INTRODUCTION

Substance abuse continues to be a large public health concern worldwide. The availability of more potent drugs, the increasing number of substances and their consecutive or sequential use among occasional or regular users poses an even greater challenge to the prevention of drug use and the treatment of drug use disorders than in the past ***(World Drug Report, 2020).***

Drug use around the world has been on the rise, in terms of both overall numbers and the proportion of the world's population that uses drugs. Drug markets are becoming increasingly complex. Plant-based substances such as cannabis, cocaine and heroin have been joined by hundreds of synthetic drugs, many not under international control. There has also been a rapid rise in the non-medical use of pharmaceutical drugs and new psychoactive substances (NPS) including synthetic cannabinoid receptor agonists ***(World Drug Report, 2020)***.

Compared to the global incidence, a higher incidence of substance abuse in Egypt especially in Great Cairo was reported by the national research for addiction from 2007 through 2014 ***(Sabry et al., 2015).***

Abuse is defined medically as "any intentional, non-therapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect" ***(Al-Maaz et al., 2019).***

People who initiate drug use and subsequently develop drug use disorders typically transit through several stages, from initiation of use to escalation, maintenance and, eventually, dependence or addiction. There is a strong association between drug use disorders and adverse health consequences of drug use, including non-fatal overdoses, requiring emergency medical attention (***World Drug Report, 2020).***

Until recently, substance abuse was seen as a law enforcement problem and not as a public health issue. Although drug overdose-related deaths attract much public attention, there are substantial consequences of nonfatal overdoses including cardiac and musculoskeletal problems, aspiration pneumonia, cognitive impairment and hypoxic brain injury, renal dysfunction, and physical injuries sustained during the intoxication event ***(Martins et al., 2015).***

Recently, it has been suggested that drug users including alcohol, prescription drugs, and illicit drugs were at higher risk for intensive care unit (ICU) admission than the general

population. Patients with substance abuse are frequently admitted critically ill with multisystem organ failure, requiring mechanical ventilation and other ICU-level resources. Given the rising costs of health care, ICU utilization and costs related to licit and illicit abuse poses a significant burden on health care systems ***(Westerhausen et al.,2020).***

Life-threatening hospital admissions need an early and appropriate management. Accurately identifying potential life-threatening cases at admission is therefore of utmost importance. In drug-overdosed patients, the immediate need for ICU monitoring can be assessed with clinical scoring systems such as APACHE II and SOFA scores ***(Nguyen et al., 2017).***

AIM OF THE WORK

1- Determining trends of drug abuse among cases presented to Poison Control Center- Ain shams University Hospitals (PCC-ASUH) in a six-month duration from 1st of July till end of December 2018.

2- Evaluation of clinical characteristics of substance abuse cases admitted in the ICU of PCC-ASUH by using APACHE II (Acute Physiology And Chronic Health Evaluation II) score and SOFA (Sequential Organ Failure Assessment) score as predictors of severity and outcome.

Chapter 1

OPIATES AND OPIOIDS

Pharmacology

Composition

The term opiate specifically refers to the relevant alkaloids naturally derived directly from the poppy plant namely morphine, codeine and, to some extent, thebaine and noscapine. Papaver somniferum was first recorded around 1500 B.C. in the Ebers papyrus, however morphine was first isolated from opium in 1806 by a German pharmacologist ***(Pasternak, 2014).***

Opioids are a much broader class of xenobiotics that are capable of either producing opium-like effects or binding to opioid receptors. A semisynthetic opioid, like heroin or oxycodone, is created by chemical modification of an opiate. A synthetic opioid is not derived from an opiate with little structural similarity, such as methadone and meperidine ***(Li and Wang, 2020).***

Opioids also include the naturally occurring animal derived peptides which are endogenous ligands for the opioid receptors. The endogenous opioid system comprises three families of opioid peptides each is a five amino acid peptide cleaved from a larger precursor peptide: β-endorphin (derived from the precursor pro-opiomelanocortin); leucine (Leu)- and methionine (Met)-enkephalins (derived from proenkephalin);

and dynorphins, including dynorphins A and B and neoendorphins (all derived from prodynorphin) (***Khademi et al., 2016; Shenoy and Lui, 2020)*.**

Opioids include strong agonists either natural or synthetic (e.g., morphine, methadone, oxycodone, and heroin), weak agonists (e.g., codeine and tramadol), agonist–antagonists (e.g., buprenorphine) and antagonists (e.g., naltrexone and naloxone). Structurally, the antagonists: naloxone and naltrexone are similar to oxymorphone, differing only in the replacement of the N-methyl group with an N-allyl 1 (naloxone) or N-methyl -cyclopropyl group (naltrexone) ***(Xu et al., 2013*).**

