

Cardiotoxicity of Methadone

Mark C. Haigney, M.D.

**Professor of Medicine and
Pharmacology**

Director of Cardiology

Edward Hebert School of Medicine

Bethesda, Maryland



Conflict of Interest

- Travel funding provided by Reckitt Benkiser
- No grants or honoraria Reckitt Benkiser or Schering-Plough
- Research funding from National Institute of Drug Abuse

Objectives

- Review the evidence that methadone is associated with excess mortality
- What is QT prolongation and why does it promote pro-arrhythmia?
- What is the evidence that methadone is associated with QT prolongation or pro-arrhythmia?
- What can be done to mitigate the risks of QT prolongation and pro-arrhythmia?

become more attuned to the need to treat chronic pain, coinvestigator Jeffrey S. Kroin, Ph.D., said

Dr. Kroin, also of the university.

Package labels for opioids caution against driving and

may not necessitate suggested.

Methadone-Related Emergency Visits and Deaths on the Rise

BY SHERRY BOSCHERT

73% of opioid-related deaths involved methadone in 2004

SAN FRANCISCO

methadone-related emergency department visits and deaths associated with the drug, according to an analysis of two national databases.

The trend is worrisome, and studies to identify the causes of methadone-related morbidity and mortality—as well as potential solutions to the problem—are critically needed, said Mario Moric, Ph.D., in a poster presentation at the annual meeting of the American Society of Anesthesiologists.

His study gathered data from the Drug Abuse Warning Network, which draws on in-hospital emergency records and coroner's data, and from the National Vital Statistics System, which provides poisoning information from death certificate data.

Records of emergency department (ED) visits from 1999 to 2005 that included mention of methadone showed an increase of 659%, accounting for 41,216 visits in 2005, according to Dr. Moric and his associates at Rush University, Chicago.

Death certificates listing methadone poisoning as the cause showed an increase from 786 deaths in 1999 to 3,849 deaths in 2004, a 390% jump that roughly paralleled a 487% rise in ED visits men-

In the past decade, methadone has become in-oxycodone, especially in its controlled-release formulation, he added.

His study also looked at ED visits and deaths related to oxycodone and to all narcotics from 1999 to 2005. ED visits mentioning oxycodone increased 566% in this period, which surprisingly was not as large as the 659% growth in methadone-associated visits, he said. In 2005, 42,810 emergency visits were associated with oxycodone.

When data on all narcotics were lumped together, ED visits mentioning any narcotic increased by 132% from 1999 to 2005. All opioid-associated deaths totalled 5,242 in 2004, compared with the 3,849 deaths in 2004 associated with methadone.

The Food and Drug Association issued an alert in 2006 about reports of deaths and respiratory depression, cardiac arrhythmias, and other life-threatening problems in patients taking methadone for chronic pain (www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.pdf).

Dr. Moric speculated that the upswing in ED visits and deaths associated with methadone may be attributed to cardiovascular issues related to methadone metabolites or to issues related to

