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Oxidative Stress and Opioids´ Toxicity: An Update

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Abstract: Opiates are the most effective treatment for acute and chronic severe pain. However, for the fact that they provoke the development of analgesic tolerance as observed in human studies, their clinical utility is often lower. Morphine is a principal opiate, but to get an equivalent pain relief with it, the doses of administration need to be constantly increasing. However, such dose increase has a therapeutic impact by on setting morphine-induced hypersensitivity. This complex pathophysiological cycle contributes significantly to decreased quality of life in the population of subjects with chronic pain. In any case, interests in new approaches that would maintain opiate efficacy during repetitive dosing without engendering tolerance or unacceptable side-effects are growing.

Recent evidence has implicated oxidative stress in the development of pain in several pathologies and most importantly in opiate antinociceptive tolerance, caused by the presence of free radicals. This mini-review on some opioids and their possible mechanisms has dual objective: to discuss the importance and role of free radicals in maintenance of pain and induction of opiate antinociceptive tolerance; and to demonstrate that opiates are rational target for therapeutic intervention in pain management, as well as to provide a pharmacological basis for developing inhibitors of free radical biosynthesis.

Keywords: Brain, free radicals, morphine, opioids, oxidative stress, pain.

OPIOIDS

An opioid is a psychoactive chemical that works by binding to opioid receptors principally found in the central and peripheral nervous system and gastrointestinal tract (GIT). The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids. Opioids are among the world oldest known drugs. The use of opium poppy for therapeutic benefits predates recorded history. The analgesic (painkiller) effects of opioids are due to their ability to decrease pain perception or reaction to pain thereby increasing pain tolerance. Opioid analgesics do not cause any specific organ toxicity. In older adults, opioid use is associated with increased adverse effects [1]. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria. Opioids can cause cough suppression, which can be an indication for its unintended side effect. Opioid dependence can develop with ongoing administration, leading to a withdrawal syndrome with abrupt discontinuation. Opioids are well known for their ability to produce a feeling of euphoria, leading to its use in recreational activities. They are non-prescription drugs and their consumptions are seen mainly in the urban areas by a large sector of the population for recreational purposes [2].

Although the term *opiate* is often used as a synonym of *opioid*, it is properly limited to the natural alkaloids found in resin of opium poppy *(Papaversomniferum)*. In some definitions, the semi-synthetic substances that are directly derived from the opium poppy are considered to be opiates as well, while in other classification systems these substances are simply referred to as semi-synthetic opioids, used for hospitalized patients.

Opioids have been used to treat acute pain such as post-operative pain, however, they are invaluable substances in palliative care to alleviate severe, chronic, disabling pain of terminal conditions such as cancer, and degenerative conditions as rheumatoid arthritis. An update frequency of opioids consumption in a private hospital services in Mexico is as follows: Fentanyl (d) (50%), Morphine (e) (30%), Sufentanil (g) (5%), Nalbuphine (i) (5%), Buprenorphine (h) (5%), Remifentanil (f) (2%), Codeine (a) (1.5%), Hydromorphone (b) (1%), Oxycodone (c) (0.5%), (Fig. **1**).

However, their use in chronic non-cancerous pain should be with precaution. High doses are not necessarily required to control the pain of advanced or end-stage disease. Opioids tolerance defined as physical reaction which makes the body less responsive to analgesic and other effect, may occur [3]. Requirements can level off for many months at a time, depending on the severity of pain. Opioids have potential for tolerance. This means that in many cases, opioids are successful long-term care strategy for patients in chronic cancer pain.

