyl has been produced and trafficked illegally in India using Indian pharmaceutical resources.

Fentanyl is absorbed in the human body via respiratory (nasal spray), sublingual (examples, sublingual tablets, sublingual spray), Trans mucosal (examples, Trans mucosal lozenges) and transdermal (examples, transdermal patches) routes. Although the highly lipophilic drug is rapidly absorbed, its short half-life leads to a brief duration of effects [1]. Fentanyl can traverse both the blood-brain barrier and the placental barrier. The long terminal clearance of the drug, with a recognized secondary peaking event is known as 'fentanyl rebound'. Fentanyl analogs have similar pharmacological effects as the original drug. The biochemical details of fentanyl analogs are listed in Table 1. Several fentanyl analogs are created by altering the three primary components that make up the fundamental structure of fentanyl.

Table 1. Biochemical Details of the Fentanyl and its Analogues

Name	Chemical Formula	Molecular Weight	Analgesc activity ED_{50} in rats (mg/kg)	LD_{50} in rats (mg/kg)	Target opioid receptor type
Acetylfentanyl	$C_{21}H_{26}N_2O$	322.4	0.021	9.3	Mu
Alfentanil	$C_{21}H_{32}N_6O_3$	416.52	0.044	47.5	Mu
Acryloylfentanyl	$C_{22}H_{26}N_2O$	334.5	0.082	0.082	Mu
alpha-Methyl fentanyl	$CH_{23}H_{30}N_2O$	350.49	0.0058	8.6	NA
Lofentanil	$C_{25}H_{32}N_2O_3$	408.5	0.0007	0.2	Mu
Butyrfentanyl	$C_{23}H_{30}N_2O$	350.51	0.047-0.220	NA	Mu-and Delta
Chlorofentanyl	$C_{22}H_{27}ClN_2O$	370.9	0.22	NA	Mu
Carfentanil	$C_{24}H_{30}N_2O_3$	394.5	0.00032	3.39	Delta
Furanylfentanyl	$C_{24}H_{26}N_2O_2$	374.5	0.02	2.52 ±0.46	NA
Isobutyrylfentanyl	$C_{23}H_{30}N_2O$	350.5	0.261	NA	NA
Norfentanyl	$C_{14}H_{20}N_2O$	232.32	3.335	0.53	NA
Ocfentanil	$C_{22}H_{27}FN_2O_2$	370.5	0.0077	NA	NA
para-fluoro fentanyl	$C_{22}H_{27}FN_2O$	354.5	0.021	9.3	NA
Remifentanil	$C_{20}H_{28}N_2O_5$	376.4	3.04	3.1	Mu
sufentanil	$C_{22}H30N_2O_2S$	386.6	0.00071	17.9	Mu
Morphine	$C_{17}H_{19}NO_3$	285.34	13.9	400	Mu, Delta, Kappa

3. METHODOLOGY

To conduct a comprehensive and systematic review of the existing literature on fentanyl abuse and its implications on health and society, we employed a multi-step methodological approach aimed at ensuring thoroughness, relevance, and scientific rigor. The methodology was designed in accordance with established guidelines for conducting narrative and systematic reviews, particularly those outlined by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, while also allowing for broader thematic synthesis given the diverse nature of the topic.

A comprehensive literature search strategy was performed across multiple electronic databases, including PubMed, Embase, Scopus, Web of Science, PsycINFO, and Google Scholar. The search terms were carefully selected to capture all relevant aspects of fentanyl use, abuse, and its societal and health impacts.

Key search terms included: "fentanyl," "fentanyl abuse," "opioid crisis," "synthetic opioids," "drug overdose," "public health impact," "societal burden," "addiction," "narcotics control," and "harm reduction." Boolean operators (AND/OR) were used to combine these terms effectively. The search was limited to peer-reviewed articles published in English from January 1960 (the year fentanyl was first synthesized) up to December 2024. Additionally, grey literature sources such as government reports, policy documents, and data from international organizations (e.g., WHO, UNODC, CDC) were reviewed to supplement academic findings and provide real-world context. This methodological approach ensures a robust and comprehensive overview of the current evidence base regarding fentanyl abuse and its multifaceted implications on health and society.

