

# FENTANYL: NEW WAVE, NEW AGE, NEW ADDICTION?

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## SUMMARY

This paper aims to take over the rampant phenomenon of the illicit use/abuse for volutary purposes of fentanyl. This synthetic drug is normally used as a potent anaesthetic and analgesic molecule. Unfortunately, in recent decades, this substance has conquered and seduced millions of people in the 'westernised' world, claiming numerous victims, especially young people. To this end, the most recent scientific literature will be examined and the pharmacological effects of both therapeutic and intentional abuse will be considered. Finally, the consequences and psychosocial damage produced will be described.

**Key words:** fentanyl - analgesic drug - illicit use - therapeutic application

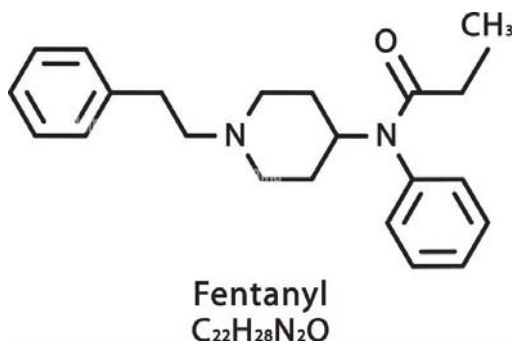
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## INTRODUCTION

Fentanyl (f) belongs to the piperidine class and was synthesised by Paul Janssen in the 1960 (Figure 1).

Since 1979 f and its analogue have been synthesized in laboratories and sold as heroin substitutes or mixed with other illicitly sourced drugs, leading to an increase in fentanyl-related overdose deaths (Han et al. 2019). Fentanyl is usually formulated as fentanyl citrate and it is used for the treatment of severe acute and/or chronic pain syndromes; in the induction phases of anaesthesia both in outpatient (day surgery) and in the operating theatre it is intended to reduce the amount of volatile anaesthetics and also for its intense analgesic property (Pre-Emptive Analgesia) (Table 1).

In addition, therapeutic uses of f is for Neuroleptoanalgesia and Neuroleptoanesthesia, and for the Treatment of Pain in Intensive care.



**Figure 1.** Structural and brute formula of Fentanyl

## THERAPEUTIC ROUTES OF ADMINISTRATION

The main pharmaceutical formulations for human use are available and are administered mainly in solution for intravenous (i.v.) or intramuscular (i.m.) use,

formulated as fentanyl citrate; buccal aerosol sprays and intranasals. A study of inhaled, aerosolised fentanyl, showed comparable pharmacokinetic and pharmacodynamic profiles to an iv injection of the same dose (Bird et al. 2023).

## ROUTES OF ADMINISTRATION FOR INTENTIONAL/ILLICIT USE

In recent decades, mixtures containing fentanyl, heroin, powders and other excipient have been produced in illegal laboratories giving rise to illicitly-manufactured fentanyl (IMF) which was taken by way of illicit Transdermal, sublingual, buccal and transnasal. One study of intranasal fentanyl reported high bioavailability (89%) and a similar profile of effects relative to iv administration (Macleod et al 2012).

Post-mortem studies have consistently found pulmonary edema, congestion and middle puncture sites in these victims. Based on data from the National Vital Statistics System, 599.255 drug overdose deaths occurred from 1979 to 2016 in the US and overall mortality rate has seen exponential growth. Fentanyl-related overdose deaths predominantly occurred in the North Eastern United States, mostly affecting younger people (20-40 years of age) and grew sharply since 2013 (Jalal et al. 2016). Fentanyl has become a major contributor to cocaine-related fatal overdoses. The rate of fentanyl-related overdose deaths increased 55% between 2015 and 2017 in New York City (Colon-Berezin et al. 2019, Nolan et al. 2019). However, the potential of fentanyl abuse and the rise in overdose deaths release a serious challenge for public health.

Analyses of adverse-event reporting systems in the US, Europe and United Kingdom have shown that cases of fentanyl-related misuse, abuse, dependence and withdrawal steadily increased between 2004 and 2018,

**Table 1.** Main analgesics used in short anaesthesia (Romano 2016)

<b>Tabella 68.9</b> Principali analgesici utilizzati nelle anestesie brevi				
	<b>Fentanyl</b>	<b>Alfentanil</b>	<b>Sufentanil</b>	<b>Remifentanil</b>
pKa	8,4	6,5	8,0	7,07
% quota ionizzata a pH 7,4	8,5	89	19,7	32
Liposolubilità	816	129	1757	18
% legame proteico	84	92	93	
% legame $\alpha_1$ -glicoproteina	44	92	83	70
VD (l/kg)	4,0	0,7	1,7	0,3-0,4
Clearance (ml/kg/min)	12,6	5,1	12,7	42
T <sub>1/2</sub> (ore)	3,6	1,6	2,7	0,16

**Tratto da:** “Anestesia Generale e Clinica” a cura di Ezio Romano – EDRA spa Milano

resulting in prolonged hospitalization or death (Schifano et al. 2019). Other mental disorders, such as depression, insomnia, and suicidality, can also occur with fentanyl abuse, contributing to relapse and a higher risk of respiratory depression or overdose death (Volkow et al. 2019). On the other hand, acute naloxone administration antagonizes fentanyl-induced analgesia more than fentanyl-induced lethality (Han et al. 2019).

## ABSORPTION

Fentanyl has a high lipophilicity and low molecular weight that facilitate rapid penetration into biological membranes and the central nervous system via  $\mu$ ,  $\mu_1$  and  $\mu_2$  receptors. M1 are located in the cerebral cortex, in the presynaptic spaces of the periaqueductal grey matter, in the superficial dorsal horn of the spinal cord or in the gelatinous substance of roland. M2 receptors are widely distributed in smooth muscle, cardiac tissue, salivary glands and glands of the gastric mucosa (Romano 2016).

## EXCRETION

The main routes of excretion are the liver and kidney. Most metabolism is governed by the liver and renal excretion. In urine, in fact, traces of metabolites are found in about 76% or in feces in about 8% at 72 hours after its intake (McClain & Hug 1980).

## CONCLUSIONS

Currently, with a view to avoid further overdose victims from illicit fentanyl use and to prevent the recruitment of new drug users, two avenues are emerging: the first, in which research and development of drugs capable of neutralising fentanyl and its active metabolites with high lethality; the second one in which extensive awareness campaigns directed at the general

population through all social agencies: schools, associations, workplaces with a high socio-psycho-educational impact.

**Acknowledgements:** None.

**Conflict of interest:** None to declare.

### Contribution of individual authors:

Alfredo Juli: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, validation, writing original draft, writing review & editing, supervision.

Giada Juli, Alfredo Juli & Luigi Juli: conceptualization, visualization, literature searches and analyses, review & editing.

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