Assessing cardiac safety among clients receiving methadone as part of opioid agonist maintenance therapy (OAMT) in Durban, South Africa

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ABSTRACT

Background: Methadone is a recommended medication for opioid agonist maintenance therapy (OAMT). However, methadone can have cardiac side effects. There is limited South African cardiac safety data on methadone.

Objective: To describe baseline and 12-month electrocardiographic (ECG) features and cardiac symptomology in people receiving OAMT in Durban, South Africa.

Methods: Twelve-lead ECGs were conducted at baseline and 12 months. Clinical interviews were used to assess cardiac symptomatology. Baseline ECG parameters (PR interval, QRS interval, QT and QTc duration, heart rate) were analyzed using descriptive statistics. Baseline and 12-month ECG characteristics were compared using paired T-tests in retained participants. The association between QTc and methadone dose was assessed using Spearman's Rho at 12 months.

Results: Fifty-three clients (51 men, 2 women [median age 29.0]) were initiated on OAMT. Normal baseline ECG variants included 4 (7.5%) with sinus bradycardia and 3 (5.7%) with ST segment elevation. Mean baseline ECG intervals were PR interval: 156 ± 23 ms, QRS duration: 87 ± 9 ms, QT interval: 404 ± 22 ms and QTc interval: 406.9 ± 21.9 ms. At 12 months, 39 participants returned for reassessment (mean methadone dose: 37 ± 8 mg in women; 27 ± 10 mg in men). QTc intervals among male participants increased (406.4 ± 22 to 417 ± 24; $p = 0.026$ [−19.6; −1.4]). No significant correlation ($r = 0.22$; $p = 0.185$) between methadone dose and QTc interval at 12 months, nor reports of adverse cardiac symptomatology, were detected.

Conclusion: Methadone at the doses provided, caused mild and clinically insignificant QTc interval prolongation in men at 12 months. We provide additional cardiac safety data for the use of methadone for OAMT among people with opioid use disorder.

KEYWORDS

Methadone; heroin; electrocardiography; opioid agonist maintenance therapy; medications for opioid use disorder (MOUD)

Introduction

Globally in 2019, 62 million people used opioids (including opiates, pharmaceutical, and synthetic opioids) for non-medical use.[1] Opioids are responsible for four out of five drug-related deaths internationally, and contribute to significant morbidity, with 70% of the 18 million "healthy" years of life lost due to disability and premature death in 2019.[1]

The resolution of opioid use disorder[2] is challenging. The World Health Organization (WHO) recommends opioid agonist maintenance therapy (OAMT) for the treatment of opioid use disorder[2,3] and lists methadone as an essential medicine for this indication.[4] Methadone reduces symptoms of opioid withdrawal by acting on opioid receptors in the brain and does not produce the euphoric effects of other opioids.[5] The WHO recommends that the average daily methadone dose should be between 60 and 120 mg per day. Dosing within this therapeutic range results in better client retention in treatment than doses <40

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the treatment of opioid use disorder and are collectively termed medications for opioid use disorder (MOUD). Despite recommendations for use, access to OAMT remains limited.[6,7]

Opioids, particularly at high doses, may cause sympathomimetic effects.[8] The prolongation of the cardiac action potential, manifests on the electrocardiograph (ECG) as lengthening of the QT interval, is a common cardiac side effect of opioids.[9] Prolongation of the QT interval is a marker of risk for the development of polymorphic ventricular proarrhythmias, particularly t*orsades de pointes*,[5] which can lead to death.[10]

Prolongation of the QT interval has been reported as an adverse effect of methadone in several studies,[11–13] with most of these studies done among clients receiving doses of methadone within the therapeutic range of 60–120 mg/day. There are discrepant data on the potential cardiac risks associated with low dose oral methadone (<30 mg/day) in the context of palliative care.[14,15] The clinical significance of QT interval prolongation as well as the need for ECG monitoring at low dosing of methadone is not well documented.[16–18]

Evidence-based recommendations developed by a panel of experts convened by the Center for Substance Abuse Treatment of the United States Substance Abuse and Mental Health Services Administration recommended baseline, 30 day and annual ECG assessments as part of OAMT to measure the QTc interval. The panel recommended additional ECG monitoring for clients receiving methadone doses exceeding 100 mg/day or if clients have unexplained syncope or seizures.[19] Routine ECG monitoring is not part of WHO OAMT guidelines.[4]

South African context

There are little data on the prevalence of heroin use in South Africa.[20] The United Nations Office on Drugs and Crime estimates that 0.5% of the population between the ages of 15–64 used opioids in 2017.[21] Heroin is the most widely used opioid in the country and is usually smoked.[22,23] There has been a significant increase (from 16% in 2012 to 20% in 2017) in opioid-related admissions to drug treatment centers across South Africa.[24] Despite the increase in opioid use in South Africa, there is limited access to OAMT, since OAMT is not available in the public sector, and access in the private sector is limited to the few who can afford it.[20] There are currently no national Department of Health guidelines for OAMT. The South African Addiction Medicine Society's guidelines for the management of opioid use disorder[25] recommend ECG assessment and monitoring in line with the United States Centre for Substance Abuse Treatment panel's recommendations. The authors did not find published data on the arrhythmogenic effects of methadone as part of OAMT in the South African context.

