



# PHARMACOVIGILANCE NEWSLETTER

VOL. 17 No.1 2024

## Facts about prescription opioids, risks and management

### Content

- Introduction
- Pharmacological properties of opioids
- Biological factors relating to Opioid Use Disorder
- Tolerance, Psychological Dependence & Withdrawal
- Risks Associated with Chronic Opioid Therapy
- Pharmacological Treatment of OUD
- Conclusion
- References

Health professionals and patients are encouraged to **report adverse events** or **quality problems** experienced with the use of **vaccines and medicines** to the nearest NAFDAC office or via [pharmacovigilance@nafdac.gov.ng](mailto:pharmacovigilance@nafdac.gov.ng) or via eReporting platform available on the NAFDAC website [www.nafdac.gov.ng](http://www.nafdac.gov.ng) or via Med Safety Application available for download on Android and IOS stores.

**Pharmacovigilance Newsletter Desk:**  
**Yvonne I. Ikhide B.Pharm., MS.Reg Sci**  
Chief Regulatory Officer/PV

### EDITOR'S NOTE...

We wish to thank our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out the quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote reporting of Adverse Drug Reactions (ADRs) and AEFIs. This edition of the newsletter focuses on: **Facts about prescription opioids, risks and management**

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions and AEFIs. Your valued comments and acknowledgement of receipt of this issue through our email addresses ([pharmacovigilance@nafdac.gov.ng](mailto:pharmacovigilance@nafdac.gov.ng), [fdic@nafdac.gov.ng](mailto:fdic@nafdac.gov.ng)) would be most appreciated.

Thank you for your relentless efforts in strengthening the Pharmacovigilance System in Nigeria.

**Uchenna Elemuwa B.Pharm., M.Pharm, MILR, FPCWA**

**National Coordinator, National Pharmacovigilance Centre (NPC), National Agency for Food and Drug Administration and Control (NAFDAC)**

Plot 2032 Olusegun Obasanjo Way, Wuse Zone 7, Abuja, Nigeria.  
PMB 5032 Wuse Abuja. Telephone: 08036047233

**E-mail: [pharmacovigilance@nafdac.gov.ng](mailto:pharmacovigilance@nafdac.gov.ng),**

[npcadr@nafdac.gov.ng](mailto:npcadr@nafdac.gov.ng), [nafdac\\_npc@yahoo.com](mailto:nafdac_npc@yahoo.com) Web site:

[www.nafdac.gov.ng](http://www.nafdac.gov.ng)

[Type here]

## Introduction

The term opiate refers to drugs derived from the opium poppy like morphine and codeine while opioid refers to opiates, as well as synthetic and semisynthetic drugs with similar properties such as fentanyl, hydrocodone and oxycodone (Lembke et al., 2016). Opioid analgesics, which fueled the origins of the opioid epidemic, are therapeutically beneficial when used properly; therefore they cannot be banned. While earlier phases (i.e., first wave) of the crisis were predominantly driven by non-medical use and addiction to prescription opioid analgesics, heroin (second wave) and subsequently illicit synthetic opioids (third wave) have become progressively important as the crisis progressed and more recently there is emerging evidence of increasing fatalities associated with the combination of psychostimulant drugs with opioids (fourth wave). These changes explain why the decreases in the number of opioid prescriptions dispensed has not amounted to a reduction in the number of opioid fatalities which has continued to rise (Volkow & Blanco, 2021).

Opioid misuse is the nontherapeutic use of opioids, including taking opioids in amounts other than prescribed, for indications other than prescribed, or by alternative routes of administration (e.g., crushing and snorting rather than ingesting). Opioid misuse is not always synonymous with an opioid use disorder (Lembke et al., 2016)

In the United States, from 1999 to 2019, opioid overdose, either regularly prescribed or illegally acquired, was the cause of death for nearly 500,000 people; it has significant

morbidity with severe risks and side effects. Consequently, opioid misuse is a cause for concern and is considered an epidemic. Largely, the prescription opioid epidemic is an almost exclusively North American problem (Biancuzzi et al., 2022).

Opioids are a class of substances that inhibit the transmission of painful stimuli. They are characterized by a strong analgesic effect. Opioids may be legally prescribed in the form of opiates such as codeine, morphine, semisynthetic opioids such as oxycodone, synthetic opioids such as fentanyl, and there are also illegal forms such as heroin. From 1999 to 2019 in the United States, opioid overdose from both regularly prescribed and illegally acquired drugs was the cause of death for nearly 500,000 people. These deaths did not occur at a consistent rate over time, but gradually increased during the period. From 1999 to 2018, opioid overdoses quadrupled. The increase in opioid overdose deaths is delineated in three distinct waves: the first from legally prescribed and manufactured opioid drugs; the second from heroin; and the third by illicitly manufactured synthetic opioids. The first wave occurred in the 1990s with the increase in opioid prescriptions and prescription-related deaths from overdoses of natural and semi-synthetic opioids. The second wave conventionally started in 2010 and is characterized by a rapid rise in deaths from heroin overdoses. The latest wave occurred in 2013 with a significant increase in overdose deaths involving synthetic opioids, mainly illicitly produced fentanyl.

