ADDICTION TREATMENT
Forum

Does Methadone Maintenance Treatment Affect Heart Health?

By Stewart B. Leavitt, PhD, Editor

Overview

Many factors can upset normal heart rhythm, provoking disturbances known as cardiac arrhythmias. Recent warnings about LAAM in that regard also raised questions about whether methadone might influence cardiac adverse events.

Persons coming into methadone maintenance treatment (MMT) programs typically have multiple risk factors for heart illness, starting with their abuses of potentially cardiotoxic substances, such as heroin, cocaine, alcohol, and tobacco. Many patients also have physical illness that may contribute to heart problems. And, the variety of medications often prescribed for these patients, in addition to methadone, may interact to produce certain cardiac electrical conduction disturbances.

Medical researchers continue to explore factors that may alter cardiac electrical conduction processes to cause arrhythmias. Laboratory studies have demonstrated an effect of methadone on cardiac electrical conduction, but such approaches have limitations and their relevance for patients in MMT programs is questionable. Assessing risks of potential heart problems in MMT patients must take into account diverse factors.

At present, based on more than 35 years of accumulated scientific research and its safety record in millions of patients, methadone itself does not appear to have clinically harmful effects on heart health. This report summarizes the conclusions of evidence-based research and the published commentary of experts in the field to provide a current and balanced perspective. Some suggested action steps for MMT clinics are provided.

Heightened Concern

Is oral methadone, as used in methadone maintenance treatment (MMT) for opioid addiction, possibly associated with disturbances of heart rhythm, called *cardiac arrhythmias*? This question was prompted by several events.

In Spring 2001, the European Agency for the Evaluation of Medicinal Products (EMEA) withdrew LAAM (levacetylmethadol or Orlaam®) from the market due to reported adverse cardiac events.[1] At the same time, the United States Food and Drug Administration strengthened warnings about potential cardiac problems associated with LAAM and highlighted them in a black box on product labeling.[2] These directives were based on a relatively small number of patients who were taking LAAM and experienced serious cardiac electrical conduction disturbances known as *Long QT Syndrome* and *Torsade de Pointes*.

Although LAAM differs from methadone by its longer-term action and metabolites, there was speculation that methadone also might influence such heart problems.[1] Further interest was stimulated by laboratory research from a team at Georgetown University, reporting methadone effects on certain electrical currents in the heart.[3]

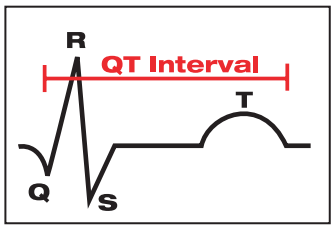
Is methadone harmful, helpful, or neutral when it comes to heart health? This question must be considered in the light of scientific evidence and also take into account the special population of patients in MMT programs.

Heart Rhythm & Arrhythmia

Electrical currents regulate heart rhythm in an orderly and time-sensitive fashion. Disruption of electrical conduction processes can lead to life-threatening arrhythmias.

ECGs Tell The Tale

An electrocardiograph (ECG) measures electrical current moving through the heart during each heartbeat, and an important portion of the characteristic waveform is the QT interval. **See figure**. It represents the time period from when the heart



ventricles discharge electrical energy and contract (called *depolarization*) to when the ventricles become recharged and ready again to pump blood through the body (*repolarization*). These processes are controlled by electrically-charged calcium, sodium, and potassium ions.[4-7] (**See sidebar for further details**.)

The QT interval, measured in fractions of a second or milliseconds (msec), is a vital indicator of healthy heart function. Prolongation of the QT interval to greater than normal length has been considered a sign of potential arrhythmia.[6-8]

Measuring QT

Heart rate affects QT length; for example, it becomes shorter as the heart speeds up. Therefore, the QT interval is usually corrected for heart rate and expressed as QTc (QT-corrected),[9] so comparisons can be made independent of heart rate. **(Also see sidebar.)**

There are several obstacles to accurately and reliably measuring QTc intervals, and there are numerous individual factors that may influence a particular person's QTc length. For example, women generally have longer QTc intervals than men.[10-12] This diversity of factors can make it difficult to interpret the significance of suspected QTc lengthening in individual patients.

Defining "Prolonged" QT

How long can the QT interval become before there is a risk of heart problems?

The EMEA[1,13] and others[5,6,11,14-17] have suggested that QTc-interval values of 500 msec or more, or increases of greater than 60[1,13] to 75[11,16] msec from baseline, could be considered abnormal and indicate risk of arrhythmia.