4. RESULTS AND DISCUSSION

4.1. Fentanyl and Neurological Implications

4.1.1. Effects of Fentanyl on the Brain and Peripheral Nervous System

Various experiments and studies have been done on fentanyl toxicity. Fentanyl-induced respiratory depression acts as a catalyst for swift cerebral hypoxia due to its rapid depletion of oxygen levels within the nucleus accumbens. Moreover, fentanyl triggers hypoxia in the basolateral amygdala, leading to subsequent elevation in blood glucose levels analogous to the amplified glucose levels within the nucleus accumbens. These effects occur prior to the gradual alterations observed in brain temperature and metabolic activity [3]. In an investigation, a blend of xylazine and fentanyl was observed to elicit a twofold oxygen response within the nucleus accumbens of rats. The combined xylazine-fentanyl concoction brought about a reduction in oxygen akin to the hypoxic reaction triggered by fentanyl in isolation. Notably, the duration of lowered oxygen levels was observed to be prolonged in the presence of the drug mixture compared to fentanyl alone. Fentanyl not only has a higher potential to cross the blood-brain barrier, but it also binds predominantly to mu-opioid receptors, present in large amounts in the cerebellum. Therefore, fentanyl can lead to deteriorating opioid-induced cerebellar toxicity [4]. There is a huge controversy with respect to the outcome of narcotics on cerebral blood flow (CBF) and the cerebral metabolic rate (CMR_{O2}). Experiments proved that fentanyl causes a remarkable dose-modulated reduction in both Cerebral Blood Flow (CBF) and Cerebral Metabolic Oxygen Rate (CMR_{O2}) [4]. CT scan images have revealed cerebral edema in the form of vasogenic, osmotic, cellular, or interstitial, as the primary symptom for toxicity. Transdermal fentanyl overdose based MRI scans have revealed abnormalities in the cerebellum resulting in Toxic Leukoencephalopathy, caused by the sudden disappearance of white matter in the brain, with or without a molecular cause [5].

4.1.2. Effects of Fentanyl on Neuropsychology

Studies show that fentanyl, along with alcohol, causes impairment in various neuropsychological parameters such as auditory reaction time, signal detection, sustained attention, and memory tests. Studies also indicate that fentanyl concentrations used in common surgical procedures can produce significant cognitive impairment. However, neuropsychological tests revealed that long-term opioid therapy with transdermal fentanyl along with acetaminophen is not responsible for fine motor or cognitive impairment [6].

4.1.3. Effects of Fentanyl on Neuro Inflammation

Neuro inflammation is a crucial mediator of neuronal damage; hence, understanding pro-inflammatory pathways is important because of the variety of drug-induced neuropathologies. Recent studies suggest that opioid agents may be able to modulate immune function in peripheral and central nervous system cells [7]. Fentanyl mainly acts on glial and neuronal cells, present mostly in the dorsal raphe nucleus (DRN), a region implicated in pain control. It thereby activates the NLRP3 inflammasome, which is a multiprotein complex that plays a crucial role in regulating the innate immune system and inflammatory signaling pathways. It is activated by diverse stimuli, including ionic flux, mitochondrial dysfunction, and the production of reactive oxygen species (ROS). The NLRP3 provides instructions for making cryopyrin, a member of NOD-like receptor (NLR) proteins, involved in the immune system [8]. Repeated fentanyl

delivery results in significant microgliosis, astrogliosis, and a distinct, NLRP3-dependent pyroptosis, a type of programmed cell death that is mediated by the NLRP3 inflammasome in the DRN [9]. Several opioids, including morphine, may lead to tolerance, but a brief antinociceptive effect can only be provided by fentanyl followed by fentanyl-induced hyperalgesia. In case of medical applications of fentanyl, local infiltration analgesia (LIA) and sciatic nerve block (SNB) have partially reduced perioperative fentanyl-induced hyperalgesia and up-regulation of pro-inflammatory cytokines in the spinal cord and dorsal root ganglia [9].

