

Memorandum

To: Psychiatrists in San Mateo County
From: Celia Moreno, MD, Outpatient Mental Health Medical Director
Barbara Liang, PharmD, Mental Health Pharmacy Manager
Date: 9/30/2009
Re: Methadone and QTc Prolongation

The Center for Disease Control reports that the number of methadone-related deaths has increased by 390% from 1999 (786 deaths) to 2004 (3,849). Methadone has been associated with QTc prolongation, resulting in fatal ventricular arrhythmia. The dose of methadone correlates with the extent of QTc prolongation, and subsequent cardiac events. Recent data indicates that doses exceeding 100mg per day significantly increases that risk.

We will revise the medication monitoring guideline to recommend EKG monitoring for clients on methadone equal to or greater than 100mg per day. QTc's between 450-500 ms are considered prolonged and discussion with PCP/cardiologist would be recommended. QTc's of 500 ms or longer significantly increase the risk of Torsade de Pointes.

In addition to methadone, other medications also have the potential to increase QTc interval. Given the likely scenario of polypharmacy in our client population, the additive cardiac risk could have fatal implications. If the client is on polypharmacy with other agents that may prolong QTc, an EKG may be indicated even if the methadone dose is less than 100mg per day.

Below is a partial list of commonly used medications in our client population that can increase the risk of QTc prolongation. For a more complete list and references, as well as non-pharmacologic risks of QTc prolongation, please see the attached article.

Analgesics:	Celecoxib, Methadone
Antihistamines:	Diphenhydramine, Hydroxyzine
Antihypertensives:	Isradipine, Nicardipine, Furosemide, Indapamide
Antidepressants:	Citalopram, Escitalopram, Fluoxetine, Maprotiline, Paroxetine, f Sertraline, Trazodone, Tricyclic Antidepressants, Venlafaxine
Antipsychotics:	Aripiprazole, Clozapine, Fluphenazine, Haloperidol, *Mesoridazine, Olanzapine, Paliperidone, Perphenazine, *Pimozide, Quetiapine, Risperidone, *Thioridazine, Trifluoperazine, Ziprasidone
Miscellaneous:	Amantadine, Atomoxetine, Droperidol, Lithium

* Black box warning on QTc prolongation.

Drug-induced Prolongation of the QT Interval and Torsades de Pointes

The QT interval is the period between the beginning of the QRS complex and the end of the T wave.¹ Thus, it is the estimate of the time interval between the earliest ventricular depolarization and the latest ventricular repolarization.¹ Since the QT interval is affected by changes in the heart rate, corrections are usually made to the QT interval for these changes (QTc).^{1,2,3} There is no commonly accepted definition of a normal or prolonged QTc interval. The Committee for Proprietary Medicinal Products has suggested ranges for normal (ie, men less than 430 msec, women less than 450 msec), borderline (ie, men 430 to 450 msec, women 450 to 470 msec), and prolonged (ie, men greater than 450 msec, women greater than 470 msec) QTc intervals.⁴ Moderate and clinically important increases in the QT interval over baseline have been considered to be 15% and 25% increases, respectively.¹

Numerous drugs, representing a wide range of pharmacologic classes, have been implicated in prolonging the QT interval. Concern about serious and possibly fatal consequences of drug combinations that may cause prolongation of the QT interval has led to contraindicating the use of many drug pairs, even though coadministration may not have been studied. The potential of bepridil (Vascor), astemizole (Hismanal), grepafloxacin (Raxar), and terfenadine (Seldane) to prolong the QT interval played an important role in their removal from the market.

The precise mechanism by which QT interval prolongation (ie, long QT syndrome [LQTS]) occurs is unknown; however, it appears to be related to ion exchange (eg, outward repolarizing potassium current, inward depolarizing calcium or sodium current).^{1,5,6,7} Class III antiarrhythmic agents prolong the QT interval by blocking potassium flow.⁸ A prolonged QT interval may be congenital (eg, genetic) or acquired (eg, drug-induced).^{1,2,4,7} In some instances, patients may have an underlying predisposition toward a prolonged QT interval (eg, longer than normal QT interval before drug administration).⁵

Drug-induced prolongation of the QT interval may be suspected if there are dose-related changes in the QT interval, the same drug causes QT prolongation in a number of patients, or prolonged QT interval recurs when a patient is rechallenged.¹ Drug-induced QT prolongation may be prevented by 1) not exceeding the recommended drug dose; 2) limiting use of the drug in patients with preexisting heart disease; 3) avoiding coadministration of agents that increase plasma levels of the drug in question; 4) avoiding concurrent use of other medications that prolong the QT interval; and 5) identification and correction of risk factors (eg, hypokalemia) before giving a drug known to prolong the QT interval.⁸