'Dear Doctor' On Risks of B

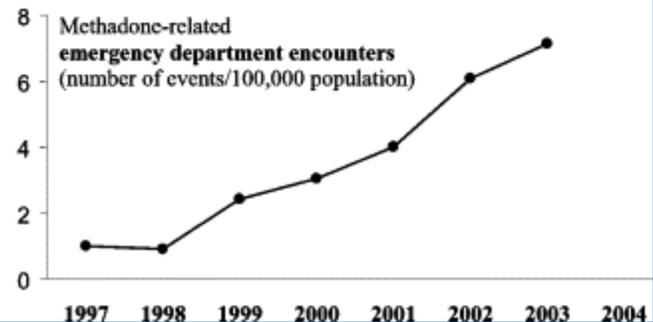
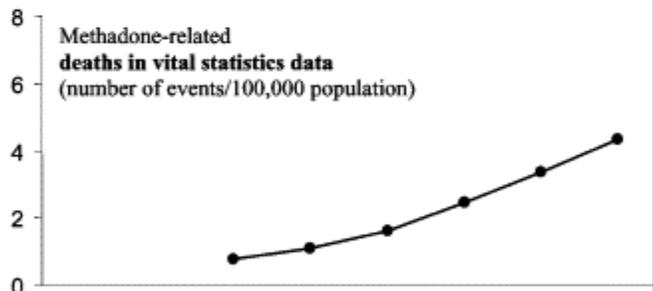
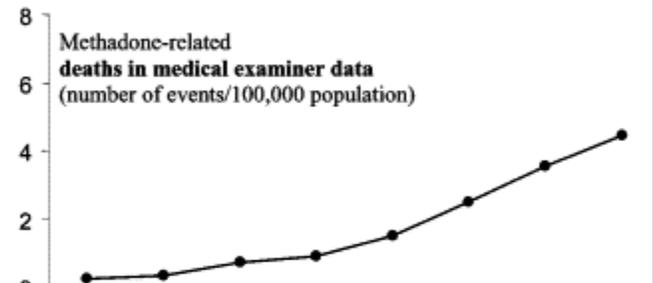
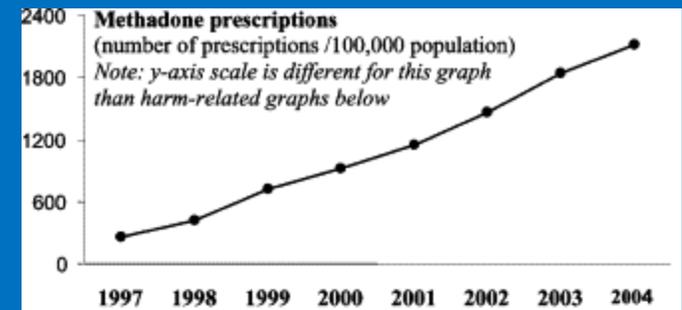
The manufacturer of the buccal formulation of fentanyl is notifying health care professionals about serious adverse events, including deaths, that have been reported in patients treated with the opioid analgesic drug, a result of improper patient selection and other factors

A "Dear Healthcare Provider" and a "Dear Doctor" letter were issued by Cephalon Inc. and posted on the Food and Drug Administration's MedWatch Web site in September. Cephalon markets fentanyl buccal tablet under the trade name Fentora, an opioid agonist that is a schedule II controlled substance. Fentora is approved only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Use in opioid-nontolerant patients is among the causes of deaths in patients treated with Fentora. In addition to improper patient selection, deaths have resulted from improper dosing and/or improper product substitution, according to the let-

Utah experience

- Prescriptions for Methadone rose 727% over 7 years
- Non-suicide deaths rose 1770 %
- “largely due to the treatment of pain”
 - Journal of Biomedical Informatics 2007



Contributory Drugs Involved in Unintentional Pharmaceutical Overdose Fatalities, West Virginia, 2006

Table 4. Contributory Drugs Involved in Unintentional Pharmaceutical Overdose Fatalities, West Virginia, 2006

Contributory Prescription Drug	Deaths, Total (%)	Prescribed, % ^a	Dispensed Within 30 d of Death, % ^b	Taken With Other Contributory Substances, %			
				Other Prescription Drugs	Illicit Drugs ^c	Alcohol	None
Opioid analgesic	275 (93.2)	44.4	29.1	63.3	16.0	13.5	21.5
Methadone	112 (40.0)	32.1	26.8	62.5	13.4	9.8	25.9
Hydrocodone	67 (22.7)	85.1	NA	83.6	9.0	11.9	7.5
Oxycodone	61 (20.7)	60.7	39.3	70.5	14.8	9.8	18.0
Morphine	46 (15.6)	21.7	15.2	54.3	28.3	28.3	21.7
Fentanyl	31 (10.5)	41.9	32.3	77.4	19.4	9.7	12.9
Other Schedule II opioid analgesic ^d	4 (1.4)	25.0	25.0	100	25.0	0	0
Other Schedule III opioid analgesic ^e	24 (8.1)	50.0	NA	91.7	8.3	8.3	0
Psychotherapeutic	144 (48.8)	54.9	NA	93.8	8.3	20.8	0.7
Diazepam	66 (22.4)	45.5	NA	92.4	7.6	19.7	0
Alprazolam	54 (18.3)	64.8	NA	100	5.6	11.1	0
Other benzodiazepine ^f	5 (1.7)	80.0	NA	100	0	20.0	0
Antidepressant ^g	49 (16.6)	71.4	NA	93.9	10.2	20.4	2.0
Other psychotherapeutic ^h	16 (5.4)	68.8	NA	93.8	0	37.5	0
Other prescription drug ⁱ	33 (11.2)	60.1	NA	97.0	9.1	12.1	3.0
All decedents	295 (100)	36.9	NA	62.4	15.9	17.3	20.7

Abbreviation: NA, not applicable.