This study therefore describes baseline and 12-month electrocardiographic features and demographic and drug using practices of people with opioid use disorder[2] who participated in an OAMT demonstration project in Durban, South Africa.

Methodology

Study setting

This analysis is part of a larger study that aimed to document quality-of-life changes amongst 53 people with opioid (heroin) dependence receiving methadone as part of OAMT over 18 months in the eThekwini Municipality, Durban, South Africa. The eThekwini municipality is situated in KwaZulu-Natal (KZN) and is one of South Africa's nine provinces. The population is diverse, with a total of 3,442,358 individuals, and a sex ratio of 96 males per 100 females.[26] The most recent statistics indicate that the majority of inhabitants come from the African community (74%), with 17% of Indian descent, 7% from the White community, 2% from community members of mixed descent and 0.4% of other nationals. The eThekwini area is industrialized with a number of social development challenges (e.g., high levels of unemployment, poverty, crime and limited access to formal housing).[26]

Most participants in this study were young men with most having used heroin for around ten years. Most (80%) of the participants smoked heroin, and the remainder injected it.[22]

Eligibility criteria for the larger study included: 18 years or older; used heroin for at least 12 months; high risk opioid use (WHO Alcohol Smoking and Substance Involvement Screening Test opioid score >27),[27] and had a support person. Exclusion criteria included: pending criminal record; lack of stable accommodation; acute alcohol or benzodiazepine use disorder; psychotic disorder; history of severe injury, or serious cardiac, respiratory or liver condition.[22]

Clinical procedures and methadone dosing

OAMT procedures followed local guidelines.[25] Baseline screening involved history taking, urine drug screen, physical examination (including an assessment of the cardiovascular system). Participants were initiated on 15 mg methadone daily by a trained general practitioner. Doses were slowly up titrated, based on self-reported symptoms toward an individualized maintenance dose. No ceiling dose was instituted. Doctor visits took place monthly. Clinical symptomatology was assessed during follow-up visits to ascertain any episodes of presyncope, syncope, dizziness or sudden cardiac death. Examinations and investigations were done based on clinical need. Study participants were down titrated to zero, or to a low dose of methadone between 15 and 18 months after initiation.

ECG assessments

Standard resting 12-lead ECGs were recorded using a WelchAllyn CP50 405881 (WelchAllyn Inc) portable electrocardiographic recorder. Parameters analyzed were the PR interval, QRS interval, QT and QTc duration and heart rate. Abnormalities in P wave morphology, PR and ST-interval deviations were also documented. The QT interval was defined as the interval between the Q-wave and the end of the T-wave, and was measured in Lead II, together with the RR interval. Bazett's formula ($QTc = QT/\surd R–R$)[28] was used to calculate the QTc. QTc intervals were considered prolonged if they were >450 ms for men and >470 ms for women.[29] Because the QT intervals differ according to gender, males and females were analyzed separately. ECGs were conducted at baseline and at 12 months.

Data capture and analysis

Each ECG recording was inputted with the participant's study number, date of birth and date of recording. The ECG was analyzed independently by two clinicians, and the waveforms of interest were measured and captured onto Excel software which allowed verification, categorizing and sorting of the data.

Statistical analysis was performed using SPSS version 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Demographic and clinical data were extracted from the participant files and are presented descriptively as median and inter-quartile ranges (IQR) and mean ± standard deviation (SD). Descriptive parameters included age, sex, HIV status, urine drug screening (at baseline), methadone dose (at 12 months), blood pressure and ECG parameters.

Each particpants' ECG data at 12 months was compared with their baseline value and the differences tabulated. The paired *t*-test was used to determine changes in QTc intervals across time for the same person.[30] A scatterplot, using the best-fitting line to demonstrate a dose-response effect was constructed to ascertain the distribution of QTc at 12 month follow-up, and Spearman's Rho[31] was used to ascertain the association between QTc and the corresponding methadone doses for all participants seen at 12 months. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical clearance was received from the Durban University of Technology (REC 29/15) and from the KwaZulu-Natal Department of Health (KZ_2016RP14_267). Participants provided informed consent. No remuneration was provided.

