

This entry is our account of a review or synthesis of research findings selected by Drug and Alcohol Findings as particularly relevant to improving outcomes from drug or alcohol interventions in the UK. Unless indicated otherwise, permission is given to distribute this entry or incorporate passages in other documents as long as the source is acknowledged including the web address <http://findings.org.uk>. The original review was not published by Findings; click on the [Title](#) to obtain copies. Free reprints may also be available from the authors – click [Request reprint](#) to send or adapt the pre-prepared e-mail message. Links to source documents are in [blue](#). Hover mouse over [orange](#) text for explanatory notes. The Summary is intended to convey the findings and views expressed in the review. Below are some comments from Drug and Alcohol Findings.

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► [QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel.](#)



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Martin J.A., Campbell A., Killip T. et al.

Journal of Addictive Diseases: 2011, 30, p. 283–306.

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Concerned that this might on balance cause more deaths by limiting an effective treatment for opiate addiction, an expert panel convened by the US government has changed its mind on whether the risk of a fatal heart attack potentially posed by methadone justifies routine electrocardiogram screening of patients.

Summary The QT interval (or QTc as corrected for the heart rate) is an indicator of heart function derived from electrocardiogram measures. It refers to the delay between two phases of the electrical activity of the heart which drives it in pumping blood round the body. The health risks associated with a prolonged interval are not clear. It can lead to torsades de pointes, a potentially life threatening heart attack, but some medications prolong the interval yet rarely cause this condition, and it can occur even when the interval is normal. The risk threshold has been set variously at for example 450ms (0.45 seconds) for men and 460ms to 470ms for women or 450ms for both, though it is generally accepted that intervals greater than 500ms pose a significant risk of torsades de pointes.

Some studies have reported that methadone may contribute to the elongation of the QT interval, heightening the risk of torsades de pointes. In response the US government convened an expert panel to assess the risk to patients and make recommendations to enhance their cardiac safety. The featured article is the latest report of that panel, superseding an [earlier version](#).

The panel framed its recommendations on the understanding that methadone must remain widely available because it has been associated with an overall reduction in deaths, there are few therapeutic alternatives, and it is cost-effective. Treatment providers are encouraged to consider the report and take action to the extent that they are clinically, administratively, and financially able to do so, but nothing in the report is

intended to create a legal standard of care or accreditation requirement, or to interfere with the judgment of the clinicians treating the patients.

Main findings

Based on evidence published in the peer-reviewed literature, the panel concluded that both oral and intravenous methadone are not just associated with QT prolongation but actually cause it. Prolongation to over 500ms is thought to confer a significant risk of heart arrhythmias. In all but one study of methadone maintenance treatment, a QT of this level was seen in 2% of patients. Taken in the aggregate, the evidence also supports the view that as methadone doses increase, so too does the likelihood of significant QT prolongation.

The panel's recommendations

Panel members agreed that their recommendations must preserve patients' access to addiction treatment. Among patients with QT prolongation related to relatively high doses of methadone, it is unclear to what degree reducing doses would risk them relapsing [to illicit opiate use], but higher doses are associated with better treatment retention and better outcomes.

The Panel affirmed that methadone can be used with reasonable assurance that it is effective and that its benefits exceed its risks, providing that the potential for QT prolongation is recognised, that patients receive electrocardiogram screening at indicated intervals, and that appropriate clinical action is taken in the presence of significant QT prolongation.


Panel members agreed that, to the extent possible, every opioid treatment programme should have a cardiac risk management plan with the following elements:

- *Clinical assessment*: Intake assessments should include: a complete medication history; personal and family history of structural heart **disease**; any personal history of arrhythmia or syncope (fainting); and use of QT-prolonging medications or illicit drugs such as cocaine which also have this effect.
- *Electrocardiogram assessment*: Largely due to concerns over the resource implications and its effectiveness in achieving meaningful reductions in methadone-associated cardiac events, panel members and ex officio members could not agree whether to recommend routine electrocardiogram screening within the first 30 days of treatment. However, they did agree that a baseline electrocardiogram at the time of admission and within 30 days should be performed on patients with **significant risk factors** for QT prolongation. Among these patients, additional tests should be performed annually or whenever the methadone dose exceeds 120mg a day. In addition to scheduled electrocardiograms, any patient who experiences unexplained syncope or generalised seizures should be tested. If marked QT prolongation is documented, torsades de pointes should be suspected and the patient hospitalised for monitoring through telemetry.
- *Risk stratification*: If the QT interval is over 450ms but less than 500ms, methadone may be initiated or continued, accompanied by a risk-benefit discussion with the patient and more frequent monitoring. For methadone-maintained patients with marked QT prolongation of 500ms or more, strong consideration should be given to adopting a risk minimisation strategy, such as reducing the methadone dose, eliminating other contributing factors, transitioning the patient to an alternative treatment such as

buprenorphine, or discontinuing methadone treatment.