^aFor decedents with multiple contributory drugs from a given category, percentage includes only those who had all drugs prescribed to them.

^bApplicable to 227 decedents with Schedule II drugs, which can be dispensed as no more than a 30-day supply with no refills in West Virginia. For decedents with multiple contributory drugs from a given category, percentage includes only those who had all drugs dispensed to them within 30 days of death.

^cIncludes cocaine, heroin, and methamphetamine.

^dIncludes hydromorphone and meperidine.

^eIncludes codeine, dihydrocodeine, and propoxyphene.

^fIncludes clordiazepoxide, clonazepam, and temazepam.

^gIncludes amitriptyline, bupropion, citalopram, desipramine, doxepin, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, trazodone, and venlafaxine.

^hIncludes carbamazepine, hydroxyzine, phenobarbital, quetiapine, topiramate, and zolpidem.

ⁱIncludes butalbital, carisoprodol, cyclobenzaprine, diltiazem, phenytoin, promethazine, and tramadol.

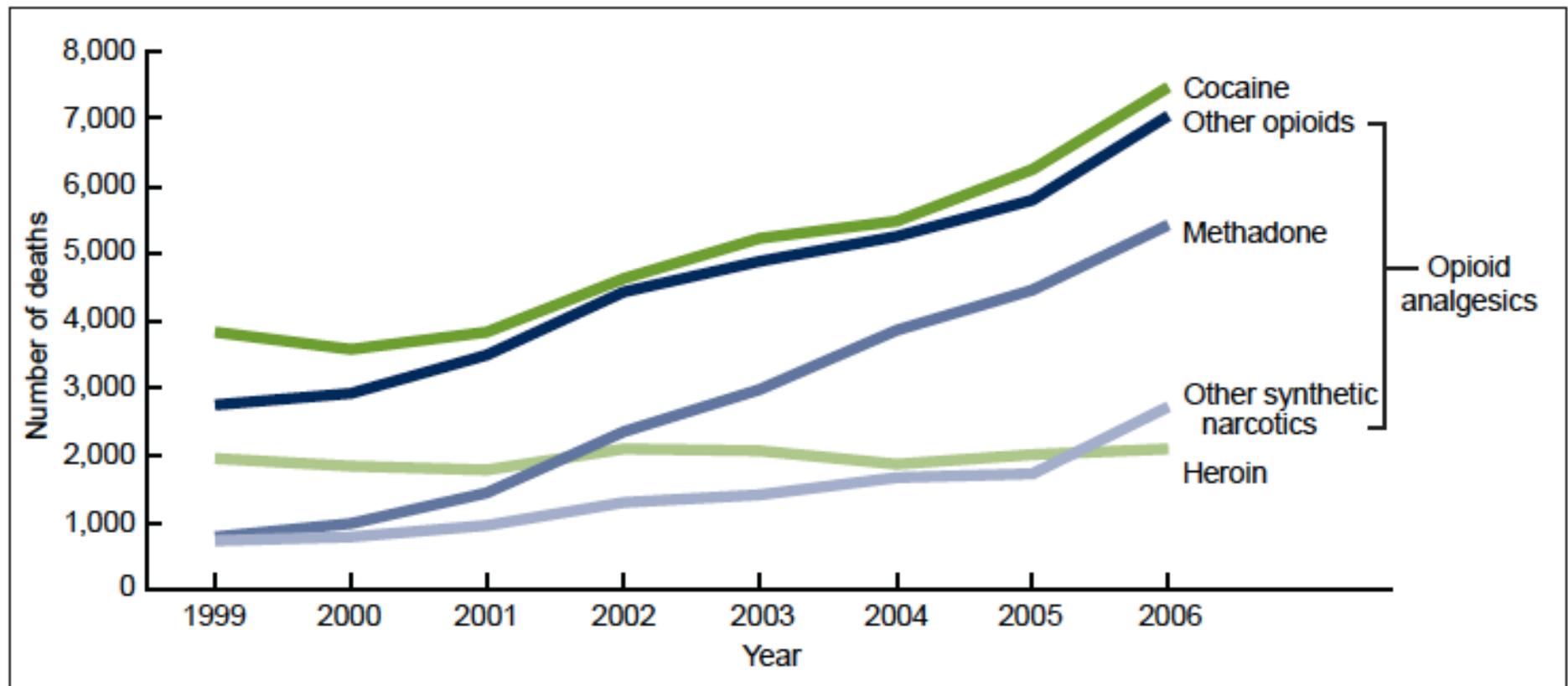
Hall, A. J. et al. JAMA 2008;300:2613-2620.

Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006

Margaret Warner, Ph.D.; Li Hui Chen, M.S., Ph.D.; and Diane M. Makuc, Dr.P.H.

From 1999 through 2006, poisoning deaths involving methadone rose more rapidly than those involving other opioid analgesics, cocaine, or heroin.

Figure 2. Poisoning deaths involving opioid analgesics, cocaine, and heroin: United States, 1999–2006



NOTES: Drug categories are not mutually exclusive. Deaths involving more than one drug category shown in this figure are counted multiple times. Access data table for Figure 2 at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/Data_Briefs/db022/fig02.xls.

SOURCE: CDC/NCHS, National Vital Statistics System.

Compared to other opiates for pain

- Adverse events of long-acting opioids in Florida state Medicaid program
- ER oxycodone safest
- Methadone highest risk for “overdose” HR 1.57; 95% CI 1.03 to 2.40 c/w ER morphine
 - Ann Pharmacother. 2007 Jun;41(6):921-8.

Sudden Death in the Community

	Cases with Methadone*	Cases without Methadone	P value*
Cardiac disease or abnormalities	5 (23%)	64 (60%)	.002
CAD	5	47	
HCM/severe LVH	0	12	
Cardiac or coronary anomaly	0	2	
Myocarditis	0	2	
Dilated cardiomyopathy	0	1	
No cardiac abnormalities	17 (77%)	42 (40%)	
Normal heart	13	28	
Unexplained isolated fibrosis	1	5	
Mild/severe LVH	0	0	

72 of 178 sudden deaths had methadone detected in their blood

	Cases with Methadone*	Cases without Methadone	P value*
Any other medication on toxicology screen	10 (45%)	31 (29%)	.14
Psychotropic medications†	1	2	
Antidepressants	6	7	
Antiseizure	0	2	
Benzodiazepines	1	2	
Opioid analgesics (non-methadone)	1	11	
Other pain medications or muscle relaxants	1	4	
Antihistamines	4	7	
Ephedrine	0	3	

LVH = left ventricular hypertrophy; CAD = significant coronary artery disease; HCM = hypertrophic cardiomyopathy.

*Pearson chi-square test, any cardiac disease or abnormality versus none, and any other medication versus none.

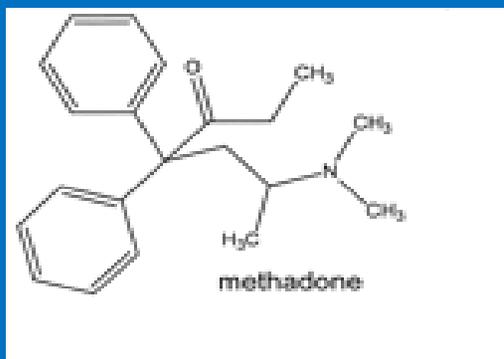
†Individual medications add to more than the "any other medication" sum because some patients took more than 1 other medication (2 cases with and 7 cases without methadone had 2 other medications in blood; 1 case with methadone had 3 other medications in blood).

*Methadone levels of 0.1-0.9 mg/L

The American Journal of Medicine (2008) 121, 66-71

Why would methadone result in sudden death?

Pharmacokinetics



μ -opiate receptor agonist 10 times more potent than morphine. Putative NMDA antagonist effective in neuropathic pain.