4.2. Effect of Fentanyl on the Heart and Circulatory System

Apart from sporadic fluctuations in heart rate (HR) and blood pressure (BP), the intravenous administration of fentanyl as an anaesthetic agent frequently results in little cardiovascular effects after cardiac surgery [10]. However, when fentanyl is combined with benzodiazepines, which belong to the category of depressant medications, significant changes in the cardiovascular system can arise. These changes encompass reductions in stroke-volume (SV) and cardiac output (CO), considerable lowering of blood-pressure (BP), and eventual marked decline in cardiovascular function. A distinct study demonstrates that fentanyl administration prompts bradycardia, characterized by an abnormally slow heart rate. This outcome is ascribed to fentanyl's suppression of GABAergic signalling targeting cardiac vagal neurons situated in the nucleus ambiguous, leading to the eventual manifestation of bradycardia induced by opioids [11].

Fentanyl can cause tremendously low BP, especially when an individual stand from a sitting or lying posture, leading to dizziness and fainting. The risk is higher for patients taking hypertensive medicines or antipsychotics like phenothiazines. Numerous studies on various animal models reveal that fentanyl, like Intravenous (IV) artificial or internal opioids, causes hyperglycaemic effects. Opioids also demonstrated hyperglycemic effects in situations involving insulin tolerance tests and glucose tolerance tests [12]. Opioid administration impacts blood glucose levels, triggering the release of endogenous opioids. Obesity increases β-endorphin levels, while diabetes mellitus effects are inconsistent. Obesity is linked to increased opioid receptor expression in skeletal muscle cells and decreased availability of μ-opioid receptors in the brain.

4.3. Effect of Fentanyl on Respiration

Respiratory depression is the most hazardous sign of acute opioid intoxication. This effect seems to be a shared response among all opioid receptor agonists, leading to brain hypoxia and ultimately, mortality [13]. In comparison to morphine, oxycodone, and heroin, fentanyl has been observed to be the most effective and potent substance. At a relatively low dose of 3 g/kg, it causes a very slight but significant temporary reduction in N-acetylcysteine (NAC) oxygen. Dosages of 10 and 40 g/kg, though still considerably lower than the LD_{50} determined in rats through self-administration drug delivery (1-3 mg/kg), induce a significant hypoxic response [14]. Autopsies reports suggested that death caused by overdose of fentanyl and its analogs may be due to a condition known as ‘wooden chest syndrome’. Such fentanyl-induced skeletal muscle rigidity causing ventilatory failure differs from traditional opioids, which result in rigidity in the diaphragm, upper airway, and chest muscles, as well as laryngospasm [15].

4.4. Effect of Fentanyl on the Digestive System

Numerous microbes residing in the mammalian gut govern digestive homeostasis, forming gut microbiota. It has been long suspected that the symptoms of fentanyl overdose are related to the interaction of the opioid with the gut microbiome that determines the detrimental effect of fentanyl on the body. This is because the gut and brain are relatively connected by the vagus nervous connection Clinical studies show that there are instances of decreased intestinal side effects with Trans dermally administered fentanyl compared to orally administered morphine [16]. The intriguing aspect of this association lies in its potential dependence on the gender of the subjects involved. The corresponding study indicated that male mice, with attenuated gut microbiota induced by antibiotics, exhibited an increased inclination for self-administering fentanyl, even at higher dosages [17]. In contrast, the self-administration tendency in female mice with gut microbiota attenuation remained at normal levels. These findings suggest that microbial metabolites play

a significant role in influencing the self-administration rate. Notably, the reintroduction of these microbial metabolites through the utilization of short chain fatty acids reinstated the self-administration behavior to its typical patterns. Although this area of research is currently receiving significant attention, the absence of groundbreaking evidence still characterizes its novelty.

