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Editorial

# Cardiac arrhythmia and opioids: Be watchful

Rajeev Gupta [a,*], Neelesh Gupta [b], Vineet Meghrajani [c], Abdallah M. Shehab [d]

[a] Mediclinic Al Jowhara Hospital, Al Ain, United Arab Emirates
[b] University of South Alabama Medical Center, Mobile, AL, USA
[c] Maimonides Medical Center, Brooklyn, New York, NY, USA
[d] College of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates

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Opioids are increasingly prescribed in the United States. The statistics show the sales of prescription opioids in the US nearly quadrupled from 1999 to 2014 [1]. However, in view of their addiction liability, they are commonly misused/abused. The abuse is rapidly rising, the National Survey on Drug Use and Health (2012) indicate that 12.5 million Americans have abused prescription opioids, a 2.5-fold increase from 4.9 million in 1992 (over 20 years) [2].

The supervised and time-limited use of opioids is safe and effective for conditions like moderate-severe pain including but not limited to fracture of major bones, post-operative pain, and uncontrollable pain associated with severe end-stage medical problems, particularly terminal cancers. However, many U.S. adults currently receive long-term opioid therapy for chronic non-cancer pain and are shown to have significantly greater all-cause mortality, including non-overdose related mortality [3]. As per Centers for Disease Control and Prevention (CDC) data, out of 70,237 deaths due to a drug overdose, 47,000 deaths were due to opioid-overdose (67.8% of all drug-related deaths) [4] and 30% had concomitant use of benzodiazepines with opioids [5]. Thus it is clear, the abuse and the chronic use of opioids are invitations to serious side-effects including sudden unexpected deaths (arrhythmic and non-arrhythmic). Not only deaths due to opioids could be linked with arrhythmia, but other factors like sleep-disordered breathing, adverse vasomotor/psychomotor and endocrine factors are also implicated particularly if opioids are used/abused with benzodiazepines (a deadly combination, if unsupervised) [3].

The strong association between cardiac arrhythmia and opioid addiction is well-documented in recent review literature [1]. The arrhythmogenicity of opioids differs. The opioids such as methadone (used for de-addiction of opioids like heroin and sometimes to relieve severe pain in the terminal illnesses) are high-risk even at low doses and may prolong QT-interval and cause torsades de pointes (TdP), with sudden cardiac deaths. Some opioids like tramadol and oxycodone are intermediate-risk drugs and may prolong QT-interval and may precipitate TdP in high doses. Opioids like morphine and buprenorphine are low-risk drugs and do not affect QT-interval and do not produce TdP at least in routine doses. Apart from life-threatening arrhythmia like ventricular tachycardia (VT), ventricular fibrillation (VF), and ventricular flutter, the consumers of opium are at higher risk of supraventricular arrhythmias, sinus bradycardia, sinoatrial blocks particularly in patients with latent or manifest sick sinus syndrome, and atrial fibrillation (AF) [1]. Though ADHERE analysis in 2008, conducted in patients with decompensated heart failure could not show the difference in the prevalence of AF among patients with regard to the use of morphine [6]. However, subsequent studies including a recent one, showed an increased prevalence of AF with opioids (hydrocodone, propoxyphene, and tramadol) [7]. The opium consumption was linked with postoperative atrial fibrillation following coronary artery bypass grafting and was surmised to be a new predictor of AF [8]. Likewise, Mirzaiepour et al. (Acta Med Iran. 2012) documented the greater prevalence of sinus tachycardia, sinus bradycardia, and AF following acute myocardial infarction in patients with opium addiction compared with non-opium addicts. The precise reason for the predisposition of AF is not known. The proposed mechanism maybe endogenous opioid-peptides open mitochondrial $K^{+}_{ATP}$ channels, making mitochondria resistant to oxidative stress during episodes of ischemia. Loss of this protective mechanism (with opioid abuse) against oxidative stress may render atrial-myocytes amenable to damage and thus lead to AF [9].

In this issue Rajkumar Doshi and coworkers [10] (with limitations of the retrospective data from the National Inpatient Sample of the USA, in which only hospitalization data is available, without any ECG, laboratory data, radiology data, and details about treatment during hospitalization and ingestion of any concomitant drug prior to hospitalization etc.) have shown AF complicates in 4.14% of opioid overdose-related-hospitalizations with a rising trend over last 10 years (2005 to 2015) along with increase in all-cause in-hospital mortality (8.8% with any

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* Corresponding author.
*E-mail address:* Rajeev.Gupta@mediclinic.ae (R. Gupta).

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arrhythmia, and around 2.5% without any arrhythmia). As expected, the all-cause in-hospital mortality was highest with VF/ventricular Flutter (60.6%), and VT (14.9%). Not unusual the mortality doubled in those with AF, along with an increase in hospital stay and accompanying cost of hospitalization [10]. Notwithstanding the limitations of the study, the message is clear: watch for arrhythmia, they predispose to deaths.

The treating intensivist/physician/cardiologist/psychiatrist must be mindful of high-risk features like type/dose/duration/route of administration of the opioid abused (methadone, tramadol, oxycodone, illicitly manufactured fentanyl or others), and the disease states (like non-cancerous conditions etc.), characteristics of the patients (compromised renal/hepatic/respiratory functions), symptoms suggestive of arrhythmia like palpitation, dizziness, syncope or resuscitated cardiac arrest, importantly concomitant ingestion of benzodiazepines (not uncommon in patients with shock and/or respiratory depression), and prolonged QT-interval on electrocardiogram (ECG), ventricular and supraventricular arrhythmia like VT, TdP, or AF, etc. The co-administration of opioids particularly methadone (lesser possibility with tramadol, and oxycodone), with other drugs having the potential to affect QT-interval like class Ia (quinidine, procainamide etc.) and class III (amiodarone, sotalol etc.) antiarrhythmic drugs, bepridil, and others like some antidepressants (imipramine, desipramine, nortriptyline, maprotiline, clomipramine etc.), some antibiotics (pentamidine, clarithromycin, halofantrine, sparfloxacin etc.), and some antipsychotics (haloperidol, thioridazine, droperidol, pimozide, mesoridazine etc.) should be avoided if possible.

The best treatment of opioid abuse/overdose is: prevention by careful patient selection, limiting the use, dose, and duration of opioids, particularly for conditions like chronic use in non-severe painful and non-cancerous states, and in non-terminal illnesses. The opioids for de-addiction like methadone must be closely supervised, with frequent ECG tracings for QT-interval, and avoiding concomitant use of alcohol, benzodiazepines, and all QT-interval affecting drugs, and other drugs like antidepressants, antibiotics, antipsychotics etc. as mentioned above (the list is not inclusive). The use of prescription drug monitoring program must be employed by all states/countries to avoid multiple prescriptions. The anesthesiologists must be vigilant about hypotension and early signs of respiratory depression, particularly with co-administered benzodiazepines during anesthesia.

## Conflict of interest

We declare no competing interests.

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