A great deal of attention has been focused on drug-induced prolongation of the QT interval and association of the prolongation with life-threatening ventricular arrhythmias, especially torsades de pointes. Torsades de pointes, meaning twisting of points, refers to a ventricular arrhythmia in which the QRS complexes change amplitude and contour, appearing to twist around the isoelectric line on the electrocardiogram (ECG).^{5,7} In patients who develop drug-induced torsades de pointes, the QT interval measured prior to drug exposure tends to be longer than in patients who receive the drug safely.^{5,7} In patients with drug-induced torsades de pointes, ventricular repolarization is prolonged and characterized by marked prolongation of the QT interval (greater than 500 msec) and QTc interval (greater than 470 msec) of the ECG.⁷ In individuals with a drug-induced increase in the QTc interval of more than 65 msec above normal (ie, greater than 500 msec), the risk of torsades de pointes may be greater than 3%.^{3,4} This risk of torsades de pointes increases greatly when the QT interval exceeds 600 msec.¹ In the presence of a prolonged QT interval, women are at greater risk than men of developing torsades de pointes.^{2,3,5,6}

Amiodarone (eg, Cordarone)^{5,7}prolongs the QT interval but rarely causes torsades de pointes.¹However, class I antiarrhythmic agents (eg, procainamide [eg, Procanbid]) are more likely to cause torsades de pointes but have a moderate effect on the QT interval.¹ Drug interactions may further prolong the QT interval and increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.⁷Thus, administration of cisapride (eg, Propulsid), which prolongs the QT interval, with an inhibitor of cytochrome P450 (CYP) 3A4 (eg, grapefruit products, erythromycin) may increase cisapride plasma levels and the risk of life-threatening cardiac arrhythmias.⁹

Identification and correction of risk factors (eg, hypokalemia) before giving a drug known to prolong the QT interval or cause torsades de pointes are important in preventing drug-induced torsades de pointes.⁷Agents that prolong the QT interval are contraindicated in patients with a history of drug-induced torsades de pointes.⁷

Summary: Numerous drugs from a wide range of pharmacologic classes can prolong the QT interval and precipitate torsades de pointes. However, the consequences of QT interval prolongation and the occurrence of torsades de pointes can be minimized or prevented by identification and correction of risk factors. Use of drugs that prolong the QT interval is contraindicated in patients with a history of torsades de pointes.

Drugs reported to prolong the QT interval^{1, 2, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41}.

Analgesics

- Celecoxib (Celebrex)*
- Methadone (eg, Dolophine)*
 - Anesthetic agents
- Enflurane (eg, Ethrane)
- Isoflurane (eg, Forane)
- Halothane
 - Antiarrhythmic agents
- Class IA
 - Disopyramide (eg, Norpace)*
 - Procainamide (eg, Procanbid)*
 - Quinidine*
- Class IC
 - Flecainide (eg, Tambocor)^{*a}
 - Propafenone (eg, Rythmol)^{*b}
- Class III
 - Amiodarone (eg, Cordarone)^{*b}

- Bretylium*
- Dofetilide (Tikosyn)^{*b}
- Ibutilide (Corvert)^{*b}
- Sotalol (eg, Betapace)^{*b}

Anticonvulsants

- Felbamate (Felbatol)*
- Fosphenytoin (Cerebyx)
Antiemetics
- Dolasetron (Anzemet)^b
- Droperidol (eg, Inapsine)^{*b}
- Ondansetron (Zofran)
Antihistamines
- Desloratadine (Clarinex)^b (overdose)
- Diphenhydramine (eg, Benadryl)*
- Fexofenadine (Allegra)
- Hydroxyzine (eg, Vistaril)
Anti-infectives
- Amantadine (eg, Symmetrel)*
- Antimalarials
 - Mefloquine (eg, Lariam)^b
 - Quinine*
- Antivirals
 - Efavirenz (Sustiva)*
- Azole antifungal agents
 - Fluconazole (eg, Diflucan)^{*b}
 - Itraconazole (eg, Sporanox)
 - Ketoconazole (eg, Nizoral)
 - Voriconazole (Vfend)^{*b}