4.5. Effect of Fentanyl on the Renal System

An overdose of fentanyl can cause acute kidney injury, marked by a sudden deterioration in kidney function. This occurs because fentanyl can induce reduced blood flow to the kidneys, causing ischemic damage, or it can directly harm the kidneys. Furthermore, prolonged fentanyl usage can give rise to chronic kidney disease, a clinical condition characterized by progressive kidney function. Chronic kidney disease (CKD) can lead to end-stage renal disease, requiring treatment such as dialysis or kidney transplantation. Alleviation of fentanyl-induced acute kidney injury includes avoiding fentanyl overdose, maintaining appropriate dosing, and careful monitoring of individuals at risk for kidney damage (example, kidney disease or dehydration). Fentanyl can have many side effects in people with CKD. Fentanyl is primarily metabolized in the liver, but a small percentage of the drug is also metabolized in the kidneys. In CKD patients, reduced kidney function may lead to slower or altered metabolism and clearance of fentanyl, which have the potential to increase the risk of undesirable effects and toxic dosage. There are chances of potential drug interactions and reduced effectiveness of other medications. Fentanyl has the potential to influence the secretion of antidiuretic hormone (ADH), causing fluid retention and disruptions in electrolyte levels among individuals with CKD. Overall, fentanyl should be used with caution in CKD patients, and the dose should be adjusted according to the patient's kidney function and other medications. It is essential to monitor for signs of respiratory depression, fluid retention, and drug interactions when using fentanyl in CKD patients [18].

4.6. Effect of Fentanyl on the Reproductive System

Several studies and data collection have been done to emphasize the fact that fentanyl and its derivatives have a deep effect on reproduction, not only due to its effect on fertility, but also on reproductive psychology. Through experimentation, it has been tested that fentanyl use reduces the potency of sexual hormones and increases the risk of both male and female fertility with prolonged abuse, including erectile dysfunction in males and pregnancy loss in females [19]. For pregnant women, fentanyl abuse can lead to adverse neonatal outcomes, including preterm birth and congenital anomalies. The underlying factor behind this occurrence stems from the opioid's lipophilic properties, enabling it to traverse the placental barrier effectively. To mitigate these implications on newborn babies, strategies like rooming-in skin-to-skin bonding and maintaining a tranquil environment with subdued lighting have been proposed. These interventions aim to ameliorate the severity of Neonatal Abstinence Syndrome (NAS), either in isolation or when combined with the administration of morphine and clonidine for management. The noteworthy surge in the utilization of fentanyl as an addictive substance among pregnant women during the COVID-19 pandemic has yielded adverse repercussions for both mothers and their progeny. This escalation in misuse can be attributed to multifaceted factors, encompassing unstable housing situations, financial limitations, heightened isolation, increased apprehension regarding health and well-being, and restricted access to maternal healthcare resources [20].

4.7. Effect of Fentanyl on Thermoregulation

Shivering, sweating, and vasoconstriction have been noticed during general anesthesia, with vasoconstriction being crucial in preventing hypothermia. It has been determined that infants and children are unable to raise their metabolic rate in response to mild intraoperative hypothermia on anesthesia with fentanyl and propofol. In anesthetized infants, there might be a conjunction of vasoconstriction and heightened metabolic activity. Conversely, unanesthetized neonates rely on non-shivering thermogenesis, leading to a twofold increase in heat production. Again, fentanyl is frequently used with lidocaine to enhance epidural blockade quality and lessen adverse effects. Yet, adding fentanyl to lidocaine increases the probability of hypothermia in patients [21]. Numerous investigations utilizing assessments of peripheral cutaneous vasoconstriction have shown that opioids and nitrous oxide (N_2O), particularly the

mixture of N_2O/fentanyl, reduce thermoregulatory responses in animals and decrease the thermoregulatory threshold in humans [22].

4.8. Effect of Fentanyl on the Immune System

Public health concerns involving opioid overdoses and opioid use disorder (OUD) are spreading throughout the world, especially in the US. The perturbation of both the instant natural and postponed adaptive neuro-immune response to foreign substances, particularly viruses, is reportedly linked to opioid tolerance and withdrawal. Nonetheless, there is still much to understand about neuro-immune function from opioid usage to more advanced stages of OUD. Ultimately, identifying the origins of innate immune dysregulation associated with opioids will contribute to enhancing treatments for OUD during specific stages of the OUD cycle. Male rats were employed to emulate a short-duration, low-dose opioid consumption pattern, analogous to the initial stages of opioid abuse in humans. During the early phase of abstinence (within 24 hours), various immune modulators, cytokines, and chemokines were detected within the limbic-mesocorticostriatal system nodes, a region related to rapid innate immunity responses [23].