It has been suggested that the upper limits of normal QTc-interval values are greater than usually acknowledged[8,15] and might range from 420 to 500 msec.[17] Yet, many studies have used that range to indicate abnormal QTc lengthening, reporting 8% to 23% of patients at risk for arrhythmia.[8] Thus, premature alarms may have been sounded in many cases.

Long QT Syndrome (LQTS)

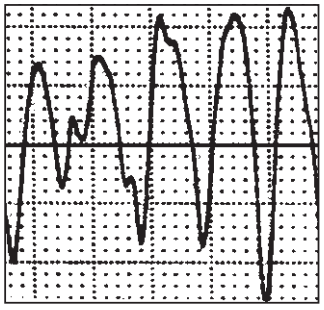
A consistent, persistent, and abnormally prolonged QTc interval is referred to as *Long QT Syndrome* or *LQTS*. It can be an inherited condition, called *congenital LQTS*, involving defects in genes that control electrical conduction channels in heart muscle.[18]

LQTS also may be caused by certain drugs or toxins, abnormal levels of electrolytes (e.g., potassium, calcium, or magnesium), or certain physical ailments. This is known as *acquired LQTS*.[18]

As a syndrome, there may be multiple aspects of LQTS. If the heart muscle recharging process (repolarization) is extremely delayed, such as by drugs that block electrical currents, it can greatly slow normal heartbeat, which may influence arrhythmia. Or, the ventricles may fire before they are fully recharged, producing weak contractions.[15,18]

A Lethal Twist: Torsade de Pointes (TdP)

When the QTc becomes prolonged, there also is the risk of a rapid, abnormal heart rhythm called *ventricular tachycardia* occurring. The particular ventricular tachycardia most frequently associated with LQTS displays an ECG waveform that becomes distorted in a series of undulating peaks twisting about a central axis. **See figure**. This is called *Torsade de Pointes (TdP)*, a French phrase meaning "twisting of the points."[15,19-21]

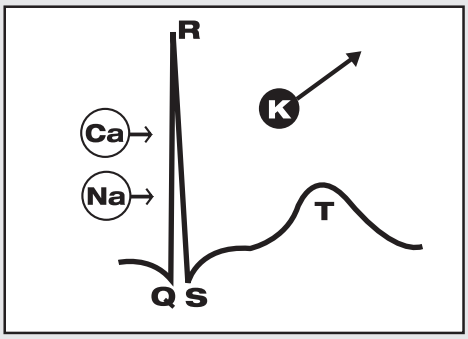


During a TdP episode, often brought on by exercise or sudden stress, the person may experience palpitations, dizziness, or lightheadedness. In more extreme cases, the person may faint (called *syncope*) or have what appears as a seizure due to insufficient blood flow to the brain.[15,21]

TdP can resolve on its own, with a return to more regular heart rhythm and the person recovering. However, further TdP episodes may quickly follow and possibly degenerate into ventricular fibrillation (convulsive twitching), causing death if the person is not resuscitated.[21]

A Closer Look at Arrhythmia

After accumulated electrical energy reaches a sufficient level in the ventricles, calcium (Ca) and sodium (Na) ions flow *into* muscle cells, serving as a discharging "trigger" mechanism. This *depolarization* process reaches a peak at the R position of the ECG waveform, causing the ventricles to contract.[6,7] **See figure.**



Ventricular recharging primarily involves a flow of potassium ions (K) *out of* heart muscle cells. At least 7 different types of potassium ion channels have been identified, and the channel most often involved in acquired LQTS is called the *rapid component of the delayed rectifier potassium current*. This *repolarization* process extends to the end of the recovery T wave.[6,7,22]

The QT interval is most commonly corrected for heart rate using Bazett's formula: QTc = QT interval divided by the square root of the preceding RR interval. However, accurate measurement of QT on the ECG rhythm strip is complicated by a lack of standardization in ECG recorders, subtle changes in waveforms, and differences in interpreting readings.[10,11,13-15]

Furthermore, individual patient differences may affect QT length: e.g., abnormal electrolyte levels, physical illness, and drug or alcohol consumption,[6,23] shift work or time of day the ECG reading is taken,[24,25] postural changes during ECG recording,[26] and even a full stomach.[27] Calculated QTc intervals may be 10% longer in women until age 50, when the QTc in men lengthens to equal that of women.[12,18]