Results

Baseline characteristics

The baseline demographic, clinical, and electrocardiographic findings are shown in Table 1. Data from 53 clients were analyzed with 51 men and two women (median age IQR 29.0; 26–33 years) at baseline (Table 1). All participants tested

positive for opioids, while 32.1% of participants tested positive for multiple substances. There were ten participants who reported injecting of heroin, while the others smoked heroin in various combinations with tobacco and or cannabis.

Normal variants on ECGs recorded at baseline were as follows: 4 (7.5%) participants had sinus bradycardia and 3 (5.7%) had ST segment elevation. The mean electrocardiographic (ECG) intervals at baseline were PR interval: 156 ± 23 ms, QRS duration: 87 ± 9 ms and QT interval: 404 ± 22 ms (Table 1). The mean QTc interval at baseline was 406.9 ± 21.9 msec, and the distribution is shown in Figure 1. Two male participants (3.8%) had baseline QTc prolongation (QTc = 467 msec & 460 msec) before methadone was started.

Table 1. Baseline demographics, drug use and ECG characteristics of the sample ($n = 53$).

Characteristic	
Age (years) median IQR	29.0 (26–33)
	n (%)
Males	51 (96.2%)
HIV positive	7 (13.2%)
Recent injecting (last 12 months)	10 (18.9%)
Urine drug screening	
Number with urine positive for cocaine	8 (15.1%)
Number with urine positive for benzodiazepines	1 (1.9%)
Number with urine positive for opioids	53 (100%)
Number with urine positive for cannabis	17 (32.1%)
Number with urine positive for amphetamine	1 (1.9%)
Number with urine positive for methamphetamine	6 (11.3%)
Number with urine positive for multiple substances	17 (32.1%)
Cardiovascular findings	
Systolic blood pressure (mmHg)	116 ± 12
Diastolic blood pressure (mmHg)	76 ± 10
HR (beats per minute)	62 ± 9/min
ECG findings	
PR interval (ms)	156 ± 23
QRS duration (ms)	87 ± 9
QT interval (ms)	404 ± 22
QTc (ms)	406.9 ± 21.9
<430 ms	46 (86.8%)
≥430 < 450 ms	5 (9.4%)
≥450 < 470 ms	2 (3.8%)
Males with QTc ≥450 ms: n (%)	2 (4.0%)
Females with QTc ≥470 ms: n (%)	0 (0.0%)
Baseline ECG abnormalities	
Bradycardia (HR <50 bpm)	4 (7.5%)
ST segment elevation	3 (5.7%)

Twelve-month assessment

At 12 months, 39 participants returned for reassessment (37 [73%] men; two [100%] women).

The remaining 14 clients did not complete a 12-month study visit. Two clients died while on the programme (one linked to pulmonary tuberculosis and HIV infection and the other completed suicide). One client completed the program, five clients voluntarily exited (1 opted for abstinence based 'rehabilitation'; 2 reported to no longer require treatment; 2 found work outside of Durban). Six clients were lost to follow-up and could not be contacted.

The mean methadone dose at the 12-month follow-up was 37 ± 8 mg in women and 27 ± 10 mg in men ($p = 0.12$). There were no reports of presyncope, syncope, dizziness or sudden cardiac