Methadone has $t_{1/2}$ of 22 hours (range 4.2 to 130) but analgesic $t_{1/2}$ 4-6 hours

metabolized by CYP3A4 and 2D6;
increased by cipro, fluconazole, SSRIs
carriers of *CYP2B6 allele *6* have higher levels

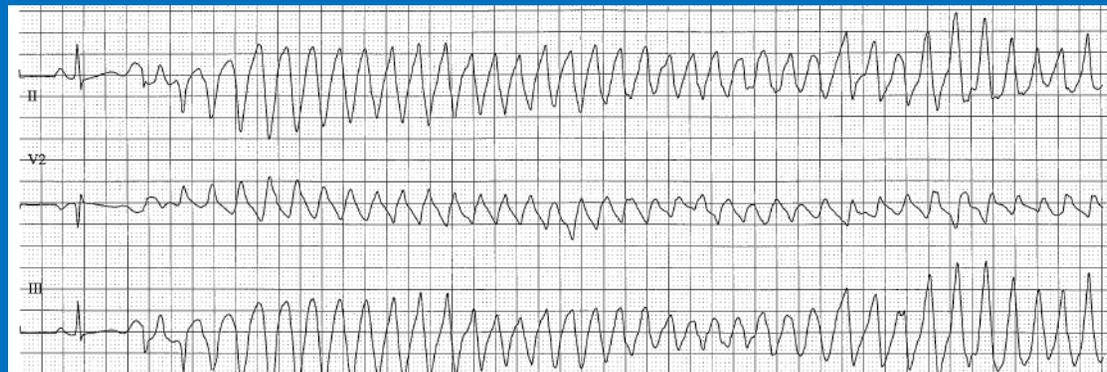
Approximately 90% protein bound but **6-fold variance** between subjects in % free

Dirt cheap.

Therapeutic drug monitoring 1997; Postgrad Med J 2004;80:654–659.

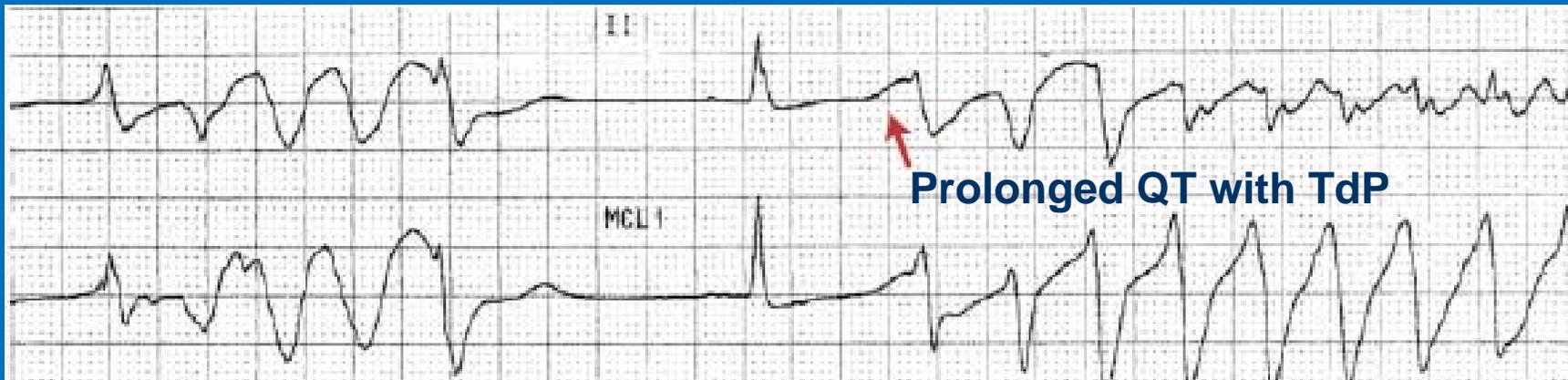
Drugs and Pro-arrhythmia

- 1990 Terfenadine found to cause QT prolongation and torsade de pointes (TdP) in presence of metabolic inhibitor
 - Monahan BP, JAMA 1990
- Enhanced FDA scrutiny of QT interval
 - surrogate for pro-arrhythmia
- QT prolongation the most common reason for removal of drug from development



Torsade de pointes

- “Polymorphic Ventricular tachycardia in the setting of QT prolongation”
- “twisting of the points”



Torsade de pointes fortuitously recorded in a 42-year-old woman with asymptomatic congenital LQTS