## Pharmacological properties of opioids

In addition to their effect on mu- opioid receptors (MOR), opioid drugs also bind to kappa- (KOR) and delta-opioid (DOR) receptors, their affinity, intrinsic efficacy, pharmacokinetics and bioavailability vary by drug. In particular opioid drugs with fast uptake into the brain and full agonist effects at MOR such as heroin and fentanyl are particularly rewarding. A strategy for developing opioid medications with lower abuse liability entails opioids formulations with slower entry into the brain and/or formulations that cannot be injected, since this route of administration results in the faster rate of drug uptake in brain. For instance, the intrinsic efficacy of full agonist drugs such as heroin and fentanyl leads to greater rewarding effects than for partial agonists such as buprenorphine. In addition, the rate of clearance of opioid drugs from the brain determines their duration of action and the severity of withdrawal symptoms when discontinued. Consequently, heroin is associated with a much more severe withdrawal than a drug such as buprenorphine, which clears the brain more slowly. Opioids drugs with longer half-lives, slower clearance rates and slower brain uptake are suitable for the treatment of OUD. By binding to MOR, they decrease craving and prevent the emergence of withdrawal symptoms. Methadone enters the brain rapidly, which is why it is given orally when used for OUD treatment. Also, while it is a full MOR agonist, it has agonist effects at galanin receptors, which are co-expressed with MOR in brain reward regions antagonizing them, and thus reducing methadone's rewarding effects (Volkow & Blanco, 2021).

Tolerance is the physiologic adaptation to opioid therapy, as evidenced by the need for increasing doses to get the same effects, or the loss of effectiveness at a given dose. Physiologic dependence is the process whereby the body comes to rely on the drug to maintain biochemical homeostasis. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as signs and symptoms of withdrawal. Opioid withdrawal occurs in patients with physiologic dependence when lowering or discontinuing opioids, but it can also happen when changing the type or method of delivery, or when transitioning from one opioid to another with less bioavailability. Opioid withdrawal symptoms include arthralgias, myalgias, piloerection, rhinorrhea, diaphoresis, nausea, emesis, muscle cramps/spasms, and diffuse muscle and bone pain. Common behaviour and mood changes experienced during withdrawal include insomnia, dysphoria, irritability, and anxiety. Opioid withdrawal can present similarly to influenza. When patients receiving chronic opioid therapy exhibit sudden-onset "flu-like" symptoms, physicians should consider a recent decrease or discontinuation of opioids as the cause (Lembke et al., 2016).

## Biological factors relating to Opioid Use Disorder

## Tolerance, Psychological Dependence & Withdrawal

Tolerance is the physiologic adaptation to opioid therapy, as evidenced by the need for increasing doses to get the same effects, or the loss of effectiveness at a given dose. Physiologic dependence is the process whereby the body comes to rely on the drug to maintain biochemical homeostasis. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as signs and symptoms of withdrawal. Opioid withdrawal occurs in patients with physiologic dependence when lowering or discontinuing opioids, but it can also happen when changing the type or method of delivery, or when transitioning from one opioid to another with less bioavailability. Opioid withdrawal symptoms include arthralgias, myalgias, piloerection, rhinorrhea, diaphoresis, nausea, emesis, muscle cramps/spasms, and diffuse muscle and bone pain. Common behavior and mood changes experienced during withdrawal include insomnia, dysphoria, irritability, and anxiety. Opioid withdrawal can present similarly to influenza. When patients receiving chronic opioid therapy exhibit sudden-onset "flu-like" symptoms, physicians should consider a recent decrease or discontinuation of opioids as the cause (Lembke et al., 2016).

## Risks Associated with Chronic Opioid Therapy

**Constipation** is a well-recognized adverse effect of opioid use, with a reported prevalence of 15% to 90%. With chronic opioid use, constipation can become refractory to stool softeners and laxatives, and in some cases can lead to bowel obstruction, perforation, and death. Chronic opioid therapy can also cause worsened or new-onset **abdominal pain** (narcotic bowel syndrome) which is much less common than constipation (Lembke et al., 2016).

