Appendix 5: Cardiac assessment and monitoring for methadone prescribing[2]

Drug-induced prolongation of the QTc interval
The QTc interval is measured on an ECG* from the beginning of the QRS complex (caused by contraction of the ventricular mass) until the end of the T wave (caused by the return of the ventricular mass to the resting state). The QT corrected (QTc) interval is the QT interval (in milliseconds) corrected for heart rate using a standard formula (for example, Bazett's formula: QTc (ms) = QT (ms) / RR½ – QT divided by the square root of the R-R interval). QTc calculators are available on the internet.

The QTc interval is a useful indicator of risk of polymorphic ventricular tachycardias, or torsade de pointes which can be fatal. QTc interval prolongation beyond normal limits (440 ms for men and 470 ms for women) is associated with increased risk of cardiac arrhythmias and sudden death, especially above 500 ms.

Various psychotropic medications have recently been identified as causing QT prolongation and sudden death. In the past decade, this has become the most common reason for a drug to be withdrawn from the market. In the drug treatment field, this was the reason for levacetylmethadol (LAAM or ORLAAM) being withdrawn in 2001.

Methadone and risk of QTc prolongation
Methadone may prolong the QTc interval and induce torsade de pointes. However increases in QTc interval following methadone induction may not exceed specified thresholds (440 ms in adult males and 470 ms adult females). Findings in relation to the effect of methadone dose have been varied but recently there have been a number of case reports of patients on high-dose methadone experiencing QT prolongation and torsade de pointes. Reducing or stopping methadone was followed by reduction in the QT interval.

Cocaine has been shown to increase QTc intervals acutely. Other confounding factors may be the use of antipsychotic and tricyclic antidepressants.

In summary, the evidence, as currently available, points towards methadone as a risk factor for QTc prolongation and torsade de pointes, with a possible dose-dependent action.

MHRA guidance 2006
In May 2006 the Medicines and Healthcare Products Regulatory Agency (MHRA) drew attention to reports in Europe and elsewhere which "highlighted the risk of QTc prolongation in patients taking methadone, especially at high doses". The MHRA recommended that: "patients with the following risk factors for QTc interval prolongation are carefully monitored whilst taking methadone:

- heart or liver disease
- electrolyte abnormalities
- concomitant treatment with CYP 3A4 inhibitors
- or medicines with the potential to cause QT interval prolongation
- in addition any patient requiring more than 100 mg of methadone per day should be closely monitored." (MHRA, 2006)

Patient consent and information
The patient should be fully informed of the available evidence, the reasons for the clinical assessment and fully involved in the decision making process for their treatment.

Clinical assessment of patients on methadone maintenance
A standard physical health assessment and physical examination should be carried out on all patients entering methadone maintenance treatment. For patients already in methadone treatment, the clinical assessment should cover assessment of heart or liver disease, concomitant treatment with CYP 3A4 inhibitors, other drugs with the potential to cause QT interval prolongation and the presence of electrolyte abnormalities.

Clinical assessment of patients when initiating methadone
At present, the decision to perform an ECG prior to commencing methadone treatment should be based on a risk-benefit analysis. A baseline ECG should be considered in patients with evidence of heart or liver disease, concomitant treatment with CYP 3A4 inhibitors, use of other QTc prolonging drugs or electrolyte abnormalities.

If QTc prolongation is detected, alternatives to methadone should be considered, and other QTc risk factors (such as cocaine use) should be reassessed. It is important that the patient is fully informed and involved in the decision making process.

Summary

- Methadone may be a risk factor for QT prolongation and torsade de pointes with a possible dose-dependent action.
- The MHRA recommends monitoring for patients on high dose methadone (>100 mg daily) and with other QT interval prolongation risk factors where appropriate.
- Patients should be fully informed of the reasons for the clinical assessment and involved in the decision making process for their treatment.
- Screening before commencing methadone treatment is not currently advocated but may be considered.
- Any QT prolongation needs full investigation, consideration of specialist referral, identification of options for QT risk factor modification as well as ongoing ECG monitoring.