Methadone-related cardiac risk should be mentioned in the informed consent document presented to patients at intake, and patients should receive plain-language educational materials explaining this risk. Medical staff too should be educated about the risks posed by a prolonged QT interval and trained in assessing patients for risk of torsades de pointes and other cardiac problems.

The panel acknowledged that acting on these conclusions will challenge many opioid addiction treatment programmes. Identifying clinically relevant QT prolongation remains difficult, given the variability of electrocardiogram machine measurements and the difficulty of defining the precise risk a prolonged QT portends for any given individual. Programmes will find it a challenge to integrate cardiac arrhythmia risk assessment into the care of opioid-addicted patients without reducing access to vital addiction treatment services. The panel was also aware that not all methadone maintenance treatment providers can administer an electrocardiogram to every patient in all the circumstances they recommended. Opioid addiction treatment programmes and other providers are encouraged to consider implementing these conclusions to the extent that they are practically or financially capable of doing so.

 These recommendations differ in content and in their directiveness from those released by the panel in 2009, [described](#) by a panel member as "preliminary". That [earlier version](#) recommended electrocardiogram screening of all methadone patients when they start treatment and then a month and a year later, with extra tests as indicated, and in particular for anyone on doses exceeding 100mg daily.

There was immediate controversy over whether the so far largely theoretical and circumstantial risk of death from torsades de pointes due to methadone's effects justified routine and repeated electrocardiogram screening of all patients. The preliminary report was followed by [critical letters](#) concerned that such a requirement might restrict the availability of methadone treatment, with a net increase in deaths. An [editorial](#) in the same issue of the journal which published the report complained that its recommendations had "venture[d] well beyond the evidence presented". Additional to possibly counterproductively limiting treatment and/or doses, the editorial said there was no evidence that screening was an effective preventive measure.

As well as now limiting its call for routine screening to high risk patients, this new version of the panel's recommendations does not replicate earlier advice to screen every patient over a certain dose of methadone. A [risk of setting such a threshold](#) is that it may justify and reinforce the tendency in the USA (also in the UK) to prescribe sub-optimal doses of methadone which put patients at risk from continued illicit drug use. Instead the corresponding recommendation is now limited to the same high risk patients, among whom screening should be intensified if doses exceed 120mg a day.

The panel's recommendations are now also much more clearly framed as suggestions to be considered subject to resources and clinical judgement, and with the overriding concern that access to methadone treatment should not be curtailed in order to minimise the risk of cardiac complications, when the risk of not being in effective treatment is, from the available evidence, much greater.

Division in the panel over blanket electrocardiogram screening prompted the issue of the journal which

published its latest conclusions to also publish two commentaries arguing for and against. For a [cardiologist](#) who favoured blanket screening, the issue was simple: "the best way to predict who will develop significant QTc prolongation on drug is to see who has a long QTc off drug. To a cardiologist, [electrocardiogram] screening of patients receiving a QT-prolonging drug is the proverbial 'no-brainer'." The alternative of identifying high risk patients by questioning them about their medical and family history was useful but, it was suggested, inadequate, because few patients know they have a prolonged QT interval or a family history of arrhythmias. But even this authority limited his recommendation to an "ideal" if resources allow: "if one has access to the resources, universal screening remains the ideal risk evaluation and management approach".

[On the other side](#) was (it seems) an addiction specialist who commended the recommendations regarding obtaining a history from the patient and making a physical examination, but (as others have done) saw the reliance on QTc measurement to assess risk as misguided because "there is no evidence that identification of QTc prolongation saves lives in a general population ... QTc prolongation is absent in the majority of [sudden cardiac deaths] and is not a necessary antecedent to ventricular arrhythmia. In other words, it lacks predictive value". Focusing on this unreliable indicator could, he suggested, threaten patient safety by diverting attention from other important risk factors.