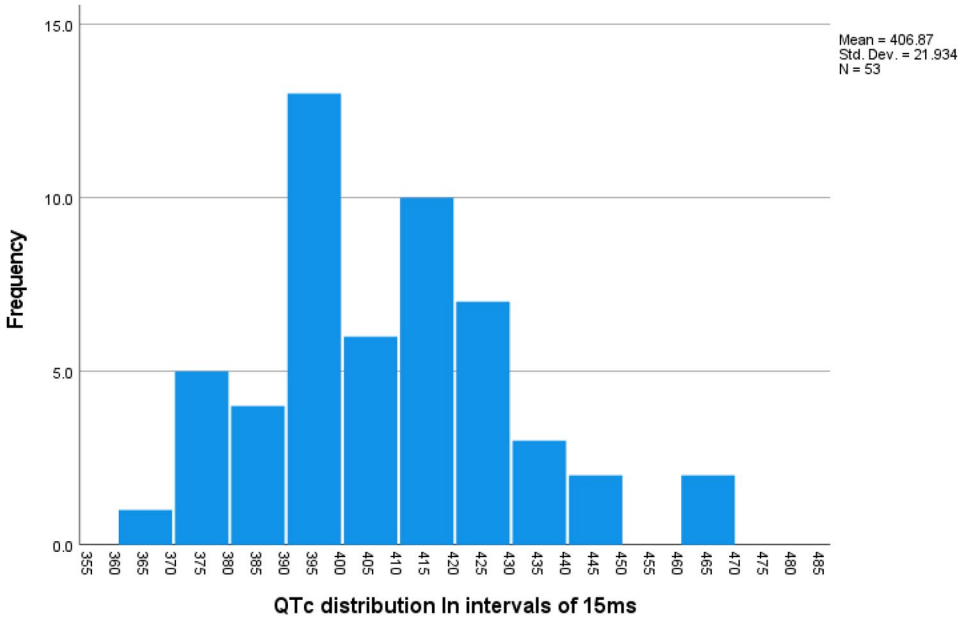

Figure 1. Distribution of QTc (ms) at baseline ($n = 53$).

death, nor were any cardiac arrhythmias observed during this study.

The ECG parameters of the 37 men who completed a 12-month study visit are shown in Table 2. At one year there was an increase in QTc intervals in men (406.4 ± 22 to 417 ± 24; $p = 0.026$ [−19.6; −1.4]), although values remained within the normal range (QTc <450 ms in men). The prolonged QTc intervals observed in the two men (4%) at baseline (Table 2), reverted to normal at 12 months. Another two male participants developed mildly prolonged QTc intervals (452; 460 ms respectively) at 12 months.

Our data points toward a correlation between the methadone dose and the QTc interval lengthening at 12 months (Figure 2); however, this was not statistically significant ($r = 0.22$; $p = 0.185$).

Only one serious adverse event related to methadone was reported during the reporting period. This related to a participant who was briefly admitted to hospital for taking his dose of methadone after a night of heavy alcohol consumption. He was referred to the local public hospital and was released after receiving symptomatic treatment.

Discussion

This study provides data on the safety of low-dose methadone used for OAMT in a South Africa setting. After 12 months of methadone treatment, there was a statistically significant increase in QTc intervals in men that remained within the normal range. Two clients developed asymptomatic mild QTc prolongation at 12 months. One of

Table 2. Comparison between baseline and 12-month follow-up among men retained ($n = 37$).

	Baseline	12 months	p-value (95% CI)
Methadone dose (mg daily)	15 ± 0	27 ± 10	$p < 0.0001$(−15.5; −9.0)
Parameter			
Baseline heart rate	62.0 ± 9.7	68 ± 13	0.011(−10.3; −1.4)
PR interval	158.2 ± 21.7	156 ± 20	0.36(−4.8; 13.3)
QRS duration	86.1 ± 7.7	88 ± 10	0.065(−5.0; −1.9)
QT interval	402.4 ± 28.9	398 ± 36	0.344(−5.1; 14.4)
QTc	406.4 ± 22.8	417 ± 24	0.026(−19.6; −1.35)
<430 ms	31 (83.8%)	25 (67.6%)	$p < 0.0001$
≥430 < 450 ms	5 (13.5%)	10 (27.0%)	
≥450 < 470 ms	1 (2.7%)	2 (5.4%)	
≥470 < 500 ms	0	0	
≥500 ms	0	0	