THERAPEUTIC USE

In recent years, there has been an increase in the use of opioids in the management of non-malignant chronic pain. This practice has now led to a new and growing problem of addiction and misuse of these substances [4]. The effects of opioids, either adverse or otherwise, can be reversed with

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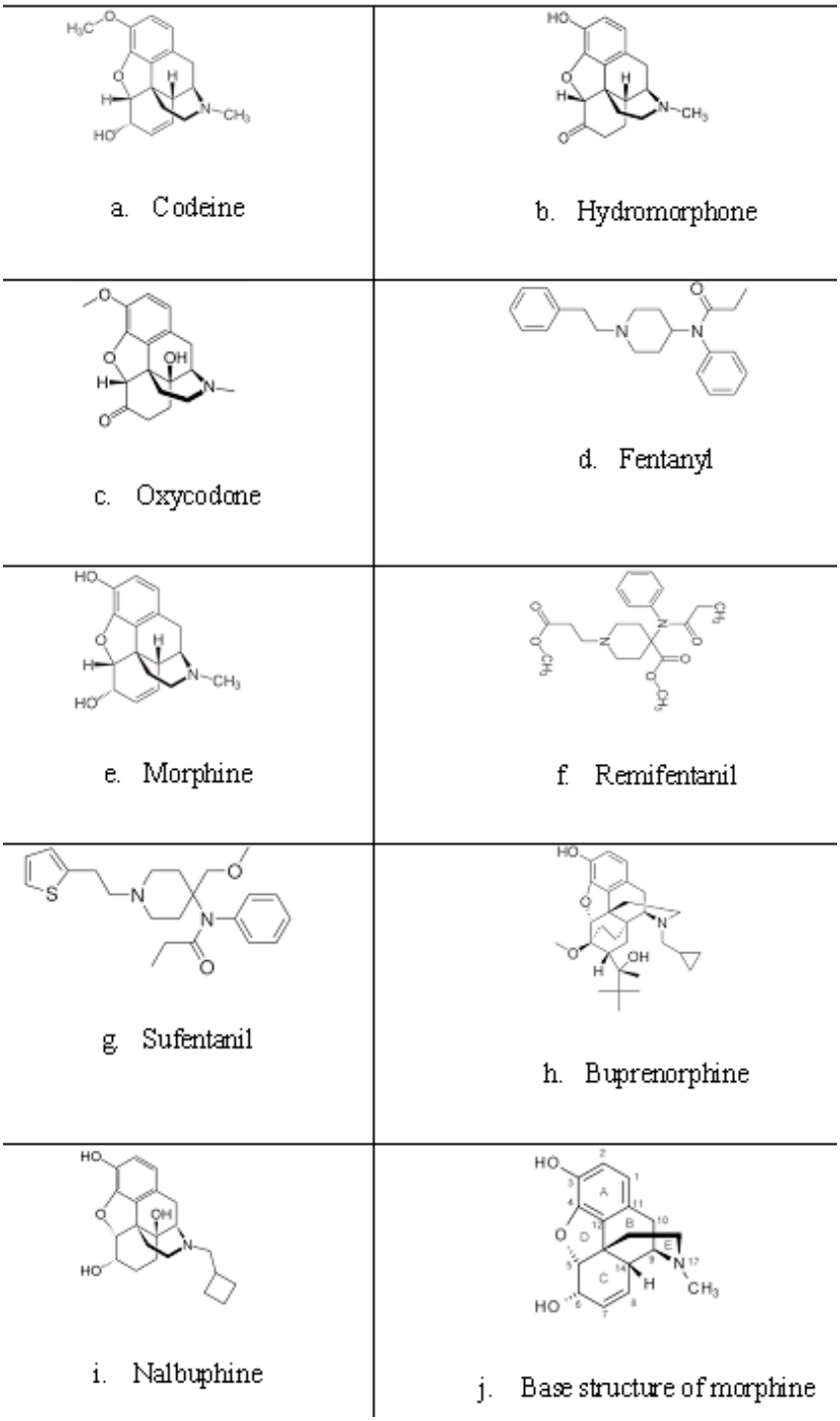

Fig. (1). Opioids used in a private hospital of Mexico.

naloxone (an opioid antagonist) which acts as competitive antagonist. This drug binds to opioid receptors with an affinity higher than the agonists without activating the receptors, and in this way it displaces the agonist thereby attenuating and/or reversing their effects [5]. However, since opioid antagonists block the beneficial effects of opioid analgesics, they are generally useful only for the treatment of overdoses. The use of opioid antagonists alongside with opioid analgesics to reduce side effects requires careful dose titration and should be low enough to allow the maintenance of analgesia.