It has been noted that essential innate immune proteins showed twofold or greater increases in the nucleus accumbens and decrease in the hippocampus. The hippocampus has been shown to exhibit decreased levels of some cytokines (such as numerous interleukins) and the proteins that stimulate interferon genes, namely, stimulator of interferon genes (STING). Exceptionally substantial positive correlations have been observed between the expression of the STING proteins, interleukin (IL) 4, and IL7 in the hippocampus [24]. While the role of IL7 in the hippocampus remains poorly understood, the decline in hippocampal IL4 in mice is connected with age-related learning impairments. IL4, crucial for spatial learning and neurogenesis, plays a vital role in this context [24]. Vaccination may be a promising possible treatment for accidental overdoses of fentanyl and heroin, which are taken together to boost their effects as well as lessen the likelihood of drug abuse. It was revealed that the monovalent vaccinations for heroin and fentanyl, which contained the haptens 6-AmHap for heroin and para-AmFenHap for fentanyl, respectively, were coupled to tetanus toxoid (TT). Such effective bivalent vaccination might neutralize the effects of heroin and fentanyl [25].

5. CONCLUSION

Fentanyl has been a good analgesic player with strong analgesic power and few side effects. It has been used to treat painful conditions like cancer that cause pain and inflammation. The American subcontinent has seen an increase in fentanyl use as an addictive substance recently. This stems especially from the extensive accessibility of fentanyl and its artificial analogs, either on their own or mixed with potent opioids such as heroin. During the early years, fentanyl was not kept under proper surveillance and thus got an opportunity to spread as an addiction agent in the population, but this has changed over time, and work is progressing slowly, but steadily. Many studies have revealed that fentanyl misuse negatively affects not only the brain and neurocognition, encompassing cerebral edema and hallucinations, but also the rest of the body, resulting in diverse systemic impacts Figure 2. This addiction is primarily brought on by the usual triggers for addiction, such as unemployment, bankruptcy, marital stress, pandemic stress, and many more. The only known medication against fentanyl is naloxone, although research is being done to create a vaccination that will lessen the drug's impact on the body. Regulations against fentanyl have not yet been fully applied in our developing nation of India, where it is still easily accessible to the public through easily accessible internet shopping applications at relatively low prices. According to the Drug Enforcement Administration (DEA), India, and China, which house most of the world's illicit fentanyl manufacturing facilities, are the primary drivers of the growth in fentanyl usage. This paper primarily aims to increase public awareness of drug abuse, both domestically and abroad. This paper gives an extensive evaluation of both traditional and new research to provide the reader with comprehensive yet useful knowledge with the goal of a better future.

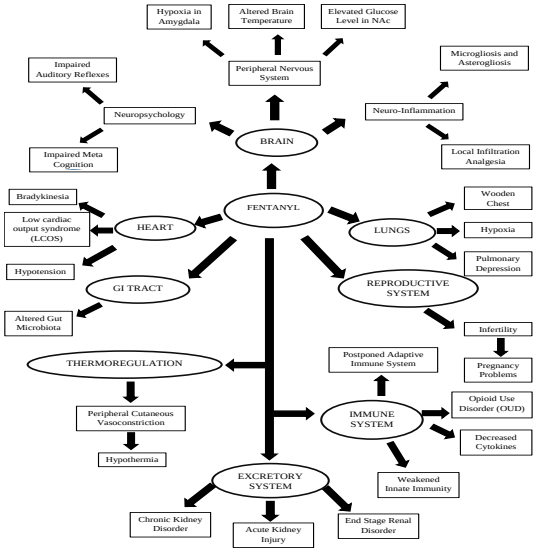

Figure 2 . Representation of Systemic Effects of Fentanyl on Human Body

Acknowledgments

The authors would like to acknowledge Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata 700016, India that supported this research. We extend our gratitude to various online resources that have significantly enriched this review.