Receptors

The effects of opioids are mediated through the endogenous opioid system that comprised four classes of opioid receptors: μ-opioid receptor (MOR), κ-opioid receptor, δ-opioid receptor and Nociceptin/Orphanin FQ receptor. All opioid-receptor subtypes are members of a superfamily of membrane-bound receptors that are coupled to G proteins. These G-protein-coupled metabotropic receptors mediate both the analgesic and rewarding properties of opioid compounds ***(Mague and Blendy, 2010).***

Despite the initial theory that each receptor subtype is linked to a specific transduction mechanism, individual

receptor subtypes may use one or more mechanisms, depending on several factors, including receptor localization (e.g., presynaptic vs postsynaptic) ***(Nelson and Olsen, 2019).***

μ-opioid receptor (MOR)

MOR is the primary receptor for endogenous opioid peptides. In addition to analgesic and euphoric effects of opioid drugs, MOR modulates numerous physiological systems including stress response, gastrointestinal motility, and immune function. By inhibiting GABA neurons, activation of MOR also results in activation of mesolimbic–mesocortical reward dopamine pathways ***(Kreek et al., 2005).***

Nociceptin/Orphanin FQ Receptor (N/OFQ) (ORL1, NOP, OP4):

The ORL1 receptor was identified in 1994 based on sequence homology during screening for opioid-receptor genes with DNA libraries. It has a similar distribution pattern in the brain and uses similar transduction mechanisms as the other opioid-receptor subtypes. Its insensitivity to antagonism by naloxone delayed its acceptance as an opioid receptor subtype ***(Modi et al., 2013).***

Tramadol has anti-nociceptive effects due to a double (opioid and non-opioid) mechanism of action. In fact, tramadol acts on m-opioid and k-opioid receptors with low affinity, exerting a weak agonist effect, and it affects monoamine

receptor systems by blocking norepinephrine (NE) and serotonin (5-HT) reuptake, responsible for the inhibition of pain transmission in the spinal cord ***(Modi et al., 2013).***

Tramadol is more advantageous than other typical opioid agents for its unique pharmacological profile, since it exhibits a lower incidence of side effects and abuse potential ***(Stoops et al., 2012).***

Pharmacokinetics and pharmacodynamics

Absorption

The injectable formulation has 100 % bioavailability and reaches peak plasma levels immediately following injection. In case of subcutaneous or intramuscular methadone injection, bioavailability is likely to approach 100 % ***(Bart and Walsh, 2013).***

Following oral administration, opioids are rapidly absorbed from the intestinal lumen with an absorption half-life of 15–60 minutes. This variability is likely due to interindividual differences in intestinal motility in addition to other causes listed in table (1). Moreover, patients already on opiates may have reduced gastrointestinal motility leading to slower absorption than opiate naïve patients ***(Bart and Walsh, 2013).***

Table (1): Physiological changes affecting opioid absorption ***(Franken et al., 2016)***

Physiological change	Potential pharmacokinetic change	Consequence	Example drugs
Decreased GI motility	Increase in T_{max}	Drug concentration is unaffected yet the effect may be delayed	Morphine and tramadol
Vomiting or administration via tube	Possible decrease in F and AUC depending on the moment of vomiting or declamping the tube	Possible decrease in drug concentration and effect	All oral drugs
Delayed gastric emptying	Increase in T_{max}	Drug concentration is unaffected yet the effect may be delayed	Morphine and tramadol
Alterations in gut wall function due to cachexia	Decrease in F and AUC	Decrease in drug concentration and effect	Morphine and tramadol
Decreased hepatic function or liver blood flow	Decrease in first-pass effect, resulting in increased AUC	Increase in drug concentration and effect	Morphine
Decreased tissue perfusion	Decrease in T_{max} and possibly F of subcutaneously or transdermal administered drugs	Decrease in drug concentration and the effect may be delayed	Fentanyl patches
Decreased subcutaneous fat	Increased T_{max} of subcutaneously or transdermal administered drugs	Drug concentration is unaffected yet the effect may be accelerated	Fentanyl patches

AUC: area under the concentration time curve, T max: time to reach maximum plasma concentration, F: Bioavailability

Metabolism

Morphine is a relatively hydrophilic drug and is only partially bound (34–37.5%) to plasma proteins, predominantly albumin. The metabolism of morphine takes place primarily in the liver. Morphine has a high extraction ratio and is metabolized mainly by Uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes into morphine-3-glucuronide (M3G) for 60%, and morphine-6-glucuorinide (M6G) for 10%. The M6G metabolite is pharmacologically

active and is 10–60 times as potent as morphine. Its ability to cross the blood–brain barrier is, however, far less (1/57th) than that of morphine ***(Franken et al., 2016).***