It should be noted that several authors have proposed that there actually is no "cutoff" level for QTc prolongation that clearly predicts the induction of cardiac arrhythmia or TdP. Also, the relationship between QTc and TdP in general is poorly defined, although women, with longer QTc intervals, are most prone to developing TdP. Many risk factors for developing heart rhythm disturbances other than the QTc interval may be more important.[8,12,15-18,28]

Risk Factors in MMT Patients

Although there can be a strong hereditary influence in developing life-threatening LQTS and/or TdP, it is believed that acquired forms due to physical illness or drugs are much more common. Many risk factors for cardiac arrhythmia are typically present in MMT patient populations.

LQTS Prevalence

In general, cardiac arrhythmias may account for more than 10% of all natural deaths.[4] There are 300,000 to 400,000 sudden cardiac deaths each year in the U.S., with most due to ventricular arrhythmia.[4,21] An estimated 7000 to 8000 of those deaths are in young persons, with LQTS accounting for roughly half of them.[4,21,29]

LQTS occurs in all races and ethnic groups, and may be more common than presently imagined. An investigation in one medical center found a 7% prevalence of LQTS in more than 34,000 patients undergoing ECG screening during a 6-month period.[30]

A genetic tendency for LQTS may exist in about 1 in 5000 persons, or roughly 50,000 in the U.S. and more than 200,000 worldwide.[4,21,29] The death rate for patients with inherited LQTS has been estimated at 1% to 2% per year.[20]

An important indicator of inherited risk for persons coming into MMT programs would be a history of blood relatives who experienced sudden cardiac death.

Substance Abuse

Besides opioid dependency, a high prevalence of other substance abuse would be expected in persons entering MMT, including: cocaine, alcohol, tobacco, and marijuana.[31]

Cocaine has long been recognized as toxic to the heart, slowing sodium channels and depressing heart rhythm,[7] and possibly causing heart attack.[32] The QTc may be prolonged in 17%[33] to 19%[34] of patients who abuse alcohol and a third of those may experience rapid heartbeat.[33] Tobacco smoking has long been known as a heart attack risk, and a recent report also has implicated marijuana smoking.[35]

In a long-term study of heroin addicts, the death rate due to cardiovascular diseases was 12%.[31] Early studies found that 61%[36] to 84%[37] of heroin addicts had adverse changes in their ECG waveforms. One study of persons entering an MMT program noted that 31% exhibited QTc prolongation.[36]

Taken together, the findings suggest that a significant proportion of patients entering MMT might be expected to have irregularities in their ECG waveforms. These might consist predominantly of longer QTc intervals than would be found in the general population.

Physical Illness

A number of physical illnesses are associated with prolongation of the QTc interval, including: anorexia, cardiovascular disease, endocrine abnormalities, central nervous system disorders, diabetes, electrolyte disturbances, HIV, liver disease, obesity, and others.[8,17] Thus, many patients in MMT programs could be at risk due to these conditions.

Medications

Medications account for most cases of acquired LQTS that can induce TdP.[17,38] Many patients in MMT programs are treated with multiple drugs that may alter electrical conduction in heart muscle tissues.[7,10,19,21,22]

Patients with preexisting heart conditions may be receiving cardiovascular drugs. Many of these, especially those with antiarrhythmic properties, affect ion channels and electrical conduction currents, and their misuse or combination with interacting medications can result in adverse events.[7]

Most conventional and some newer atypical antipsychotic agents have been associated with drug-induced QTc lengthening and potential arrhythmias.[8,17,39] Also, the tetra- and tricyclic, and some SSRI, antidepressants may provoke adverse cardiac reactions.[8,17,21] Experience over the years has demonstrated that many other noncardiac drugs sometimes used in MMT patients also may influence LQTS and/or TdP.[21,40] **See chart.**

Some* Noncardiac Drugs Influencing LQTS and/or TdP[7,8,10,17,21,39,40]

amitriptyline [Elavil]	lithium [Lithonate]
ampicillin [Omnipen]	olanzapine [Zyprexa]**
carbamazepine [Tegretol]	prochlorperazine [Compazine]
clarithromycin [Biaxin]	quetiapine [Seroquel]**
doxepin [Sinequan]	risperidone [Risperdal]
erythromycin [Ery-Tab]	sparfloxacin [Zagam]**
fexofenadine [Allegra]**	sumatriptan [Imitrex]
fluoxetine [Prozac]**	TMP/SMX [Bactrim]
haloperidol [Haldol]	tamoxifen [Nolvadex]
imipramine [Tofranil]	tetracycline [Sumycin]
ketoconazole [Nizoral]	venlafaxine [Effexor]
levofloxacin [Levaquin]**	

**Partial list based on selections from the most prescribed drugs in the U.S., Sigler & Flanders, Inc., 2000.*
***Potentially minor effects at recommended therapeutic doses.*
[Brand names are registered trademarks of the respective manufacturers.]