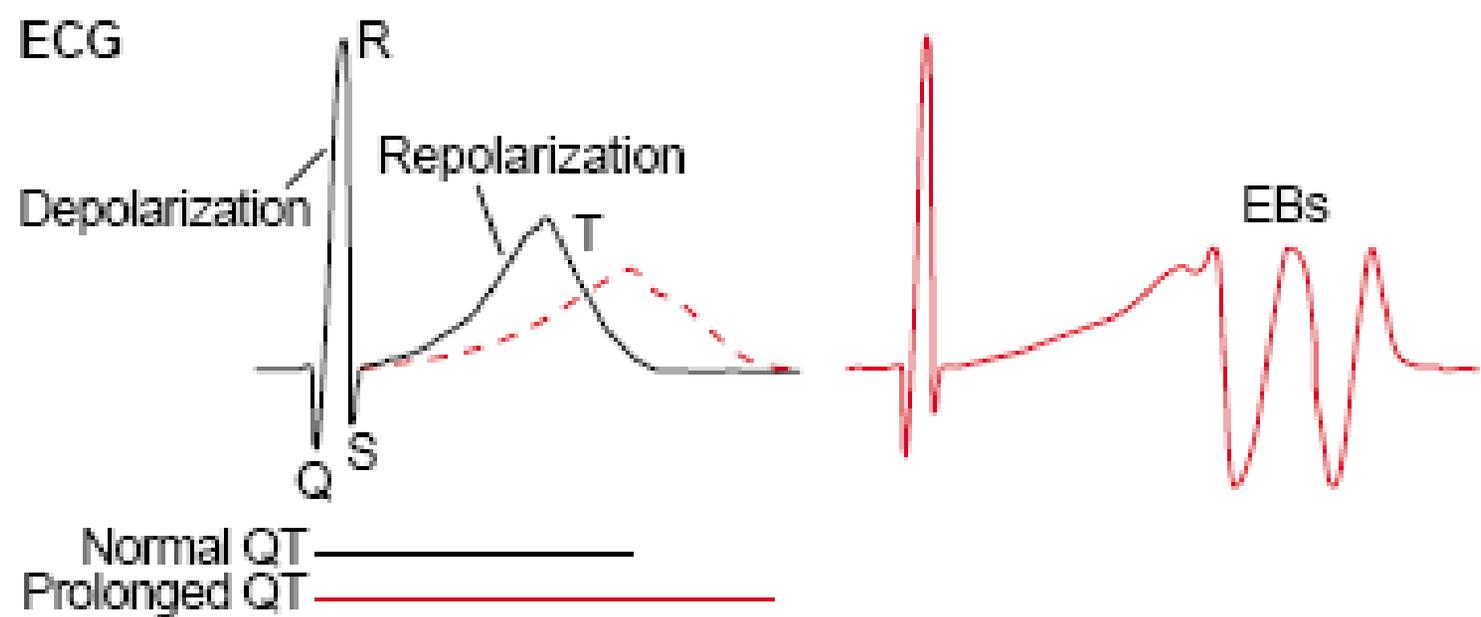
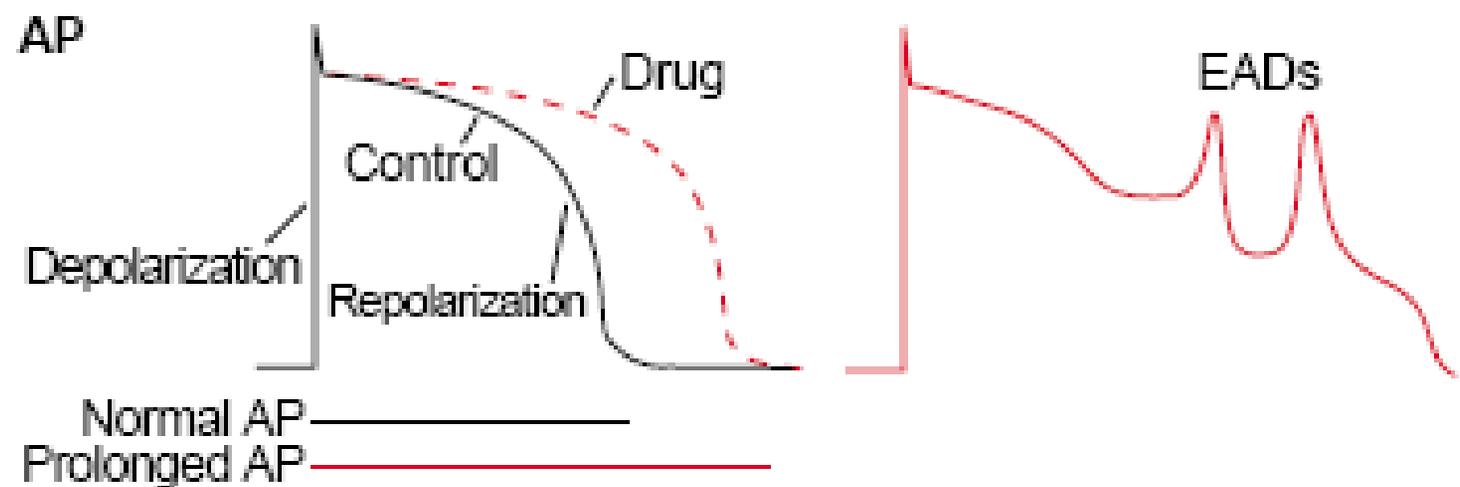
Viskin, S. et al. *Circulation* 2009;119:204-206

