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▶ Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation?

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British guidelines suggest electrocardiogram screening of methadone patients at heightened risk of a form of possibly methadone-aggravated cardiac disorder which can result in sudden death. But a London clinic found this would still mean testing most patients, with huge resource implications yet uncertain benefits.

Summary The QTc interval 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. Extended intervals may lead to torsades de pointes, a potentially life threatening irregular heartbeat. Several studies have reported that methadone may contribute to the elongation of this interval, heightening the risk. The risk threshold has been variously set at 450ms (0.45 seconds) for men and 470ms for women or 450ms for both, though it is generally accepted that intervals greater than 500ms constitute a significant risk of abnormal heart function.

UK addiction treatment guidance dating from 2007 says 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".

An addiction clinic in London assessed 155 methadone patients stabilised on their doses for at least four weeks to determine what proportion would qualify for electrocardiogram monitoring according to these criteria, and conducted electrocardiograms on 83 of the patients who attended for testing to determine whether they were at risk according to

the readings of their QT intervals.

Main findings

Three quarters of the patients would have met the criteria for electrocardiogram testing, largely due to liver disease including hepatitis infection, being prescribed over 100mg methadone or other QT-prolonging medications, and/or taking cocaine. Of the roughly half of the patients who attended for electrocardiograms, 8 in 10 did so at the addictions clinic; attendance for off-site testing was very poor.

Among those with electrocardiogram results, the total daily dose of prescribed and illicit methadone was about 99mg and other substance use was common. Just over 18% had prolonged QTc intervals defined as at least 450ms in men and 470ms in women, 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' conclusions

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. They suggested the decision to conduct an electrocardiogram should be based on a risk–benefit analysis by clinician and patient, and that if QT prolongation is found, attempts to redress this should focus on other factors before considering changes in the methadone regimen.

FINDINGS Whether the so far largely theoretical and circumstantial risk of death from torsades de pointes due to methadone's effects justifies routine and repeated electrocardiogram screening of all patients is a matter of some contention. Based on their results, the authors of the featured study effectively come down against this, suggesting that the decision to test be made on a case-by-case basis.

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 would on balance do more harm than good, even when screening is limited to patients with identified risk factors.

After initially recommending universal screening, an expert panel convened by the US government changed its mind, due largely to concern that this might on balance cause more deaths by limiting an effective treatment for opiate addiction. It could mean delays as patients await electrocardiogram testing and results, divert resources from methadone treatment, lead some patients to reject or drop out of the treatment, or to sub-optimal doses, all of which could lead to preventable deaths. Faced with these risks the panel opted for screening high risk patients only. However, as the featured study shows, this

could mean still having to screen most patients.

See this Findings analysis of the US panel's report for more on the risk of death due to methadone-provoked QT prolongation and on whether universal electrocardiogram screening is advisable given the size of this risk and the possible unintended consequences of requiring such screening.

Thanks for their comments on this entry in draft to Soraya Mayet of the Tees, Esk and Wear Valleys NHS Foundation Trust in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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