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Subject: Andrew Byrne's journal summary. Does QT tachycardia occur in methadone maintenance patients?

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A Community-Based Evaluation of Sudden Death Associated with Therapeutic Levels of Methadone. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. American Journal of Medicine 2008 121, 66-71

Dear Colleagues,

In my view this study draws a long pseudo-scientific bow, implicating methadone treatment in cardiac effects without as much as one confirmed case description of an arrhythmia in a methadone maintenance subject in the catchment area.

The study selected all 183 subjects who died of sudden death in Portland, Oregon over a 4 year period, grouping them according to whether they had 'therapeutic' levels of methadone (up to 1.0mg/L) or not. They excluded cases of proven poisoning from methadone (11 cases) or other recreational drugs (32 cases - all apparently in the methadone group). They also excluded those who did not have a full autopsy 7/29 in study group and 5/111 in the 'control' group (a rather large difference). The authors found that there was identifiable structural heart disease in 23% of the methadone group and 60% of the 'control' group. This was mostly coronary artery disease and/or ventricular hypertrophy.

Of the 22 cases with therapeutic levels of methadone, 55% were prescribed the drug for pain, 14% took it 'recreationally', 18% unknown and 14% for 'opioid withdrawal' - note that none were reported to be on *methadone maintenance treatment* (although 3 patients, 14%, were apparently prescribed the drug for addiction purposes). We are not informed of the quality and availability of addiction services in the area but I understand there are a number of large licensed methadone clinics in Portland. We are not told the details of the 3 addiction cases who died.

The authors claim their data show an association between methadone at 'therapeutic' levels and sudden death. They speculate about cardiac conduction, prolonged QT interval and ventricular tachycardia despite no reported cardiographic evidence pre-mortem. The world literature they cite only appears to contain 28 cases of methadone related tachycardia, mostly non-fatal (see below). A more likely cause of death from methadone than arrhythmia is

respiratory depression, even at 'normal' blood levels. The authors note this in their discussion but still maintain that their study provides evidence, albeit indirect, for arrhythmias.

I find the methodology of this paper bewildering. If this study were duplicated for any other drug, eg. insulin, thiazides, aspirin, fluoxetine or lipid lowering drugs, such conclusions on the cause of death would be considered laughable in my view.

The main weakness of the study is the attempt to link cases in whom no cause of death could be found with a very rare side effect of methadone, in the face of other possible causes of death. This is especially hard to understand in the majority of cases prescribed the drug for pain relief (55%) as opposed to methadone maintenance patients treated for addiction (~14%). The second weakness of the study related to the 'therapeutic' *levels* of methadone. They seem to believe (1) that therapeutic levels imply therapeutic doses and (2) that these do not cause respiratory depression and death. Neither of these assumptions is correct and no reference is given to support them, making the paper faulty and its conclusions even more questionable.

Two cited series of prolonged QT interval and/or torsades tachycardia cases (Krantz and Pearson) show a minority of patients treated under addiction program protocols (and in whom there was only one single death). Krantz's series had an average dose of about four times the usual mean dose in dependency treatment (397mg daily – and none died). Ellen Pearson's series of 59 FDA reports nationally included only 14 likely dependency patients of whom only one died (a patient on a sub-therapeutic dose of 29mg daily). Ehret's series was a retrospective study and patients took an average of 4 additional drugs (range 0-14).

Other citations given are single case reports and/or do not involve methadone maintenance patients but are patients with a variety of serious medical conditions for which methadone was used for pain management or else were overdose cases. There are only a few isolated torsades reports in dependency cases over the last 40 years and unexplained sudden death is either unreported or else exceedingly rare. It is certainly not a major public health issue as claimed by Krantz.

In order to be quite certain about all this, having been in New York for several weeks recently I met up with numerous doctors involved in methadone treatment of tens of thousands of patients over a long period. Not one of these could cite a single case of an addiction patient developing torsades in their experience. This is indirect proof to my mind that an easily diagnosed condition (torsades tachycardia) with a mortality of about 15% is no public health problem but a clinical rarity.

Colorado cardiologist Dr Mori Krantz wrote the seminal paper of this subject and while he

writes candidly of the various proven benefits of traditional methadone treatment, his clear implication is to avoid methadone treatment if possible and beware of high doses when it is the chosen treatment. Yet most addiction guidelines advise higher dose methadone for better outcomes, with the usual safeguards. Also, most authorities recommend methadone in pregnancy and in those with the most severe dependency and/or co-existing mental illness. Yet Krantz has still not provided a series of detailed individual case studies of this syndrome occurring in regular addiction treatment subjects. And this is despite giving advice about how we should treat such cases.

It is intriguing that Krantz took funding for a large survey of methadone clinic staff awareness, despite the lack of evidence (including his own) of it being a significant problem in such patients when compared to pain management cases. If torsades tachycardia is indeed associated with methadone, it does not appear to occur to any measurable extent in methadone maintenance patients. Most cases have been taking high doses (>300mg daily) and/or were taking multiple drugs with serious medical or metabolic problems. Recent alarming upsurges of methadone-related deaths in America do not involve clinic populations but seem to be associated with the increased popularity of the drug as an analgesic used by doctors and patients who may be unfamiliar with its very long half-life and consequent overdose potential.

Comments by Andrew Byrne ..

Lancet letters: <http://www.redfernclinic.com/c/2007/02/methadone-and-qtc-prolongation-letter.php4>

References:

Krantz MJ, Lewkowicz L, Hays H, Woodroffe MA, D. Robertson AD, Mehler PS. Torsade de Pointes Associated with Very-High-Dose Methadone. *Ann Intern Med.* (2002) 137:501-504

Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmcoepidemiol Drug Saf.* 2005 14;11:747-753

Grönbladh L, Öhlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand* (1990) 82:223-227