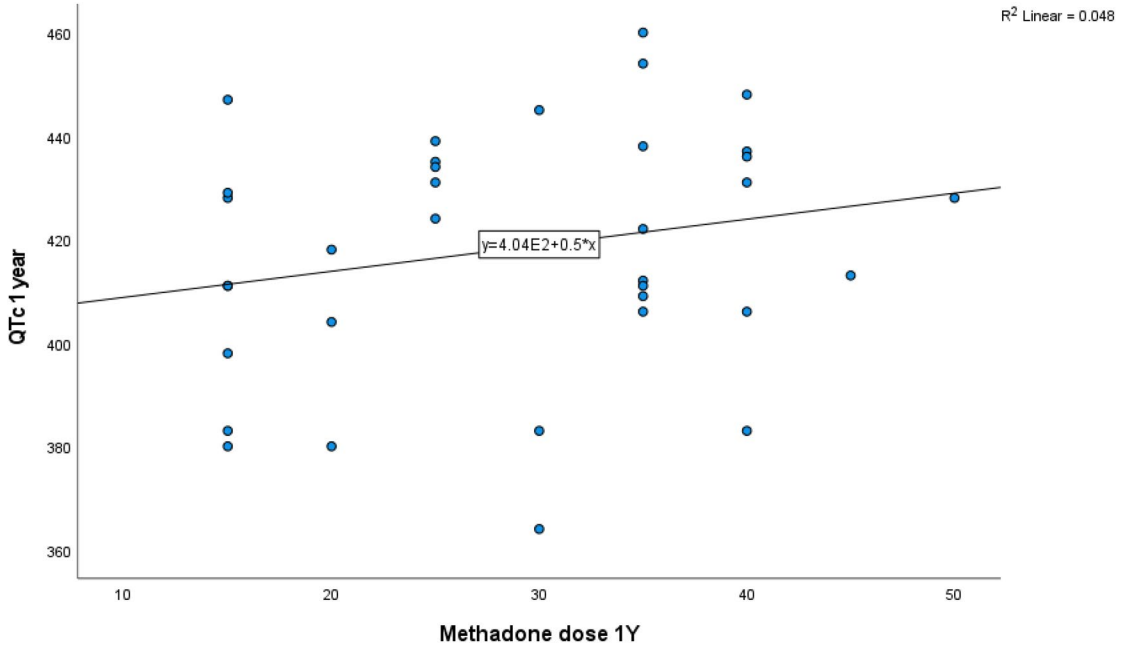

Figure 2. QTc (ms) distribution correlation with methadone dose (mg) at one-year ($n = 39$).

the people with prolonged QTc at baseline was not retained at 12 months. No arrhythmias or other forms of clinically important cardiotoxicity were identified.

Since methadone was first approved for medical use in 1947 by the United States Food and Drug Administration (FDA),[32] there has been concern regarding the potential for serious ventricular arrhythmias in the usage of methadone for the treatment of opioid use disorder.[33] The mechanism is thought to be related to alterations in the transmembrane potassium, sodium and calcium currents leading to lengthening of the duration of cardiac repolarisation, which has been described in congenital long QT syndrome.[34,35]

Methadone has been shown to cause QT prolongation in a dose-dependent manner by specifically inhibiting the cardiac ion channel KCNH2.[36] It is thought that bradycardia may serve as a trigger by permitting pause-dependent early depolarizations, and subsequent initiation of ventricular proarrhythmias.[12] The bradycardia associated with methadone use is thought to be mediated via its anticholinesterase properties and through its action as a calcium channel antagonist. Methadone has also been found to increase QT interval variability, which is a marker of heterogenous cardiac repolarization.[37] The development of cardiovascular complications is exacerbated in individuals with underlying disease, as in those with reduced coronary perfusion from epicardial coronary artery disease, severe valvular heart disease, and significant left ventricular systolic dysfunction, as a consequence of increased catecholaminergic tone and abrupt increases in myocardial oxygen consumption.[12]

In a meta-analysis, Kao et al[38] showed an association between methadone and ventricular arrhythmias, including those receiving methadone as part of OAMT and for other causes. Another study reported that higher methadone doses for OAMT was the only clinical risk factor which significantly predicted QTc prolongation. However, it did not emerge as an independent risk factor alone or in combination with other risk factors for inducing *torsades de pointes*.[39] Epidemiological studies show that the correlation between methadone dose and *torsades de pointes* mortality is not significant.[40,41]

The safety of low-dose methadone as part of OAMT has been investigated in a few studies.[41–44] In their review, Behzadi et al emphasized that methadone had a higher potential to induce QTc prolongation and dangerous arrhythmias in doses of 100 mg compared to other opioids,[42] but that the risk may also be present with low doses of methadone.

Our data points toward a correlation between methadone dose and QTc interval lengthening; however, this was not statistically significant ($r = 0.22$; $p = 0.185$). The mean doses in our sample at one-year follow-up was 27 ± 10 mg in men, which was much lower than the 40 mg/day reported to be the lowest dose at which *torsades de pointes* has been triggered.[43] The highest dose recorded in our cohort was 50 mg in one client.

Similar to Pani et al.,[39] we found that methadone maintenance treatment was associated with only a slight increase in the QTc interval, was not associated with cardiotoxicity and did not require termination of the therapy. In another study of 291 participants, Chowdry et al.[41] reported a weak and insignificant relationship between methadone dose and QTc. Although doses exceeding 200 mg per day have been found to be associated with QTc prolongation and t*orsades de pointes*, a wide range of dosages (65–100 mg/day) have been found to be arrhythmogenic.[5]

In our study, there was no ceiling on the dosage of methadone provided to participants; comfortability was self-determined and prescribed by a trained general practitioner, albeit with limited prior experience in OAMT. The doctor and the nursing team conducted regular observations of participants, daily for at least the first three months. Clients who were retained at 12 months received a median of 27 mg methadone daily. Methadone was also not associated with bradycardia as a trigger to arrhythmia susceptibility in this cohort. The absence of pathological QTc prolongation beyond 450 ms in our study is likely attributed to the low prevalence of medical comorbidities and lower methadone dosing used.[11,42,44,45] In addition, a review by the Cochrane group found no evidence to support the use of routine ECG monitoring for preventing arrhythmias in subjects maintained on methadone for opioid use disorder.[39]

