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## **Loperamide toxicity: a case report of turning bowels and twisting points**

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## CASE REPORT

# Loperamide cardio toxicity: a case report of turning bowels and twisting points

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<b>Introduction:</b>	Loperamide is a synthetic mu-receptor agonist used for treating diarrhea. Recently, it has been illicitly used for a euphoric high or to diminish symptoms of opiate withdrawal. In case reports, loperamide abuse has been associated with cardiac arrhythmias, most notably, ventricular tachycardia and torsades de pointes, presumably related to prolongation of the QTc.
<b>Clinical findings:</b>	A 32-year-old male with a history of opioid use disorder presented unresponsive, and was found to have polymorphic ventricular tachycardia, torsades de pointes, prolonged QTc and QRS, and transient left ventricular dysfunction.
<b>Diagnosis, interventions, and outcomes:</b>	When his mental status cleared, the patient reported taking up to 40 pills (80 mg) of loperamide daily with the intent of alleviating symptoms of opiate withdrawal. This misuse was believed to cause his QTc prolongation, leading to cardiac toxicity and subsequent dysrhythmia. The patient initially required a temporary pacing wire, which was removed on hospital day 3. He was discharged with a prescription for suboxone and duloxetine, and he was connected with specialists to address his substance use disorder.
<b>Conclusions:</b>	We describe a patient with cardiac toxicity associated with loperamide misuse. In the wake of the current opioid epidemic, the occurrence of loperamide toxicity may increase. It is important for physicians to understand and identify the life-threatening effects of loperamide toxicity to properly diagnose and manage the condition.
<b>Keywords:</b>	opiate use disorder, loperamide, torsades de pointes, cardiac toxicity

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## CASE PRESENTATION

A 32-year-old male with a history of opiate use disorder presented to an outside emergency department after being found unresponsive in his running car. After 1 hour, he developed non-sustained ventricular tachycardia (VT) followed by wide-complex bradycardia with first-degree block. This bradycardia converted to polymorphic VT requiring intravenous bicarbonate, single-synchronous cardioversion, and amiodarone. He then had a short, self-terminating episode of torsades de pointes (Figure 1) followed by bradycardia with a

QTc persistently over 600 msec and a QRS of 167 msec. He was transferred to the cardiac intensive care unit of this hospital for immediate placement of a temporary transvenous pacer with the purpose of overdrive pacing.

The results of his initial exam only noted arrhythmia, altered mental status, and agitation. The initial lab results showed a leukocytosis of 14,300/uL, troponin-T peak of 0.10 ng/mL (normal <0.01 ng/mL), and brain natriuretic peptide of 1303 pg/mL (normal <450 pg/dL). His urine toxicology results reflected that the emergency department administered midazolam. The echocardiogram showed a reduced ejection fraction (30-35%) with global wall motion abnormality.

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After the temporary wire was placed, the patient's mental status cleared. He reported finding internet forums suggesting opioid-like effects with high doses of loperamide, leading him to take up to 40 pills (80 mg) daily (recommended upper limit of therapeutic dosing: 16 mg/daily). Twenty-four hours after presentation, his loperamide level was 34 ng/mL (normal limit: <5 ng/mL) and his desmethyl loperamide level (a loperamide metabolite) was 250 ng/mL (therapeutic levels: <20 ng/mL).

By hospital day 2, his VT resolved, and his QTc and QRS normalized, so the temporary pacemaker was removed. On hospital day 3, a repeat transthoracic echocardiogram showed normal systolic function. He was discharged with suboxone, duloxetine, and outpatient follow-up.

## DISCUSSION

Loperamide is a synthetic opioid used to slow bowel motility in diarrheal illness and is readily available over the counter. It acts as a direct agonist at the circular and intestinal muscles via the mu-opioid receptor. At therapeutic doses, loperamide has low oral bioavailability and nominally penetrates the blood-brain barrier. Thus, it was believed to have little potential for abuse.<sup>1</sup> Recently, many reports described cases in which loperamide was misused recreationally or to alleviate symptoms of withdrawal.

Non-medical or non-prescribed use of loperamide is increasing as information on the internet regarding alternative uses continues to uptrend.<sup>2</sup> One study analyzed the occurrence of the search term "loperamide" with Google Trends.\* The analysis showed an increase in the use of the search term "loperamide" from 2009 to 2015, with an approximate 300% increase from 2011 to 2015 when combined with terms such as "high" or "withdrawal." The National Poison Database System reported a 91% increase in intentional loperamide exposures between 2010 and 2015.<sup>3</sup> To mitigate loperamide misuse, the US Food and Drug Administration changed loperamide packaging to blister packs to limit large-quantity purchases in January 2018.<sup>4</sup>

Loperamide misuse has been associated with cardiac dysrhythmias, such as ventricular fibrillation or