From the vigiflow, adverse events database, the following adverse events related to the use of opioids have been reported:

### Morphine Associated Adverse Events:

- Restlessness
- Feeling hot
- Confusion
- Pinpoint pupils
- Respiratory depression
- Pruritus

### Morphine-Sulfate Associated Adverse Events:

- Constipation
- Anal tear

### Codeine Associated Adverse Events:

- Pruritus
- Constipation
- Nasal blockage (bilateral)

- Dry throat
- Bilateral pedal oedema
- Irrational Behaviour
- Rash

### **Pethidine Associated Adverse Events:**

- Nausea
- Vomiting
- Fever
- Abdominal Pain

### **Pharmacological Treatment of OUD**

A range of pharmacological treatments exists to treat different components of OUD. Medically supervised withdrawal (formerly referred to as detoxification) is the gradual taper of opioid agonist medications (methadone or buprenorphine) guided by a

clinician to alleviate withdrawal symptoms. The use of  $\alpha_2$ -agonists such as clonidine can also help attenuate symptoms of withdrawal. However, subsequent initiation of medications for OUD (MOUD) is required to prevent relapse into drug taking. Indeed, medically supervised withdrawal is not recommended as an isolated strategy, as most patients without subsequent MOUD initiation relapse shortly thereafter and are at increased risk for overdosing due to the loss of tolerance.

### **Prevention**

A lot of emphasis is on treatment approaches however, there is growing recognition, of the need to develop effective preventive interventions for OUD. Initial preventive approaches in the US focused on improving prescription practices for opioid analgesics and increasing the availability of naloxone to prevent overdoses. Unlike for young people (students), there are no evidence-based primary and secondary prevention for OUD for adults or for youth transitioning into adulthood. Evidence-supported prevention interventions delivered in community or school settings have shown effectiveness at reducing substance use and other related problem behaviors; however, whether those interventions would work in adults is unknown. Another direction would be the development of conceptual frameworks that articulate the relationship among risk factors for OUD to help guide which interventions might be most effective given the prevalence of the risk factors, how they relate to other relevant risk factors and how modifiable the risk factors are. These models could help examine how risk factors present at birth (such as, family history of substance use

disorders) or childhood (such as, adverse childhood events) can increase the likelihood of risk factors in adolescence (for instance, early onset of psychiatric disorders and low educational achievement), which in turn increase the risk of OUD in adulthood. It will also be useful to increase the focus on populations at risk that can be accessed for screening and treatment. Improved management of opioid prescriptions and of treatment of OUD for pregnant women is also a high priority, as it could benefit the mother and simultaneously decrease the risk of neonatal abstinence syndrome (NAS) in newborns by decreasing their in-utero exposure to opioids.

The assessment of risk of OUD before opioids are prescribed, periodic assessment of the need for opioid use, and use of urine testing to rule out illicit use of other substances are useful practices. There is evidence that prescribing lower doses/fewer pills in the emergency room/post-surgery is associated with lower rates of long-term use and possibly OUD. There is also a need to assess each patient for licit and illicit use of other substances, particularly benzodiazepines and alcohol, which can increase the lethality of opioids by potentiating their depressing respiratory effects. Individuals who misuse opioids or develop OUD should be treated by their primary physicians if they have the necessary expertise and support or otherwise be referred to an addiction specialist. Prevention approaches should also consider supply approaches. The most common sources of diverted opioid analgesics are friends or relatives who were legitimately prescribed opioids. As with any other medication, it is important to educate patients who receive legitimate prescriptions about the health hazards they create for others when they give them their medications. Similarly, it is

important to educate patients about the health risks they incur when they take medications (including opioids) that were not prescribed to them. The use of Prescription Drug Monitoring Programs (PDMPs) are also recommended (Volkow & Blanco, 2021).

## Conclusion

The opioid crisis is a complex, evolving phenomenon. It involves neurobiological vulnerabilities and social determinants of health. Successfully addressing the crisis will require advances in basic science, development of more effective treatments, and public health approaches to implement current and emerging knowledge from researchers and clinicians. The advances achieved in addressing the opioid crisis could also serve to expand the science and treatment of other substance use disorders (Volkow & Blanco, 2021). In addition to its mortality burden that has increased gradually over time, opioid overdose has significant morbidity with severe risks and side effects. Therefore, opioid misuse is still a cause for concern and is considered an epidemic. (Biancuzzi et al., 2022).

## References

1. Biancuzzi, H., Dal Mas, F., Brescia, V., Campostrini, S., Cascella, M., Cuomo, A., ... & Miceli, L. (2022). Opioid misuse: a review of the main issues, challenges, and strategies. *International journal of environmental research and public health*, 19(18), 11754
2. Volkow, N. D., & Blanco, C. (2021). The changing opioid crisis: development, challenges and opportunities. *Molecular psychiatry*, 26(1), 218-233
3. Lembke, A., Humphreys, K., & Newmark, J. (2016). Weighing the risks and benefits of chronic opioid therapy. *American Family Physician*, 93(12), 982-990
4. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2021 National Survey on Drug Use and Health. SAMHSA.gov. <https://www.samhsa.gov/data/>.