The opioid analgesics, commonly exemplified by morphine, represent the best option for the treatment of severe pain and for the management of chronic pain states [6]. One of the major problems associated with the chronic use of morphine is the tolerance, however the molecular mechanism of tolerance is still unclear [7]. Mechanisms of opioid analgesia and tolerance at molecular and cellular levels are complex, and many of them require a modification in the expression and functions of signaling molecules. Aging has a significant impact on almost every aspect of opioid receptor signaling systems that underlie opioid analgesia and toler-

ance. Endogenous opioid peptides and opioid receptors are differentially expressed in different developmental stages, and aging is associated with changes in the number and/or affinity of opioid receptors and opioid receptor-like 1 (ORL1).

The expression of β-arrestin, which plays a prominent part in opioid receptor desensitization, is determined by neural differentiation and aging. The increased expression of β-arrestin is accompanied by a parallel increase in G protein-coupled receptor kinase (GRK) expression during prenatal development. The phosphorylation of opioid receptors by GRK and the binding of β-arrestin initiate the internalization of the ligand-bound receptors. The internalization of epidermal growth factor (EGF) receptors and interleukin 2 (IL2) receptors and clathrin-associated endocytosis are age-dependent, which implies that the same might be also true for opioid receptor systems. Aging affects the expression and function of N-methyl-D-aspartic acid (NMDA) receptor and its subunits (calmodulin (CaM), protein kinase C (PKC) and other isoforms) as well as other neuropeptides known to have anti-opioid effects. The expression, regulation, and function of specific G protein signaling (RGS) members are affected by age during embryonic development and neuronal differentiation. Development and aging differentially regulate G protein-mediated adenylatecyclase (AC) signaling. The activities of AC, guanylatecyclase (GC), cyclic AMP (cAMP), phosphodiesterase, and cyclic GMP (cGMP) phosphodiesterase in the frontal cortex and cerebellum show age-related changes. [8].

TOLERANCE TO OPIOIDS

In palliative care, opioids are not recommended for sedation or anxiety because experience has shown that they are ineffective agents for these roles. Management of tolerance and withdrawal symptoms remains a major challenge since opioids are widely used in the intensive care units [9], or for clinical disorders (Table **1**). Some authors suggest that a single opioid mechanism is unlikely to explain all aspects of ingestive behavior, but also conclude that opioid-mediated reward mechanisms have an important control in hedonic aspects of ingestion. They also highlight the need for further empirical work in order to elucidate the role of opioid peptides in human ingestive behavior [26]. Agonists of the mu, delta, kappa and opioid receptors (ORL) increase food intake while the blockage of opioid receptors decreases food intake [27]. Likewise, Opioids exhibit stress-limiting and gastroprotective effects in stressed animals, acting *via* mu- and delta-opioid receptors (OR). Peripheral mu-OR stimulation by endogenous and exogenous opioids increases cardiac tolerance to pathological consequences of stress. Peptide OR agonists can be considered in future clinical practice for the treatment of withdrawal syndrome, stress-related cardiac disease or myocardial injury caused by ischemia-reperfusion insult [28].

INTERACTION WITH RECEPTORS

Opioids bind to specific opioid receptors in the nervous system and other tissues. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to seventeen of them which include ε, ι, λ, and ζ (Epsilon, Iota, Lambda and Zeta) receptors have been reported. Sigma (σ) receptors were originally considered as opioid receptor but this idea has been discarded for many reasons among which are: Their activation is not reversed by naloxone which is an opioid inverse-agonist; they lack high affinity binding with classical opioids; and they are stereoselective for dextro-rotatory isomers while other opioid receptors are levo-rotatory isomer stereoselectives.