Funding Information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have declared no competing interests related to this work.

Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Priyanka De	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	
Anuvhab Mondal	✓				✓	✓	✓	✓	✓		✓			
Ayush Bhattacharya	✓				✓	✓	✓	✓	✓		✓			
Nilratan Pal	✓				✓	✓	✓	✓			✓			

C: **C**onceptualization
M: **M**ethodology
So: **So**ftware
Va: **Va**lidation
Fo: **Fo**rmal analysis
I: **I**nvestigation
R: **R**esources
D: **D**ata Curation
O: Writing - **O**riginal Draft
E:Writing - Review & **E**diting
Vi: **Vi**sualization
Su: **Su**pervision
P: **P**roject administration
Fu: **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interests and that they have no known competing financial interests or personal relationships that could have appeared to influence. The authors also declare that the manuscript is original and no parts of it has been published previously.

Informed Consent

As this is a review article based on previously published data and publicly available information, no human subjects or animals were involved in the study. Therefore, informed consent was not applicable.

Ethical Approval

This systematic review did not involve any primary data collection involving human subjects or animals. Hence, ethical approval was not required for this study.

Data Availability

Data supporting the findings of this review are derived from previously published studies and publicly available reports. All relevant sources are cited within the manuscript and listed in the reference section. Further inquiries regarding data and figures can be directed to the corresponding author.

REFERENCES

[1] T. H. Stanley, 'The fentanyl story', J. Pain, vol. 15, no. 12, pp. 1215-1226, Dec. 2014. doi.org/10.1016/j.jpain.2014.08.010

[2] P. Armenian, K. T. Vo, J. Barr-Walker, and K. L. Lynch, 'Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review', Neuropharmacology, vol. 134, pp. 121-132, May 2018.doi.org/10.1016/j.neuropharm.2017.10.016

[3] E. Solis Jr, K. T. Cameron-Burr, Y. Shaham, and E. A. Kiyatkin, 'Fentanyl-induced brain hypoxia triggers brain hyperglycemia and biphasic changes in brain temperature', Neuropsychopharmacology, vol. 43, no. 4, pp. 810-819, Mar. 2018. doi.org/10.1038/npp.2017.181

[4] C. Carlsson, D. S. Smith, M. M. Keykhah, I. Englebach, and J. R. Harp, 'The effects of high-dose fentanyl on cerebral circulation and metabolism in rats', Anesthesiology, vol. 57, no. 5, pp. 375-380, Nov. 1982. doi.org/10.1097/00000542-198211000-00005

[5] L. Foy, D. M. Seeyave, and S. A. Bradin, 'Toxic leukoencephalopathy due to transdermal fentanyl overdose', Pediatr. Emerg. Care, vol. 27, no. 9, pp. 854-856, Sep. 2011. doi.org/10.1097/PEC.0b013e31822c281f

[6] U. Schneider et al., 'Effects of fentanyl and low doses of alcohol on neuropsychological performance in healthy subjects', Neuropsychobiology, vol. 39, no. 1, pp. 38-43, 1999. doi.org/10.1159/000026558

[7] L. K. Figueroa-Hall, S. Das, C. W. Stevens, and R. L. Davis, 'Characterization of toll-like receptor 4 neuroinflammatory signaling and the effects of fentanyl citrate on CHME-5 human microglial cells', FASEB J., vol. 30, no. S1, Apr. 2016. doi.org/10.1096/fasebj.30.1_supplement.1179.5

[8] C. J. Carranza-Aguilar et al., 'Morphine and fentanyl repeated administration induces different levels of NLRP3-dependent pyroptosis in the dorsal raphe nucleus of male rats via cell-specific activation of TLR4 and opioid receptors', Cell. Mol. Neurobiol., vol. 42, no. 3, pp. 677-694, Apr. 2022. doi.org/10.1007/s10571-020-00957-5