Lengthening of the QT interval can be an important precursor to TdP; however, not all drugs that prolong the QT also cause TdP. Furthermore, TdP may be caused by drugs having no prior effect on the QT interval.[15]

Drug Interactions

Interactions during administration of multiple drugs can be a critical risk factor for LQTS and TdP.[3,5,19,22] It has been observed that nearly three-quarters of all adverse events associated with methadone, including those affecting cardiac function, involve comedications.[41]

Simultaneous use of drugs that compete for or inhibit liver enzymes needed for metabolism may result in elevated concentrations of agents that could induce arrhythmia.[3,5,19,22,39] Methadone, being variously metabolized by up to 5 liver enzymes, may interact with many other medications and result in accumulations of those agents.[42,43]

One study found that roughly 38% of 206 psychiatric patients with a prolonged QTc (defined conservatively as greater than 420 msec) were on methadone. However, virtually all of the methadone patients also received one or more antipsychotic medicines that might have affected cardiac electrical conduction.[34]

Furthermore, it has been proposed that some persons, perhaps more than commonly assumed, may be silent gene carriers for LQTS. Such persons are at genetically increased risk from certain medications and are more prone to develop drug-induced arrhythmias than patients who receive the same drug(s) safely.[44]

However, it has been suggested that use of drugs known to prolong QTc is not necessarily harmful, unless: a) the drug is administered rapidly and directly into the system (e.g., IV injection), b) concomitant metabolic inhibitors are used, and/or c) other risk factors exist. Even in these circumstances, it is difficult to determine an upper threshold for prolongation of the QTc interval that predicts development of TdP or other arrhythmia.[10]

There is an ongoing need to assess risk-benefit relationships of multidrug administration in MMT patients. As one researcher noted, "disparate factors ranging from inappropriate multidrug therapy to a glass of grapefruit juice can render the heart of any patient susceptible to ventricular arrhythmias." Physicians should become more knowledgeable regarding drug interactions and cardiac risk factors so they might prevent adverse situations before they occur.[22]

Research Observations

Results of laboratory investigations into methadone's influence on cardiac electrical conduction have been conflicting, and some might be interpreted as implying cardiac benefits of methadone. Clinical studies in MMT patients specifically focusing on cardiac issues have been limited.

Laboratory Investigations

A team at Georgetown University recently reported that methadone diminished potassium ion flow and reduced repolarization currents by half their maximal strength in human heart-cell cultures.[3] However, it is not known what this might mean clinically and the effect was seen at methadone blood concentrations nearly 9 times greater than usual therapeutic levels recommended for MMT patients.[43]

Earlier laboratory research had demonstrated similar effects. In sheep heart cells, methadone at very high concentrations delayed electrical conduction.[45] In squid and chick cells, methadone slowed potassium and, to a lesser degree, sodium and calcium electrical currents across cell membranes.[46] This effect also was demonstrated by reduced swimming speed in protozoa,[47] and the slowing was more than doubled by the addition of alcohol.[48]

In guinea-pig[45] and cat[49] heart muscle, methadone strengthened contractile force (called *inotropic effect*), which might be beneficial in some patients. However, at very high doses, 10 times peak toxic concentrations in humans, methadone produced an apparent reduction in electrical excitability in cat heart-muscle cells accompanied by a negative inotropic effect – that is, it weakened contractility.[50] This effect also was observed in rat tissues[51] and appears related to methadone's ability to retard inward calcium currents.[45,51-53]

It should be noted that laboratory research in cell cultures or animals does not necessarily translate into clinical significance in patients. Laboratory investigations allow studying pure drug effects at known concentrations;[5] however, they do not take into account the idiosyncrasies of metabolism and cardiac function in humans.[5,10,54] Differences in animal metabolism and response, and the experimental methods employed, have resulted in inconsistent reports of methadone's effects on electrical conduction.[50,55]

Furthermore, methadone was usually applied directly to heart tissues on a single-dose basis and at high concentrations, rather than simulating daily doses achieving steady-state blood serum levels that typify MMT.[54] Also, methadone concentrations in human heart muscle are unknown and may be lower than those present in blood serum.[10]

Cardiac Advantages?