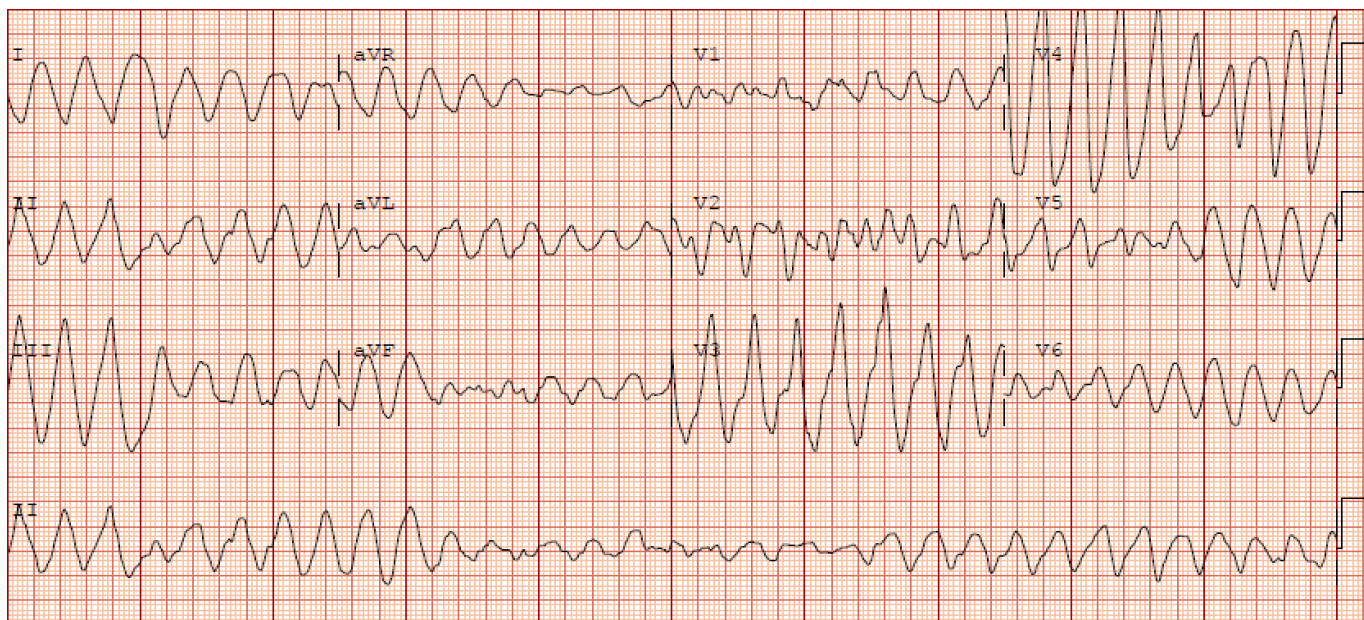
tachycardia, cardiac arrest, and death.<sup>1,5-11</sup> Transient left ventricular dysfunction is often observed with stress- or tachycardia-induced cardiomyopathy.<sup>9,10</sup> Notably, some cases reported that supratherapeutic doses of loperamide can result in onset and an increased duration of toxic effects that extend beyond the drug's reported half-life and duration of action.<sup>11</sup> The proposed mechanism is multifactorial via antagonism at cardiac L-type calcium channels, delayed rectifier potassium channels, and sodium channel blockade. These effects lead to delayed duration of action potentials, prolonged QRS, and severe prolonged QTc. In addition, loperamide inhibits the Nav1.5 sodium channel and the human ether-a-go-go (hERG) rectifier potassium channel in cloned human myocyte cells, affecting QRS and QT prolongation, respectively.<sup>12</sup> Interestingly, sodium channel blockade may be dose-dependent, as the phenomenon occurs only with high levels of loperamide.

Diagnosis hinges upon clinical history and the presence of arrhythmia at presentation. Confirmatory lab testing may take 1-2 weeks. Initial treatment should focus on establishing a perfusing rhythm, which may require cardioversion or temporary overdrive pacing with a pacing wire. Isoproterenol has also been suggested but has not been well studied. Naloxone has shown some efficacy for reversing respiratory depression, but it has ineffectively treated arrhythmias.<sup>6</sup> With aggressive supportive care, most patients improved after loperamide was discontinued.<sup>5,11</sup>

Loperamide's effect on QTc has been described only in case reports; however, the effects of other opiates on QTc prolongation have been studied in greater detail.<sup>13</sup> The predominant mechanism involves inhibition of the I<sub>Kr</sub> current.<sup>14</sup> Specifically, methadone prolongs QTc and is the leading cause of medication-associated torsades de pointes.<sup>15</sup> However, the effect of the methadone dose on QTc prolongation is mixed.<sup>16,17</sup> In contrast, buprenorphine has been associated with fewer cases of torsades de pointes and QTc prolongation.<sup>15</sup> Oxycodone has shown QTc prolongation that may be dose-dependent, but to a lesser degree than methadone.<sup>14</sup>

This case illustrates the potentially life-threatening toxicity associated with loperamide misuse. As

\* This feature reports a normalized line graph that reflects interest in a search topic as a proportion of all Google searches on all topics during the specified time and location.



**Figure 1.** Admission electrocardiogram illustrating torsades de pointes

opiate prescriptions are reduced in response to the current opioid epidemic, loperamide misuse and toxicity may increase. Physicians must be aware of these dangers, as many dysrhythmias associated with loperamide misuse can be unpredictable and may be fatal without appropriate treatment. Awareness of this condition will support the prompt identification of toxicity and treatment of electrocardiac abnormalities, reducing mortality and improving outcomes.

**Conflict of Interest:** None

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