



# Q-T prolongation secondary to methadone use for severe and resistant restless legs syndrome

Saif Mashaqi

Correspondence: [saif.mashaqi@sanfordhealth.org](mailto:saif.mashaqi@sanfordhealth.org)



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Department of sleep medicine (Sanford Health), University of North Dakota, Grand forks, ND, USA.

## Abstract

This case describes a severe restless legs syndrome that was resistant to many therapeutic modalities including first line treatment recommendations. A significant clinical improvement was noticed after the initiation of Methadone 5 mg; however, an association with Q-T interval prolongation prompted holding the medication and then reducing the dose to 2.5 mg. This side effect of Q-T prolongation has been reported in the literature. Our patient was taking other medications that can potentially cause the same side effect (e.g. Quetiapine). The patient's medical history is significant for nephrotic range proteinuria secondary to membranous glomerulonephritis. The patient does have an underlying moderate obstructive sleep apnea that was treated successfully with CPAP. We highlight through this case the importance of screening patients who get started on Methadone with EKG to get baseline Q-T intervals and monitor the dose accordingly.

**Keywords:** Restless legs syndrome, methadone, Q-T interval, EKG, polysomnography

## Introduction

Methadone is a long acting opioid agonist. It is being used mainly to prevent withdrawal symptoms in opioid abuse. Opioids (Including Methadone) have a good clinical effect in long term use for the treatment of restless legs syndrome and periodic limb movement during sleep that are resistant to first line treatment options [1]. However, side effects can develop with opioids and some of them are serious and life threatening. We report, in this case, a cardiac arrhythmia (Q-T interval prolongation) that was associated with the use of Methadone.

## Case presentation

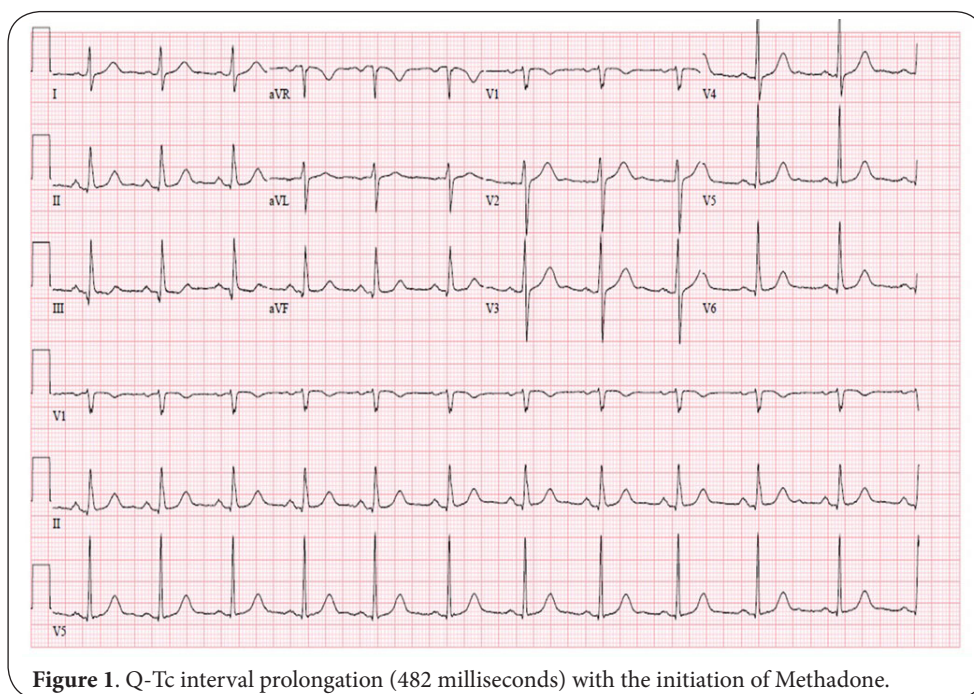
Our patient is a 41 years old white male who was evaluated at our sleep center for excessive daytime sleepiness and severe restless legs syndrome. He underwent polysomnography which showed a moderate degree of obstructive sleep apnea (AHI 17 events/hour). He was treated with CPAP 17 cmH<sub>2</sub>O which helped partially with hypersomnia. He continued to complain of severe restless legs symptoms. Multiple therapies were used, including Ropinirole 0.25 mg, the dose was gradually increased over four weeks up to 1 mg with no relief, Pramipexole 0.125 mg up to 0.5 mg over four weeks with no response, Gabapentin 300 mg up to 900 mg with no success and Pregabalin 150 mg which helped partially but caused significant drowsiness in

the morning and subsequently it was discontinued. The use of opioids (mainly Methadone) was discussed with the patient and a dose of 5 mg was started with significant improvement in RLS symptoms within a week. The patient reported better sleep quality and he denied daytime sleepiness. However, an EKG was obtained two weeks after starting Methadone that showed prolongation of Q-T interval (Q-Tc 482 milliseconds). Q-T interval before starting Methadone was 459 milliseconds. As a result, Methadone was held for two weeks and a repeat EKG showed a Q-T interval back to baseline at 453 milliseconds. Methadone was restarted at a lower dose of 2.5 mg and a repeat EKG showed Q-T interval "Q-Tc" of 460 milliseconds.

The patient does have a medical history significant for nephrotic range proteinuria secondary to membranous glomerulonephritis. Estimated Glomerular filtration rate (GFR is 27 ml/min) and creatinine clearance is 39ml/min and that did not require renal adjustment for Methadone dose. Liver function test was within normal limits.

## Discussion

Restless Legs Syndrome can sometimes be very severe and resistant to many treatment modalities. Dopaminergic agonists (Including Ropinirole and Pramipexole) are the first standard treatment [1]. Opioids can be used but their level of evidence



**Figure 1.** Q-Tc interval prolongation (482 milliseconds) with the initiation of Methadone.

is low [1]. They have a good clinical outcome especially in the long term in severe cases. One of the potential dangerous side effects is cardiac arrhythmia (mainly Q-T prolongation). This is mainly noticed with Methadone [2]. The exact pathophysiology is not clear. Methadone metabolites [3], interaction with other medications that cause Q-T prolongation (e.g., antibiotics and atypical antipsychotics) [4,5], hepatic dysfunction and electrolytes abnormalities [6] are potential mechanisms. Although our patient's medications include Quetiapine which is an atypical antipsychotic that is known to cause Q-T prolongation, he was on this medication for many years and his baseline Q-T was 459 milliseconds. The sudden increase to 482 milliseconds was noticed two weeks after the initiation of Methadone and resolved with holding the medication (Figure 1). Liver function test and basic metabolic panel was within normal limits.

This case highlights the importance of screening patients with EKG to get a baseline Q-T interval before the initiation of Methadone to treat resistant RLS. To our knowledge, this will be the first case of Q-T prolongation secondary to Methadone use is severe and resistant RLS reported in sleep medicine literature.

#### List of abbreviations

RLS: Restless Legs Syndrome  
EKG: Electrocardiogram  
CPAP: Continuous Positive Airway Pressure  
AHI: Apnea Hypopnea Index  
EGFR: Estimated Glomerular Filtration Rate  
ALT: Alanine aminotransferase  
AST: Aspartate aminotransferase  
BUN: Blood Urea Nitrogen

#### Competing interests

The author declares that he has no competing interests.

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