The featured report's recommendations are close to those [made by a team based in Italy](#) after reviewing essentially the same literature. For new patients, electrocardiograms should only be resorted to they said if assessment revealed patient or family histories of recurrent syncope of unknown origin or sudden death and/or the patient might be at risk of QT prolongation due to other drugs such as cocaine. If methadone is nevertheless prescribed, such patients should continue to be tested. The authors cautioned that case reports seemingly cumulating to a worrying mass of indications of risk might merely reflect selective attention to a single risk factor prompted by an initial report.

National monitoring records

If there is a risk of sudden cardiac death due to methadone-provoked QT prolongation, it is likely to be small and best revealed through large-scale monitoring. Such records have the weakness that the doctors concerned voluntarily report adverse events, so many may have gone unreported, and some may have been reported but the cause of death not identified as torsade de pointes. However, they do afford a national-scale feel for the minimum incidence of deaths thought due to methadone-related QT prolongation and/or torsade de pointes.

At least two major such reports are available for Europe. Between 1996 and the end of 2007 the [French](#) monitoring system collating reports from doctors of adverse effects of medications recorded one heart attack death of a patient on methadone with prolonged QT, but torsade de pointes was not recorded as the cause. If it was, this [may have been](#) the only such death yet recorded. Importantly, the final year of the reporting period included at least 11 months during which relevant doctors in France had been personally alerted to methadone-related QT prolongation and asked to closely monitor at-risk patients. Other deaths were unaccounted for, but most occurred during induction on to methadone, a high risk period for overdose. The study notes that from 1996 to 2005 about 15,000 patients were treated with methadone in France.

Among 2382 patients who started methadone treatment in [Norway](#) between 1997 and the end of 2003 (who during this time spent in total 6450 years in treatment) there was not a single case among the 90 fatalities where the cause of death was officially recorded as ventricular arrhythmia, and in particular, no mention of torsade de pointes. In just two cases was the cause of death unknown. Importantly this study did not rely on doctors'

reports but matched treatment records with death certificates.

In the 33 years from 1969 to 2002, 59 cases of QT prolongation or torsade de pointes suffered by [US methadone patients](#) were reported to a federal monitoring system, among whom there were five deaths. Just one of these patients was recorded as having suffered torsade de pointes, but in this case myocardial infarction was a complicating factor, a cause of heart failure [distinct](#) from the causes of which methadone is suspected.

UK guidance and its implications

[UK addiction treatment guidance](#) dating from 2007 incorporates the panel's earlier threshold for increased risk of 100mg of methadone a day, but says only that electrocardiograms "might be considered before induction onto methadone or before increases in methadone dose and subsequently after stabilisation – at least with doses over 100mg per day and in those with substantial risk factors". [According to UK medicines regulators](#), these factors include "heart or liver disease, electrolyte abnormalities, concomitant treatment with CYP 3A4 inhibitors, or other drugs with the potential to cause QT interval prolongation". Reflecting the controversy sparked by the US panel, the UK guidance was unclear whether QT prolongation would "prove to be a minor or a major issue measured against the many benefits afforded by methadone treatment".

An addiction clinic in London assessed 155 stabilised methadone patients to determine what proportion would qualify for electrocardiogram monitoring according to these UK criteria, and conducted electrocardiograms on 83 of the patients, mainly at the addictions clinic; attendance for off-site testing was very poor. [The study found](#) that three quarters would qualify, largely due to liver disease including hepatitis infection, being prescribed over 100mg methadone or other QT-prolonging medications, and/or taking cocaine. Just over 18% had prolonged QTc intervals, of which just one would not have been identified without the electrocardiogram. However, none exceeded the 500ms high-risk threshold and there were no known instances of torsade de pointes during the 25 months of the study. When all assessed risk factors were taken in to account, higher doses of methadone (and also stimulant use) were weakly related to longer QTc intervals, but not to the likelihood that the interval would exceed prolongation thresholds. The authors observed that following UK recommendations in this caseload would have meant electrocardiogram monitoring for up to three quarters with "huge resource implications" yet uncertain benefits.

It must be considered reassuring that in this high risk, high methadone dose caseload, no patient was significantly at risk of torsade de pointes as indicated by the generally accepted 500ms criterion, and only one with less extreme prolongation would have been missed without electrocardiogram screening. Less reassuring was the apparent need to arrange for electrocardiograms to be conducted at the addictions clinic with associated extra costs. The results sharpen the dilemma over whether diverting resources to this screening, and possibly delaying the initiation of methadone so it can be conducted, would on balance do more harm than good, even when screening is limited to patients with identified risk factors.

Last revised 17 July 2012

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