[9] Y. Han, L. Cao, K. Yuan, J. Shi, W. Yan, and L. Lu, 'Unique pharmacology, brain dysfunction, and therapeutic advancements for fentanyl misuse and abuse', Neurosci. Bull., vol. 38, no. 11, pp. 1365-1382, Nov. 2022. doi.org/10.1007/s12264-022-00872-3

[10] J. G. Klamt, W. V. de Andrade Vicente, L. V. Garcia, and C. A. Ferreira, 'Effects of dexmedetomidine-fentanyl infusion on blood pressure and heart rate during cardiac surgery in children', Anesthesiol. Res. Pract., vol. 2010, pp. 1-7, Aug. 2010. doi.org/10.1155/2010/869049

[11] K. J. S. Griffioen et al., 'Fentanyl inhibits GABAergic neurotransmission to cardiac vagal neurons in the nucleus ambiguus', Brain Res., vol. 1007, no. 1-2, pp. 109-115, May 2004. doi.org/10.1016/j.brainres.2004.02.010

[12] L. L. Koekkoek, L. L. van der Gun, M. J. Serlie, and S. E. la Fleur, 'The clash of two epidemics: The relationship between opioids and glucose metabolism', Curr. Diab. Rep., vol. 22, no. 7, pp. 301-310, Jul. 2022. https://doi.org/10.1007/s11892-022-01473-0

[13] E. A. Kiyatkin, 'Respiratory depression and brain hypoxia induced by opioid drugs: Morphine, oxycodone, heroin, and fentanyl', Neuropharmacology, vol. 151, pp. 219-226, Jun. 2019. doi.org/10.1016/j.neuropharm.2019.02.008

[14] N. J. Burgraff, N. A. Baertsch, and J.-M. Ramirez, 'A comparative examination of morphine and fentanyl: unravelling the differential impacts on breathing and airway stability', J. Physiol., vol. 601, no. 20, pp. 4625-4642, Oct. 2023. doi.org/10.1113/JP285163

[15] J. V. Pergolizzi Jr, L. R. Webster, E. Vortsman, J. Ann LeQuang, and R. B. Raffa, 'Wooden Chest syndrome: The atypical pharmacology of fentanyl overdose', J. Clin. Pharm. Ther., vol. 46, no. 6, pp. 1505-1508, Dec. 2021. doi.org/10.1111/jcpt.13484

[16] S. Ahmedzai and D. Brooks, 'Transdermal fentanyl versussustained-release oral morphine in cancer pain: Preference, efficacy, and quality of life', J. Pain Symptom Manage., vol. 13, no. 5, pp. 254-261, May 1997. doi.org/10.1016/S0885-3924(97)00082-1

[17] M. Ren and S. Lotfipour, 'Antibiotic knockdown of gut bacteria sex-dependently enhances intravenous fentanyl self-administration in adult Sprague Dawley rats', Int. J. Mol. Sci., vol. 24, no. 1, p. 409, Dec. 2022. doi.org/10.3390/ijms24010409

[18] F. Coluzzi et al., 'Safe use of opioids in chronic kidney disease and hemodialysis patients: Tips and tricks for non-pain specialists', Ther. Clin. Risk Manag., vol. 16, pp. 821-837, Sep. 2020. doi.org/10.2147/TCRM.S262843

[19] K. S. Flannagan, L. A. Sjaarda, S. L. Mumford, and E. F. Schisterman, 'Prescription opioid use among populations of reproductive age: Effects on fertility, pregnancy loss, and pregnancy complications', Epidemiol. Rev., vol. 42, no. 1, pp. 117-133, Jan. 2020. doi.org/10.1093/epirev/mxaa007

[20] D. J. Corsi and M. S. Q. Murphy, 'The Effects of opioids on female fertility, pregnancy and the breastfeeding mother-infant dyad: A Review', Basic Clin. Pharmacol. Toxicol., vol. 128, no. 5, pp. 635-641, May 2021. doi.org/10.1111/bcpt.13577