Table 1. Clinical Disorders and some Opioids Involved in their Treatment

Drugs	Clinical Disorders	Ref.
Opioids	Acute external otitis	[10]
Opioids	Post-herpetic neuralgia	[11]
Opioids	Acute breathlessness episodes	[12]
Fentanyl, sufentanil, remifentanil	Hepatic encephalopathy	[13]
Morphine	Bone metastases	[14]
Fentanyl	Chronic low back pain	[15]
Fentanyl	Sickle cell disease	[16]
Morphine and oxycodone	Knee replacement and postoperative pain	[17]
Opioids	Chronic pain	[18]
Morphine	Iatrogenic opioid abstinence syndrome	[19]
Morphine	Refractory breathlessness	[20]
Opioids	Migraine	[21]
Buprenorphine	Osteoarthritis of knee	[22]
Morphine	Visceral pain	[23]
Fentanyl	Chronic pain and breakthrough pain	[24]
Morphine	Sickle cell disease	[25]

There are three subtypes of μ-receptor: μ_1, μ_2, and the newly discovered μ_3. Opioid-receptor-like receptor 1 (ORL1) is another receptor of clinical importance involved in pain responses and plays a major role in the development of tolerance to μ-opioid agonists that is used as analgesics. Although μ-opioids do not give satisfactory result in the treatment of cancer pain and are associated with multiple debilitating side effects, recent studies show that μ and δ opioid receptors are separately expressed by (on) IB4 (-) and IB4 (+) neurons that control thermal and mechanical pain [29].

The μ-opioid receptor (MOR) which is the principal receptor involved in narcotic addiction potentially plays a key role in addiction in combination with gene regulation and synaptic remodeling [30]. MOR belongs to the family of seven-transmembrane G-protein-coupled receptors. It is a heavy N-glycosylated protein that regulates G proteins [31]. This set of proteins comprises all G-protein coupled receptors acting on GABAergic neurotransmission.

The four types of opioid receptors are coupled to the inhibitory G protein (G_i or G_o,) which in turn is regulated by RGS proteins. The analgesic effect of opioid agonists is attributed to the signal transduction through the G protein–mediated second messenger system initiated by agonist bond to an opioid receptor. Once an opioid agonist binds to its specific receptor, the conformation of the opioid receptor changes and the coupled $G_{i/o}$ protein is subsequently activated. The G_α subunit switches from a GDP-bound inactive state to a GTP-bound active state and dissociates from the $G_{ß\gamma}$ subunits. Activated G subunits then interact with downstream effectors, which further amplify the signal initiated by the opioid agonist and opioid receptor. These downstream actions include the inhibition of adenylyl cyclase (AC) to reduce the production of cyclic AMP (cAMP), the opening of potassium channels, the inhibition of calcium channels, and the activation of mitogen-activated protein kinase (MAPK) and other kinases [8]. In nervous tissues, the G proteins are always found as dimers, indicating that this association is required for their function between MOR and G subunits for the activation of antinociceptive effects.

OPIOIDS OVERDOSE

In 2008, overdoses of opioid pain relievers in the United States caused 14,800 deaths [32]. The abuse of these drugs induces a massive release of dopamine from synaptic vesicles leading to the generation of reactive oxygen species (ROS). Furthermore, nitric oxide (NO), produced in the central nervous system (CNS) mediated by the activation of microglia, appears to play a critical role in stress-induced brain damage. The induction of iNOS by drug abuse in microglial cells could be an important source of NO in CNS inflammatory disorders associated with the death of neurons and oligodendrocytes [33]. It has been demonstrated that H_2O_2 has a notable effect in mediating inflammatory hyperalgesia, which highlights that its removal is a novel therapeutic target for anti-hyperalgesic drugs in the clinic [34]. Peroxynitrite (PN) mediated nitroxidative stress ($ONOO^-$) in the dorsal horn of the spinal cord plays a critical role in the induction and development of antinociceptive tolerance to morphine, providing a valid pharmacological basis for developing peroxynitrite scavengers as potent adjuncts to opiates in the management of pain. Superoxide plays a major role as a mechanism to block the development of morphine tolerance. This effect shows that lipophilicity is a critical parameter in enhancing the potency of such novel peroxynitrite scavengers [35]. Administration of morphine stimulates ceramide synthase implicated in the development of morphine antinociceptive tolerance. Therefore, ceramide is a key upstream signaling molecule in the development of morphine antinociceptive tolerance and provides the rationale for development of inhibitors of ceramide biosynthesis as adjuncts to opiates for the management of chronic pain [36].

Other studies with morphine suggest that repeated administration induces nitric oxide overproduction and increases brain malondialdehyde level [3], and that nitric oxide (NO) may play an important role in the development of tolerance to the opiate [37], and alter the balance of oxidant-antioxidant in the brain of animals fed with a protein deficient diet [38].