Effects on cardiac electrical conduction do not automatically imply harmful consequences, and actually may be a sign of a drug's usefulness as a heart medication.[19] Over the years, certain opioids, including methadone, have demonstrated cardioprotective effects and have been important adjuncts in treating heart attacks and coronary artery disease.[32,50]

Also, as noted above, methadone appears to reduce calcium flow into heart tissues. It has been suggested that decreases in intracellular calcium may protect the heart from calcium overload during stress reactions. Furthermore, research in rats demonstrated that cocaine-related myocardial infarction could be prevented by blocking calcium channels, and experiments in mice found that opioids helped protect the heart from adverse cocaine effects.[56]

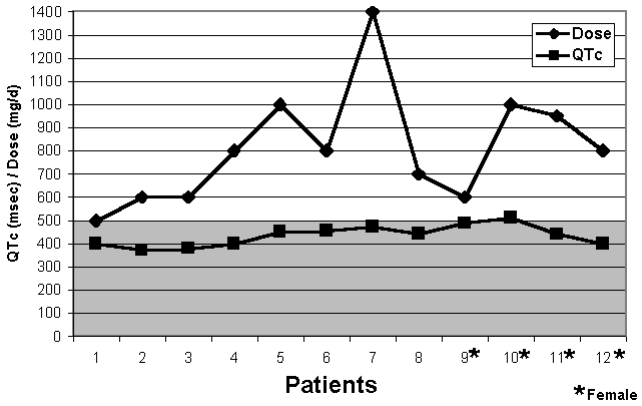
The calcium-slowing effects of methadone may be analogous to the actions of certain heart medications that suppress some forms of arrhythmia.[57] One author commented on similarities of methadone and verapamil (e.g., Calan®, Verelan®),[52] a calcium-channel-blocking agent indicated for the treatment of hypertension and angina, and to prevent arrhythmia related to rapid heartbeat. It has not appeared on any lists of agents known to prolong QTc or induce TdP and, in fact, calcium-blocking action may shorten the QTc interval.[7]

Thus, while laboratory research suggests that methadone may influence certain ion channels and cardiac electrical conduction, those effects have not been proved harmful in humans. Some of methadone's actions demonstrated in the laboratory actually may provide a degree of cardiac protection in certain MMT patients, although this still needs to be demonstrated in clinical studies.

Clinical Explorations

In one small study of MMT patients,[36] 66% had ECG alterations during their early tenure in the program, primarily QTc prolongations (of undefined length) in 34%, which were likely preexisting conditions. However, after 4 or more months in MMT, and abstinence from all illicit drugs and alcohol, the QTc irregularities vanished in 54% of those patients retested. Whereas, 4 patients who continued sporadic drug abuse while in MMT developed QTc prolongations that were not initially present.

Recently, there have been questions about whether methadone doses higher than those typically used in many MMT programs might engender added cardiac risks and justify extra precautions.[1,42] A case series from one large MMT clinic[28] examined 12 patients receiving 500 mg or more of daily methadone (average 812 mg/d; range 500-1400 mg/d). **See graph.** All patients were taking comedications and many had physical illness, such as HIV, hepatitis, liver cirrhosis, hypertension, and diabetes; although none of the patients had signs or symptoms of heart distress.



As might be expected, females exhibited higher average QTc values than males: 460 vs 422 msec. The overall average QTc interval of 435 msec was within normal limits.

Only one patient had a QTc greater than the 500 msec "abnormal threshold" – 512 msec. This was a 43-year-old woman with hepatitis C, taking several medications, and receiving 1000 mg/d of methadone. She had never experienced symptoms of heart distress and, in fact, was very athletic – an avid runner. An ECG ten years earlier, when she was receiving only 100 mg/d of methadone, had exhibited an identical QTc interval.