[21] O. Plattner, M. Semsroth, D. I. Sessler, A. Papousek, C. Klasen, and O. Wagner, 'Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol', Anesthesiology, vol. 86, no. 4, pp. 772-777, Apr. 1997. doi.org/10.1097/00000542-199704000-00006

[22] J. M. Wheelahan, K. Leslie, and B. S. Silbert, 'Epidural fentanyl reduces the shivering threshold during epidural lidocaine anesthesia', Anesth. Analg., vol. 87, no. 3, pp. 587-590, Sep. 1998. doi.org/10.1213/00000539-199809000-00017

[23] G. F. Koob, 'Neurobiology of opioid addiction: Opponent process, hyperkatifeia, and negative reinforcement', Biol. Psychiatry, vol. 87, no. 1, pp. 44-53, Jan. 2020. doi.org/10.1016/j.biopsych.2019.05.023

[24] J. Zhang et al., 'IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis', Sci. Adv., vol. 7, no. 12, p. eabb9888, Mar. 2021. doi.org/10.1126/sciadv.abb9888

[25] R. C. Barrientos et al., 'Bivalent conjugate vaccine induces dual immunogenic response that attenuates heroin and fentanyl effects in mice', Bioconjug. Chem., vol. 32, no. 11, pp. 2295-2306, Nov. 2021.doi.org/10.1021/acs.bioconjchem.1c00179

How to Cite: Dr. Priyanka De, Anuvhab Mondal, Ayush Bhattacharya, Nilratan Pa. (2025). Fentanyl abuse and its implication on health and society. Journal of Mental Health Issues and Behavior (JMHIB), 5(1), 12-22. https://doi.org/10.55529/jmhib.51.12.22

BIOGRAPHIES OF AUTHORS

Dr. Priyanka De, is currently working as an Assistant professor in the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata. She did M.Sc. (Zoology) with specialization in Genetics from the University of Calcutta. She was conferred Ph.D. from Indian Institute of Chemical Biology (CSIR-IICB), Kolkata. Her PhD work involved studies on functional significance of glucocorticoid-induced cardiac hypertrophy. She has contributed articles of varied interest in various journals of national and international repute. She has presented her papers in a number of seminars. Dr. Priyanka De has been invited as speaker in various places. She is engrossed in various cultural pursuits. She has great fervour in literature and believes in the unison of science and literature. She has many book chapters and four books to her credit till date. She can be contacted at Email: priyankade@sxccal.edu

	**Anuvhab Mondal**, is a bonafide student of the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata, who has completed postgraduate course in 2024. He has completed his Master's thesis on the NSEM map of erythrocruorin at the Saha Institute of Nuclear Physics. He had joined the same lab as a Research Assistant. Later, he pursued de novo protein design and small-molecule targeting at IIT Palakkad. Currently, he is working as a Research Assistant at the Institute of Biological Chemistry, Academia Sinica, Taiwan, under a European collaboration with the Max Planck Institute of Biophysics. He can be contacted at Email: anubhabmondal2001@gmail.com
	**Ayush Bhattacharya**, is a bonafide student of the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata, who has completed postgraduate course in 2024. As a Junior Research Fellow at IIT Bombay's Proteomics Lab under Dr. Sanjeeva Srivastava, he employs mass spectrometry-based proteomics, metabolomics, and lipidomics to study pituitary adenoma, meningioma, and acute kidney injury. Since December 2024, he has contributed to the RePORT India project, collaborating with Johns Hopkins University to identify novel biomarkers for tuberculosis recurrence. His work aims to advance precision medicine for complex diseases. He can be contacted at Email: ayushbhattacharya71@gmail.com
	**Nilratan Pal**, is a bonafide student of the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata, who has completed postgraduate course in 2024. His academic focus spans bioinformatics, structural enzymology, and microbial stress mitigation. He has co-authored peer-reviewed publications and contributed to departmental journals. He has also worked on gut microbiome metagenomic analysis and pangenome studies of ESKAPE pathogens. Passionate about scientific communication and interdisciplinary research, he blends creativity with scientific rigor. He can be contacted at Email: nilratanpal2001@gmail.com