Morphine decreases the effectiveness of both natural and acquired immunity, interfering with intracellular pathways involved in immune regulation. The impact of the opioid-mediated immune effects could be particularly dangerous in selective vulnerable populations, such as the elderly or immune-compromised patients [39]. As with all body organs, the immune system is subjected to attack by a variety of toxins related to abuse of drugs.

OXIDATIVE STRESS AND TOXICITY

Although the mode of action is multifaceted, the focus is on electron transfer (ET), reactive oxygen species (ROS), antioxidants (AOs), cell signaling, and receptors. It is significant that the toxins or their metabolites incorporate ET functionalities capable of redox cycling with resultant generation of ROS and accompanying oxidative stress [40]. For example, in neuropathological abnormalities of human immunodeficiency virus (HIV-1) of patients abusing morphine, the role of HIV-1 transactivating protein (Tat) and morphine jointly elicited high levels of reactive oxygen species that were NADPH dependent. Likewise, platelet derived growth factor (PDGF-BB) can give protection against simultaneous exposure of Tat and morphine thus, strengthening its role as a neuroprotective agent that could be considered for therapeutic intervention [41]. NADPH oxidase may be a critical mechanism governing neuroprotection, and so, constitutes a novel avenue for anti-inflammatory and neuroprotective therapy [42]. Probably, the activation of mu-opioid receptor (MOPr) of the rat leads to an increase in phospholipase D2 (PLD2) activity which plays a key role in the regulation of NADH/NADPH-mediated ROS formation by opioids [43].

FREE RADICALS INVOLVED

The drugs of abuse induce cell death and production of reactive oxygen species involved in neurodegeneration. Opioid drugs are associated with a decrease in intracellular dopamine and an increase in DOPAC levels as well as with the formation of ROS. Its effect is correlated with a decrease in intracellular dopamine levels, which can be associated with an increased dopamine turnover and oxidative cell injury [44].

Toxicity and addiction based on electron transfer (ET), reactive oxygen species (ROS), and oxidative stress (OS) are principally associated to abused drug metabolites such as quinones and imines (iminiums). Minor types are nitroxide metabolite from cocaine, and alpha-dicarbonyl from alcohol. The case of Dopamine (DA) mediation in drug abuse has been the focus of much attention during the past decades, and their oxidative metabolism yields o-quinones and semiquinones which can redox cycle with oxygen to provide various ROS. Electrochemical studies support the possibility of ET transformations by these quinones in biological domain. In relation to cell signaling, DA is involved in the formation of cAMP followed by a cascade of other events. Stimulation of mediator production by abused drugs can occur with subsequent oxidation by ROS, some of which may be supplied by the drugs. In addition to prevention, the difficult topic of addiction mechanism is addressed from the viewpoint of ET and ROS involvement [45].

Reactive oxygen species (ROS) are considered to be chemically reactive with and damaging to biomolecules including DNA, protein, and lipid, and excessive exposure to ROS induces oxidative stress and causes genetic mutations. However, Nox and Duox enzymes generate ROS in a variety of tissues as part of normal physiological functions. By far, the most common conditions associated with Nox-derived ROS are chronic diseases that tend to appear late in life. The authors propose that these pathological roles of Nox enzymes can be understood in terms of antagonistic pleiotropy: genes that confer a reproductive advantage early in life can have harmful effects late in life. Such genes are retained during evolution despite their harmful effects, because the force of natural selection declines with advanced age [46].