Morphine undergoes glucuronidation while most opiates are metabolized by CYP450 isoenzymes. Therefore, the effects of the weaker opioids (codeine and tramadol) are dependent upon the formation of more potent hydroxyl metabolites mainly mediated by CYP2D6. As for methadone, oxycodone, fentanyl, and buprenorphine, they are mainly metabolized to inactive metabolites by N-demethylation catalyzed by CYP3A4 ***(Hajj et al., 2013).***

Tramadol is extensively metabolized in the liver via cytochrome isoenzymes P450 2D6, and P450 2B6 and P450 3A4, to O-desmethyltramadol (M1) and N-desmethyltramadol (M2) respectively, being the main phase-1 metabolites. These are further metabolized to three secondary metabolites. All metabolites are finally conjugated with glucuronic acid and sulfate before excretion in urine ***(Lorenzini et al., 2012).***

The mean peak plasma concentration of tramadol occurs after 2 h and its bioavailability is approximately 70% as a result of the first-pass metabolism in the liver. About 20% of the drug is bound to plasma proteins ***(Eassa and El-Shazly, 2013)***

Excretion

The route of elimination of opioids almost totally involves the kidneys. The half-life of opioids is demonstrated in table (2).

Table (2): Half-life of opioids ***(Rasimas and Sinclair, 2017)***

Opioid	Half-life
Buprenorphine	Intravenous: 2.2–3 h Sublingual tablet:37 h Transdermal patch:26 h
Butorphanol	2–9 h
Codeine	3 h
Fentanyl	Intravenous: 2–4 h Transdermal patch: 20–27 h Transmucosal products: 3–14 h Nasal spray: 15–25 h
Hydrocodone	3.3–4.4 h
Hydromorphone	Immediate release: 2–3 h Extended release:11 h
Levorphanol	11–16 h
Meperidine	Adults: 2.5–4 h Liver disease: 7–11 h
Methadone	Adults: 8–59 h. May be prolonged with alkaline pH
Morphine	Immediate release forms: 2–4 h
Oxycodone	Oral: Immediate release: 7–9 h Extended release: 9–11 h
Tapentadol	Immediate release: 4 h Long-acting formulations: 5–6 h
Tramadol	Tramadol: 6–8 h

Clinical Manifestations

Among opioids' side effects, the respiratory depression is probably the most life-threatening, followed by ‘torsades de pointes’ associated with methadone. Nausea, vomiting, euphoria, sedation, and constipation are other extremely frequent side effects of treatment. Miosis is observed with almost all agonists ***(World Health Organization, 2017).***

Acute toxicity

An opioid overdose (OOD) can be easily identified by a combination of 3 symptoms called the OOD triad or the opioid syndrome: mental status depression, respiratory depression, and pinpoint pupils ***(Schiller and Mechanic, 2019).***

Common OOD symptoms are respiratory and mental depression, miosis, mydriasis (if hypoxic), nausea or uncontrolled vomiting, and atypical snoring. Less common symptoms include acute lung injury, QT prolongation, seizure, bowel obstruction, and noncardiogenic pulmonary edema ***(Parthvi et al., 2019).***

Decreased respiratory drive is one of the most dangerous side effects of OOD and is the reason that opioids are responsible for a high proportion of drug overdose deaths around the world. Respiratory depression indicated by a respiratory rate of less than 12 breaths per minute or apnea also

rules out other common toxicities that present with miosis and coma, such as antipsychotics drugs, anticonvulsant agents, alcohol, or other sedative hypnotic medications ***(World Health Organization, 2017).***

Negative pressure pulmonary edema can occur because of fluid extravasation secondary to decreased intrathoracic pressure from breathing against a closed glottis. Also, acute lung injury may arise from sympathetic vasoactive response after reversal of intoxication resulting in leakage from pulmonary vessels causing noncardiogenic pulmonary edema ***(Parthvi et al., 2019).***

Central Nervous System

Toxicity from opioids progresses from analgesia to anesthetic CNS depression, coma, and death. Respiratory depression is particularly pronounced with opioid overdose, and the tidal volume or respiratory rate can be diminished before decreases in blood pressure or pulse occur. Patients will have minimal respiratory drive and quickly develop manifestations of shock ***(Rasimas and Sinclair, 2017).***

Tramadol can cause seizures and serotonin syndrome, more likely in patients receiving the drug in overdose, or when co-administered with antidepressants. This is probably because of the inhibition of serotonin (5-HT) and NE reuptake. Moreover, the inhibition of gamma amino- butyric acid (GABA)