Limitations

Firstly, the total sample size for this study was small. Limited resources affected the number of participants. Furthermore, only two women were recruited for this study, despite concerted efforts to recruit more women. The low participation of women mirrors the national and international trend and may be attributed to the stigma and social exclusion experienced by women who use drugs.[46] Consequently, the results should be inferred in light of the sample size, specifically in respect to women. Secondly, 14 (26%) of the enrolled participants were not retained at the one-year mark. At least five subjects were known to have returned to heroin use. The reasons for return to heroin use were not assessed; however, sub-optimal methadone dosing may have been a factor.[4] The QTc intervals of the subject who died while on TB treatment is not known. This is important since anti-tuberculous therapy is known to be associated with QT prolongation.[47] A control group, monitored at baseline and at 12 months would have strengthened the study design. This study did not include a control group. Therefore, it is not possible to infer changes in ECG over time in relation to people with opioid use disorder who were not on methadone. Furthermore, the absence of larger doses in our dose range may explain the lack of a significant correlation between methadone dose and the QTc intervals. As neither electrolyte analyses nor serial Holter electrocardiographic analysis were performed, the possibility that high grade ventricular arrhythmias may have occurred undetected cannot be excluded.[48] Finally, it must be noted that any variability in cardiac function and ECG which might have occurred between baseline and twelve-month ECGs may have been missed.

Conclusion

This study shows that methadone produced mild prolongation of the QTc interval in men after a year of treatment which was not associated with overt or symptomatic serious ventricular arrhythmias. Also, methadone was not associated with bradycardia as a trigger to arrhythmia susceptibility. Our findings confirm those from other settings around the cardiac safety of low-dose methadone for opioid use disorders.

In the absence of guidelines on the lowest dose of methadone at which an ECG should be performed,[49] future studies should revolve around modeling of the risks and benefits, as well as the determination of optimal cut-points for routine ECG monitoring. Since the adverse effects of methadone appear to be dose-dependent, this study supports routine ECG monitoring to reduce the risk of and manage *torsades de pointes* in participants who have risk factors for dysrhythmia, or those taking higher doses (>100 mg),[19] in an attempt to balance minimizing the harms of treatment and failing to treat for fear of causing harm.[50]

This study provides evidence for the use of methadone in the treatment of opioid use disorders, particularly in the South African context where there is extremely limited state provision of such treatment either in public hospitals or in primary health care facilities.

Sources of support

- Methadone was donated by Equity Pharmaceuticals for the study.

Conflict of interest

None to declare.

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References

1. UNODC. World drug report. [Internet]. Vienna: UNODC; 2021. Available from: https://wwwunilibraryorg/content/books/9789210606233c003.

2. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, Compton WM, Crowley T, Ling W, Petry NM, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry. 2013;170(8):834–51. doi:10.1176/appi.ajp.2013.12060782.
3. WHO U. International standards for the treatment of drug use disorders. Vienna & Geneva: UNODC & WHO; 2020.
4. World Health Organisation. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneve, Switzerland: WHO Press - World Health Organization; 2009.
5. Chhabra S, Bull J. Methadone. Am J Hosp Palliat Care. 2008;25(2):146–50. doi:10.1177/1049909107312597.
6. NIDA. Overview. National Institute on Drug Abuse website. https://nida.nih.gov/publications/research-reports/medications-to-treatopioid-addiction/overview. January 21, 2022. Accessed April 14, 2022.
7. Harm Reduction International. The Global State of Harm Reduction 2020. London: Harm Reduction International; 2020.
8. Frishman WH, Del Vecchio A, Sanal S, Ismail A. Cardiovascular manifestations of substance abuse: part 2: alcohol, amphetamines, heroin, cannabis, and caffeine. Heart Dis. 2003;5(4):253–71. doi:10.1097/01.hdx.0000080713.09303.a6.
9. Delk C, Holstege CP, Brady WJ. Electrocardiographic abnormalities associated with poisoning. Am J Emerg Med. 2007;25(6):672–87. doi:10.1016/j.ajem.2006.11.038.
10. Mattick RB, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2003;2:CD002209.
11. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy. 2003;23(6):802–5. doi:10.1592/phco.23.6.802.32186.
12. Krantz MJ, Palmer RB, Haigney MCP. Cardiovascular complications of opioid use: JACC state-of-the-art review. J Am Coll Cardiol. 2021;77(2):205–12. doi:10.1016/j.jacc.2020.11.002.
13. Fan C-Y, Tan HK-L, Chien I-C, Chou S-Y. Prevalence of psychiatric disorders among heroin users who received methadone maintenance therapy in Taiwan. Am J Addict. 2014;23(3):249–56. doi:10.1111/j.1521-0391.2014.12090.x.
14. Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. J Palliat Med. 2013;16(6):616–22. doi:10.1089/jpm.2012.0612.
15. Chalker C, O'Neill H, Cranfield F. Efficacy of low-dose and/or adjuvant methadone in palliative medicine. BMJ Support Palliat Care. 2019; bmjspcare-2018-001695. doi:10.1136/bmjspcare-2018-001695.
16. Titus-Lay EN, Jaynes HA, Tomaselli Muensterman E, Ott CA, Walroth TA, Williams G, Moe PR, Wilbrandt M, Tisdale JE. Accuracy of a single-lead mobile smartphone electrocardiogram for QT interval measurement in patients undergoing maintenance methadone therapy. Pharmacotherapy. 2021;41(6):494–500. doi:10.1002/phar.2521.
17. Edmonds KP, Saunders IM, Willeford A, Ajayi TA, Atayee RS. Emerging challenges to the safe and effective use of methadone for cancer-related pain in paediatric and adult patient populations. Drugs. 2020;80(2):115–30. doi:10.1007/s40265-019-01234-6.
18. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550. doi:10.1136/bmj.j1550.
19. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009;150(6):387–95. doi:10.7326/0003-4819-150-6-200903170-00103.
20. Scheibe A, Marks M, Shelly S, Gerardy T, Domingo AK, Hugo J. Developing an advocacy agenda for increasing access to opioid substitution therapy as part of comprehensive services for people who use drugs in South Africa. S Afr Med J. 2018;108(10):800–2. doi:10.7196/SAMJ.2018.v108i10.13397.
21. UNODC O. United nations office on drugs and crime. World drug report. 2017.
22. Scheibe A, Shelly S, Gerardy T, von Homeyer Z, Schneider A, Padayachee K, Naidoo SB, Mtshweni K, Matau A, Hausler H, et al. Six-month retention and changes in quality of life and substance use from a low-threshold methadone maintenance therapy programme in Durban, South Africa. Addict Sci Clin Pract. 2020;15(1):13. doi:10.1186/s13722-020-00186-7.
23. Mthembi PM, Mwenesongole EM, Cole MD . Chemical profiling of the street cocktail drug 'nyaope' in South Africa using GC-MS I: stability studies of components of 'nyaope' in organic solvents. Forensic Sci Int. 2018;292:115–24. doi:10.1016/j.forsciint.2018.08.001.
24. Harker N, Lucas WC, Laubscher R, Dada S, Myers B, Parry CD. Is South Africa being spared the global opioid crisis? A review of trends in drug treatment demand for heroin, nyaope and codeine-related medicines in South Africa (2012–2017). Int J Drug Policy. 2020;83:102839. doi:10.1016/j.drugpo.2020.102839.
25. Weich LP, van Zyl N, Rataemane P, Naidoo L, Nowbath H. South African guidelines for the management of opioid dependence. S Afr Addict Med Soc. 2013;100:1–18.
26. COGTA. Integrated Development Plan (IDP). By 2030, eThekwini will be Africa's most caring and liveable City. 2020/21. In: Affairs CGaT, editor. 2021. available on: https://www.cogta.gov.za/cgta_2016/wp-content/uploads/2021/02/Final-eThekwini-Plain-English-2020_21-IDP.pdf. Accessed 13 Jan 2022.
27. World Health Organisation. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST); 2010.