As the graph demonstrates, there was only a moderate correlation between methadone dose and QTc interval in these patients (r = 0.53). Methadone blood serum levels were not tested, and it is likely that any potential influence on QTc might relate more to methadone blood concentrations rather than dose.[42]

As this study seems to confirm, it has been proposed that patients at higher methadone doses do not necessarily present greater risks of cardiotoxicity induced by methadone. However, those patients with known abnormal QTc prolongation and/or multiple cardiac risk factors might merit extra precautions.[42]

MMT Practice Implications

There currently does not appear to be conclusive research evidence suggesting that oral methadone itself is clinically harmful to heart health.[1] This is supported by methadone's successful use for the treatment of opioid dependency in millions of patients during the past 35 years.

Long History of Safety

Long-term clinical studies in large populations of methadone patients have found the medication to be safe and generally without toxic effects,[58-60] even though risks for cardiac complications were numerous in many patients. In one of the studies, 15% of deaths were due to tobacco-smoking-related heart disease, 20% were due to HCV, 15% were AIDS-related, and 5% were associated with morbid obesity.[61] In another study, 40% of deaths were drug-abuse-related, primarily alcohol.[62]

Investigations of drug-related fatalities worldwide consistently have found few if any deaths directly related to methadone.[61,62] Toxicity due to multidrug abuse has been the leading cause of death.[41]

The methadone induction phase is sometimes problematic,[41,42] although 80% of deaths during this period have been attributed to mixed-drug overdose.[41] This period prior to methadone stabilization could be a time of increased cardiac risk, since there might be unexpected surges in blood levels of cardioactive comedications and/or abused substances due to metabolic interactions with methadone.

Steps To Consider

Sound medical practice dictates a need for continued vigilance to identify individual patient risk factors for cardiac illness. Added to these are risks that may be imposed by treatment regimens involving multiple medications – *iatrogenic risk factors*.

The goal is to provide individualized treatment plans that preserve heart health. To help achieve this, clinics may want to adopt certain practices:

- Patients entering MMT should be screened for cardiac risk factors and medical records for all patients should be periodically updated in this regard.
- Records should note prior heart problems and current heart health status, family history of heart conditions, past and current substances abused (including tobacco), and current medications (including OTC and herbal products).
- Patients with prior heart problems or significant current risk factors should be more closely monitored during MMT, *particularly during the start-up induction phase*.
- These patients should be educated on symptoms to watch for – e.g., "racing" heartbeat, dizziness, or fainting spells – and encouraged to contact the clinic immediately. Staff should be trained in handling such calls from patients.
- In some cases, it may be useful to perform baseline ECGs in patients with significant cardiac risk factors upon entering treatment or when they are prescribed medications with known cardiac effects. An ECG should be repeated within two weeks to detect any significant changes.
- In patients taking comedications that have demonstrated harmful cardiac effects or interactions with other drugs, it might be advisable to adjust therapy (e.g., change in dose or medication) and/or to monitor those patients for adverse reactions.

The early identification and ongoing monitoring of factors predisposing to QTc prolongation and/or TdP or other arrhythmias can be vital for heart health in MMT patients. Even if some factors, such as female gender or genetics cannot be modified, others such as electrolyte imbalances or potentially interacting medications might be easily remedied once identified.