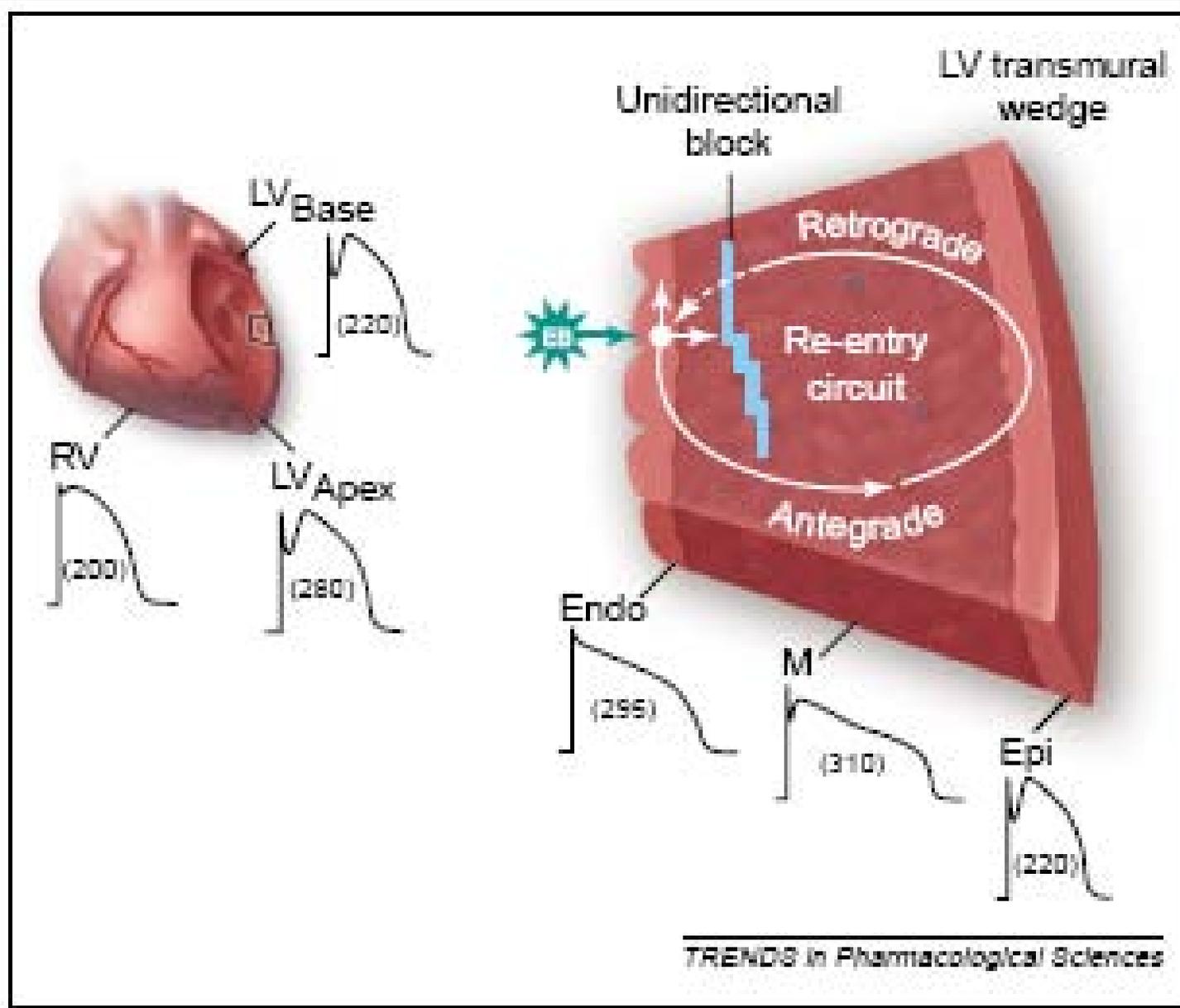
Circulation

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Learn and Live