The pharmacodynamic responses to an opioid depend on the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist, or an antagonist. For example, the supraspinal analgesic properties of opioid agonist morphine are mediated by activation of μ_1 receptor; respiratory depression and physical dependence on μ_2 receptor as well as sedation and spinal analgesia by the κ receptor. Each group of opioid receptors elicits a distinct set of neurological responses, with the receptor subtypes (such as μ_1 and μ_2 for example) providing even more specific responses. Unique to each opioid is its distinct binding affinity to the various classes of opioid receptors (e.g. μ, κ, and δ opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid). Their individual molecular structure is also responsible for the difference in their duration of action, while their metabolic breakdown (such as N-dealkylation) is responsible for opioid metabolism. The chemical structures of morphine and its metabolites are closely related to the clinical effects of the drugs as analgesia, their side-effects, and to their ability to cross the blood brain barrier (BBB). Morphine-6-glucuronide (M6G) and Morphine-3-glucuronide (M3G) are highly hydrophilic, but only M6G can penetrate the BBB. Accordingly, M6G is considered a more attractive analgesic than the parent drug and M3G [47], while hydroxyl group in C-6 of ring C (Fig. **1J**) offers potential activity [48].

IMPLICATION WITH SOME DISEASES

Opioids have many deleterious effects that could lead to severe acute poisoning with the development of opiate toxicohypoxic encephalopathy [49]. Also, it has been reported that opioid increases tau protein phosphorylation. Hyperphosphorylation of tau is also a pathological feature of Alzheimer's disease and other chronic neurodegenerative disorders. Indeed, morphine induced tau hyperphosphorylation, and increased levels of phospho-JNK and phospho-p38. JNK/p38 MAPK activated by morphine in an opioid receptor-dependent manner, may lead to tau hyperphosphorylation [50].

On the other hand, different tissues display defective mitochondrial oxidative phosphorylation (OXPHOS). The tissues that are highly dependent on oxygen such as cardiac muscle; skeletal and smooth muscle; central and peripheral nervous system; kidney; and insulin-producing pancreatic beta-cell are specially susceptible to defective OXPHOS. Defective OXPHOS may be caused by abnormal mitochondrial biosynthesis due to inherited or acquired mutations in the nuclear (n) or mitochondrial (mt) deoxyribonucleic acid (DNA), insufficient fuel supply, defective electron transport

Table 2. Recent Studies of some Opioids and Biomarkers of Oxidative Stress on Tissue (↓ under), (↑ up)

Opioids	Free Radical	Tissue	Ref.
Delta-opioid receptor	GPx, SOD ↑ NO,Caspase ↓	Cortex	[52]
Morphine, methamphetamine	NMDA receptor ↑	Brain	[53]
Low doses Morphine	Hemo-oxigenase ↑	Glomerular epithelial cell	[54]
Morphine	GSH ↓	Cerebrospinal fluid	[55]
Morphine	Up-regulated MAPK p38	Left ventricles	[56]
δ-opioid-receptors	Proinflammatory cytokines ↓	Retin	[57]
Morphine	NO ↑	Human hepatic cells	[58]
Morphine	SOD, Cat, GPx↓	C6 cells	[59]
Morphine	SOD ↑	human monocyte-derived macrophages	[60]
Heroin	Lipid peroxidation ↑ GSH ↓	Blood	[61]
Low doses Morphine	GSH ↓	Brain	[62]
Morphine	Malondialdehyde↑	Plasma	[63]
Morphine	GSG ↓	Brain	[64]
Morphine, fentanyl	Protein oxidation ↑	Cortex, striatum, midbrain	[65]
Morphine	GSH ↓ SOD, GPx↑	Plasma	[66]

chain enzymes (Complexes I - IV), lack of electron carrier coenzyme Q10, lack of oxygen due to ischemia or anemia, or excessive membrane leakage, all of which could result in insufficient mitochondrial inner membrane potential for ATP synthesis by the F0F1-ATPase. Human tissues can counteract the defects of OXPHOS by stimulating mitochondrial biosynthesis; however, above certain threshold, the lack of ATP causes cell death [51], or oxidative damage on organ tissues (Table **2**).

CONCLUSION

Opioids are often used in combination with adjuvant analgesics (drugs which have an indirect effect on pain). Pain associated with inflammatory diseases is often difficult to treat in the clinic due to insufficient understanding of the nociceptive pathways involved. For example: opioids should not be used for the treatment of migraine, because they decrease the gray matter; release of calcitonin gene-related peptide, dynorphin, and pro-inflammatory peptides; and activation of excitatory glutamate receptors [67]. Finally, this information suggests that the inhibition of oxidative damage may be a useful strategy for the development of a new protection for morphine administration as well as opiate abuse.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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