References
1. European Agency for the Evaluation of Medicinal Products. *EMEA public statement on the recommendation to suspend the marketing authorization for Orlaam (levacetylmethadol) in the European Union*. 2001(19 April);EMEA/8776/01. Available online at: www.emea.eu.int/.
2. US Food and Drug Administration. *FDA Talk Paper T01-15*. April 20, 2001.
3. Katchman AN, Ebert SN, McGroary KA, Woosley RL. *Methadone blocks HERG current in transfected HEK cells*. Presentation at the American Society for Pharmacology & Experimental Therapeutics (ASPET) conference, March 2001. Abstract LB253.
4. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. *Mayo Clin Proc*. 1998;73(3):250-269.
5. Moss AJ. The QT interval and torsade de pointes. *Drug Saf*. 1999;21(Suppl 1):5-10, 81-87.
6. Kemp JP. Antihistamines – is there anything safe to prescribe [editorial]? *Ann Allergy*. 1992;69(4):276-280.
7. Symanski JD, Gettes LS. Drug effects on the electrocardiogram. A review of their clinical importance. *Drugs*. 1993;46(2):219-248.
8. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotic drug therapy in psychiatric patients. *Lancet*. 2000;355:1048-1052.
9. Bazett HC. An analysis of time relations of electrocardiograms. *Heart*. 1920;7:353-367.
10. DePonti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. *Eur J Clin Pharmacol*. 2000;56:1-18.
11. Bonate PL, Russell T. Assessment of QTc prolongation for non-cardiac-related drugs from a drug development perspective. *J Clin Pharmacol*. 1999;39(4):349-358.
12. Wolbrette D, Patel H. Arrhythmias and women. *Curr Opin Cardiol*. 1999;14:36-43.
13. Committee for Proprietary Medicinal Products (CPMP). *Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products*. The European Agency for the Evaluation of Medicinal Products. December 1997. CPMP/986/96.
14. Moss AJ. Drugs that prolong the QT interval: regulatory and QT measurement issues from the United States and European perspectives. *Ann Noninvasive Electrocardiol*. 1999;4(3):255-256.
15. Morganroth J. Relations of QTc prolongation on the electrocardiogram to torsades de pointes: definitions and mechanisms. *Am J Cardiol*. 1993; 72:10B-13B.
16. Tschida SJ, Guay DRP, Straka RJ, Hoey LL, Johanning R, Vance-Bryan K. QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. *Pharmacotherapy*. 1996;16(4):663-674.
17. Welch R, Chue P. Antipsychotic agents and QT changes. *J Psychiatry Neurosci*. 2000;25(2):154-160.
18. Ebert SN, Liu X-K, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *J Women's Health*. 1998;7(5):547-557.
19. El-Sherif N, Turitto G. The long QT syndrome and torsade de pointes. *PACE*. 1999;22 (Pt I):91-110.
20. Janeira LF. Torsades de pointes and long QT syndromes. *Amer Fam Phys*. 1995;52(5):1447-1453.
21. Vincent GM. Long QT syndrome. *Cardiol Clin*. 2000;18(2):309-325.
22. Priori SG. Exploring the hidden danger of noncardiac drugs [editorial]. *J Cardiovasc Electrophysiol*. 1998;9(10):1114-1116.
23. Rossinen J, Sinisalo J, Partanen J, Nieminen MS, Viitasalo M. Effects of acute alcohol infusion on duration and dispersion of QT interval in male patients with coronary artery disease and in healthy controls. *Clin Cardiol.* 1999;22:591-594.
24. Murata K, Yano E, and Shinozaki T. Cardiovascular dysfunction due to shift work. *J Occup Environ Med*. 1999;41:748-753.
25. Molnar J, Zhang F, Weiss J, Ehlert FA, Rosenthal JE. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol*. 1996;27:76-83.
26. Cuomo S, DeCaprio L, DiPalma A, et al. Influence of autonomic tone on QT interval dispersion. *Cardiologia*. 1997;42:1071-1076.
27. Nagy D, de Meersman R, Gallagher D, et al. QTc interval (cardiac depolarization): lengthening after meals. *Obes Res*. 1997;5:531-537.
28. Center for Addictive Problems (CAP), Chicago, IL. Data on file, courtesy of M. Shinderman, MD.
29. Vincent GM, Timothy K, Fox J, Zhang L. The inherited long QT syndrome: from ion channel to bedside. *Cardiol Rev*. 1999;7(1):44-55.
30. Kocheril AG, Bokhari SA, Batsford WP, Sinusas AJ. Long QTc and torsades de pointes in human immunodeficiency virus disease. *Pacing Clin Electrophysiol*. 1997;20(11):2810-2816.
31. Hser Y-I, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001:58:503-508.
32. Backmund M, Meyer K, Zwehl W, Nagengast O, Eichenlaub D. Myocardial Infarction Associated with Methadone and/or Dihydrocodeine. *Eur Addict Res.* 2001;7(1):37-39.
33. Takehana H, Izumi T. Alcoholic heart disease [Japanese, English abstract]. *Nippon Rinsho*. 2000;58(1):151-156.