https://wwwwhoint/publications/i/item/978924159938-2. Accessed 22 Jan 2022.
28. Viskin S. The QT interval: too long, too short or just right. Heart Rhythm. 2009;6(5):711–5. doi:10.1016/j.hrthm.2009.02.044.
29. Ajayi T. Drug Misuse and Dependence: UK Guidelines on Clinical Management-Department of Health (England) and the devolved administrations, Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive, 2007, 128. Psychiatr Bull. 2008;32(9):360. pp. doi:10.1192/pb.bp.108.021287.
30. Rietveld T, van Hout R. The paired t test and beyond: Recommendations for testing the central tendencies of two paired samples in research on speech, language and hearing pathology. J Commun Disord. 2017;69:44–57. doi:10.1016/j.jcomdis.2017.07.002.
31. Fredricks GA, Nelsen RB. On the relationship between Spearman's rho and Kendall's tau for pairs of continuous random variables. J Stat Plan Inference. 2007;137(7):2143–50. doi:10.1016/j.jspi.2006.06.045.
32. Dole VN. A medical treatment for diacetylmorphine (heroin) addiction: A clinical trial with methadone hydrochloride. J Am Med Assoc. 1965;193:80–4.
33. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Heart Rhythm Society, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15(4):321–37. doi:10.1016/j.jpain.2014.01.494.
34. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf. 2005;14(11):747–53. doi:10.1002/pds.1112.
35. Fonseca F, Marti-Almor J, Pastor A, Cladellas M, Farré M, de la Torre R, Torrens M. Prevalence of long QTc interval in methadone maintenance patients. Drug Alcohol Depend. 2009;99(1-3):327–32. doi:10.1016/j.drugalcdep.2008.06.018.
36. Raffa RB, Burmeister JJ, Yuvasheva E, Pergolizzi JV. QTc interval prolongation by d-propoxyphene: what about other analgesics? Expert Opin Pharmacother. 2012;13(10):1397–409. doi:10.1517/14656566.2012.682150.
37. Mujtaba SR, Taub CC. Methadone, QTc prolongation and torsades de pointes: Current concepts, management and a hidden twist in the tale? J Cardiovasc Dis Res. 2013;4:229–35.
38. Kao D, Bucher Bartelson B, Khatri V, Dart R, Mehler PS, Katz D, Krantz MJ. Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: an analysis of registry data. Ann Intern Med. 2013;158(10):735–40. doi:10.7326/0003-4819-158-10-201305210-00008.
39. Pani PPT, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. Cochrane Database Syst Rev. 2013;6:CD008939.
40. Vieweg WVR, Hasnain M, Howland RH, Clausen T, Koneru JN, Kogut C, Crouse ELB, Hancox JC, Fernandez A, Pandurangi AK. Methadone, QTc interval prolongation and torsade de pointes: case reports offer the best understanding of this problem. Ther Adv Psychopharmacol. 2013;3(4):219–32. doi:10.1177/2045125312469982.
41. Chowdhury M, Wong J, Cheng A, Khilkin M, Palma E. Methadone therapy in underserved urban community: QTc prolongation and life-threatening ventricular arrhythmias. Cardiovasc Ther. 2015;33(3):127–33. doi:10.1111/1755-5922.12120.
42. Behzadi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: a literature review. Med Princ Pract. 2018;27(5):401–14. doi:10.1159/000492616.
43. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz J-M, Perrier A, et al. Drug-induced long QT syndrome in injection drug users receiving methadone. Arch Intern Med. 2006;166(12):1280–4. doi:10.1001/archinte.166.12.1280.
44. Maremmani I, Zolesi O, Aglietti M, Marini G, Tagliamonte A, Shinderman M, Maxwell S. Methadone dose and retention during treatment of heroin addicts with Axis I psychiatric comorbidity. J Addict Dis. 2000;19(2):29–41. doi:10.1300/J069v19n02_03.
45. Price LC, Wobeter B, Delate T, Kurz D, Shanahan R. Methadone for pain and the risk of adverse cardiac outcomes. J Pain Symptom Manage. 2014;48(3):333–42. doi:10.1016/j.jpainsymman.2013.09.021.
46. United Nations. A needs assessment of women who use drugs (WWUD) in four cities in SA. In: Crime UNOoDa, editor. United Nations Office on Drugs and Crime, Vienna: United Nations:2019. Available from https://www.unodc.org/documents/southernafrica//Publications/Health/UNODC_WWUD_506_web1.pdf.
47. Guglielmetti L, Tiberi S, Burman M, Kunst H, Wejse C, Togonidze T, Bothamley G, Lange C. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: a Tuberculosis Network European Trialsgroup (TBnet) study. Eur Respir J. 2018;52(2):1800537. doi:10.1183/13993003.00537-2018.
48. Toce MS, Chai PR, Burns MM, Boyer EW. Pharmacologic treatment of opioid use disorder: a review of pharmacotherapy, adjuncts, and toxicity. J Med Toxicol. 2018;14(4):306–22. doi:10.1007/s13181-018-0685-1.
49. Ehret GB, Desmeules JA, Broers B. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. Expert Opin Drug Saf. 2007;6(3):289–303. doi:10.1517/14740338.6.3.289.
50. Gourevitch N. First do no harm … reduction? Ann Intern Med. 2009;150(6):417–8. doi:10.7326/0003-4819-150-6-200903170-00111.