- Chloroquine (eg, Aralen)*
- Clindamycin (eg, Cleocin)
- Foscarnet (Foscavir)
- Macrolides and related antibiotics
 - Azithromycin (eg, Zithromax)
 - Clarithromycin (eg, Biaxin)*^b
 - Erythromycin (eg, Ery-Tab)*^b
 - Telithromycin (Ketek)^b
 - Troleandomycin
- Pentamidine (eg, Pentam 300)*
- Quinolones
 - Gatifloxacin*^b
 - Levofloxacin (eg, Levaquin)*^{a,b}
 - Moxifloxacin (eg, Avelox)^b
 - Ofloxacin (eg, Floxin)*^b
- Trimethoprim/sulfamethoxazole (eg, Bactrim)*
Antineoplastics
- Arsenic trioxide (Trisenox)*^b
- Doxorubicin (eg, Adriamycin)
- Tamoxifen (eg, Nolvadex)
Bronchodilators
- Albuterol (eg, Proventil)^b
- Formoterol (Foradil)^b
- Isoproterenol (eg, Isuprel)
- Salmeterol (Serevent)^b
- Terbutaline (eg, Brethine)^b
Calcium channel blockers
- Isradipine (DynaCirc)

- Nicardipine (eg, Cardene)
 - Contrast media
- Ionic contrast media*
- Non-ionic contrast media
 - Iohexol (Omnipaque)
 - Corticosteroids
- Prednisolone (eg, Prelone)
- Prednisone (eg, Deltasone)*
 - Diuretics
- Furosemide (eg, Lasix)
- Indapamide (eg, Lozol)
 - GI agents
- Cisapride (Propulsid)*^b
- Famotidine (eg, Pepcid)*
 - Immunosuppressants
- Tacrolimus (Protopic)*^b (postmarketing)
 - Miscellaneous
- Levomethadyl
- Moexipril/Hydrochlorothiazide (Uniretic)
- Octreotide (Sandostatin)^b
- Oxytocin (eg, Pitocin; IV bolus)
- Papaverine (eg, Pavaden TD)*
- Probucol*
- Vasopressin (eg, Pitressin)*
 - Psychotropics
- Droperidol (eg, Inapsine)*
- Haloperidol (eg, Haldol)*
- Lithium (eg, Eskalith)*
- Maprotiline*
- Phenothiazines

- Chlorpromazine (eg, Thorazine)*
- Fluphenazine (eg, Prolixin)*
- Perphenazine
- Thioridazine*^b
- Trifluoperazine
- Pimozide (Orap)*^b
- Quetiapine (Seroquel)^b
- Risperidone (Risperdal)^b (overdose)
- SSRIs
 - Citalopram (eg, Celexa)*
 - Fluoxetine (eg, Prozac)*^a
 - Paroxetine (eg, Paxil)*
 - Sertraline (Zoloft)*^{a,b} (postmarketing)
 - Venlafaxine (Effexor)^b (postmarketing)
- Trazodone (eg, Desyrel)
- Tricyclic antidepressants
 - Amitriptyline*
 - Clomipramine (eg, Anafranil)
 - Desipramine (eg, Norpramin)*
 - Doxepin (eg, Sinequan)*
 - Imipramine (eg, Tofranil)*
 - Nortriptyline (eg, Pamelor)
- Ziprasidone (Geodon)^b
 - Serotonin 5-HT₁ agonists
- Naratriptan (Amerge)
- Sumatriptan (Imitrex)^b
- Zolmitriptan (Zomig)^b

Skeletal muscle relaxants

- Tizanidine (eg, Zanaflex)^b (animals)

^c Drugs for which torsades de pointes has also been reported.^{2 7 19 23 36 42}

^a Association unclear.²³

^b QT, QTc, and/or torsades de pointes association listed in FDA approved product labeling.³⁶

Factors that increase the risk of torsades de pointes^{3 5 6 7 25 26 42 43}:

- Administration of drugs that prolong the QT interval
- Altered nutritional states (eg, anorexia nervosa, liquid protein diet)
- Baseline QTc interval greater than 460 msec
- Coadministration of certain drugs that prolong QT interval with drugs metabolized by CYP3A4
- Congenital LQT syndrome
- Female gender
- Electrolyte imbalance (eg, hypokalemia, hypomagnesemia)
- Liver disease
- Hypothyroidism
- Nervous system injury (eg, stroke, subarachnoid hemorrhage)
- Preexisting cardiac disease (eg, congestive heart failure, heart failure, ventricular hypertrophy)
- Renal disease
- Slow heart rate (ie, bradyarrhythmia)

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