34. Mathot F, Kurz X, Noel Ch, Firket P. Long QTc and psychotropic drug use. *Int J Neuropsychopharm*. 2000;3(suppl 1):S173. Abstract P.02.18.
35. Report links heart attacks to marijuana. *New York Times*. March 3, 2000.
36. Stimmel B, Lipski J, Swartz M, Donoso E. Electrocardiographic changes in heroin, methadone and multiple drug abuse: a postulated mechanism of sudden death in narcotic addicts. *Proc Natl Conf Methadone Treat*. 1973;1:706-710.
37. Glauser FL, Downie RL, Smith WR. Electrocardiographic abnormalities in acuteheroin overdosage. *Bull Narc.* 1977;29(1):85-89.
38. Drici M-D, Barhanin J. Cardiac K+ channels and drug-acquired long QT syndrome. *Therapie*. 2000;55(1):185-193.
39. Gury C, Canceil O, Iaria P. Antipsychotic drugs and cardiovascular safety: current studies of prolonged QT interval and risk of ventricular arrhythmia [French, English abstract]. *Encephale*. 2000;26(6):62-72.
40. Woosley RL. *International Registry for Drug-Induced Arrhythmias*. Georgetown (University) Center for Education and Research on Therapeutics. Available online at: http://QTdrugs.org. Access checked May, 2001.
41. Leavitt SB. The safety of methadone, LAAM, buprenorphine in the treatment of opioid dependency. *Addiction Treatment Forum*. 2001(Spring);10(2). Available online at: www.atforum.com.
42. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokin*. 2001; in press.
43. Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P. When "enough" is not enough: new perspectives on optimal methadone maintenance dose. *Mt Sinai J Med*. 2000;67(5-6):404-411.
44. Viskin S. Long QT syndromes and torsade de pointes. *Lancet*. 1999;354:1625-1633.
45. Mantelli L, Corti V, Bini R, Cerbai E, Ledda F. Effects of dl-methadone on the response to physiological transmitters and on several functional parameters of the isolated guinea-pig heart. *Arch Int Pharmacodyn Ther.* 1986 Aug;282(2):298-313.
46. Horrigan FT. Methadone block of neuronal K current. *Biophysical J*. 1990;57:515A. Abstract W-Pos392.
47. Wu C, Fry CH, Henry JA. Membrane toxicity of opioids measured by protozoan motility. *Toxicology*. 1997;117:35-44.
48. Wu C, Henry JA. Interaction between ethanol and opioids in a protozoan assay. *Hum Exp Toxicol*. 1994;13:145-148.
49. Huidobro F, Tamayo L, Contreras E. Effects of methadone on the action of catecholamines in isolated preparations. *Arch Int Pharmacodyn Ther*. 1971;192:168-178.
50. Rendig SV, Amsterdam EA, Henderson GL, Mason DT. Comparative cardiac contractile actions of six narcotic analgesics: morphine, meperidine, pentazocine, fentanyl, methadone and l-alpha-acetylmethadol (LAAM). *J Pharmacol Exp Ther.* 1980 Oct;215(1):259-265.
51. Lee CH, Berkowitz BA. Calcium antagonist activity of methadone, l-acetylmethadol and l-pentazocine in the rat aortic strip. *J Pharmacol Exp Ther.* 1977;202(3):646-653.
52. Seyler DE, Borowitz JL, Maickel RP. Calcium channel blockade by certain opioids. *Fundam Appl Toxicol.* 1983;3(6):536-542.
53. Wu C, Fry CH, Henry JA. The mode of action of several opioids on cardiac muscle. *Exp Physiol*. 1997;82:261-272.
54. Champeroux P, Martel E, Vannier C, et al. The preclinical assessment of the risk for QT interval prolongation. *Therapie*. 2000;55:101-109.
55. Garrido MJ, Troconiz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. *J Pharmacol Toxicol Methods*. 1999;42(2):61-66.
56. McCormack KJ, Chapleo CB. Opioid receptors and myocardial protection. Do opioid agonists possess cardioprotective effects? *Clin Drug Invest*. 1998;15(5):445-454.
57. Boachie-Ansah G, Sitsapesan R, Kane KA, Parratt JR. The antiarrhythmic and cardiac electrophysiological effects of buprenorphine. *Br J Pharmacol.* 1989;97 (3):801-808.
58. Kreek MJ. Medical safety and side effects of methadone tolerant individuals. *JAMA*. 1973;223(6):665-668.
59. Novick DM, Richman BL, Friedman JM, et al. The medical status of methadone maintenance patients in treatment for 11-18 years. *Drug Alcohol Dep*. 1993;33:235-245.
60. Rettig RA, Yarmolinsky A, eds. *Institute of Medicine: Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press; 1995.
61. Salstiz EA, Joseph H, Frank B, et al. Methadone medical maintenance (MMM): treating chronic opioid dependence in private medical practice - a summary report (1983-1998). *Mt Sinai J Med*. 2000;67(5-6):388-397.
62. Appel PW, Joseph H, Richman BL. Causes and rates of death among methadone maintenance patients before and after the onset of the HIV/AIDS epidemic. *Mt Sinai J Med*. 2000;67(5-6):444-451.

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