Why do drugs that prolong the QT
cause TdP?

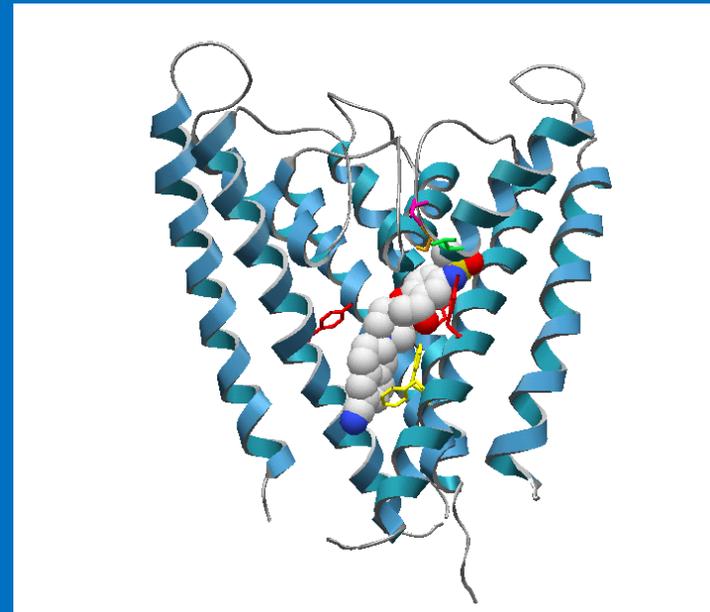




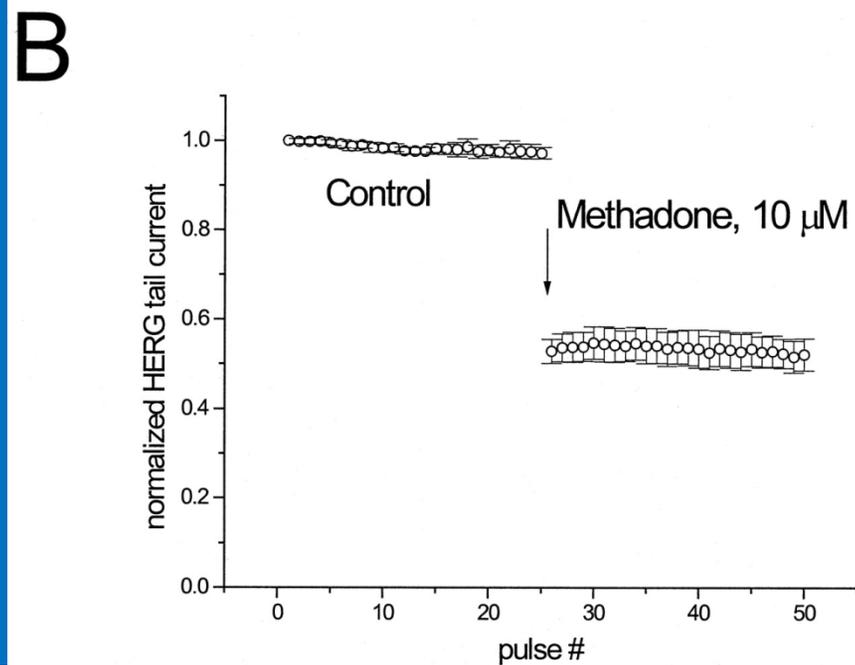
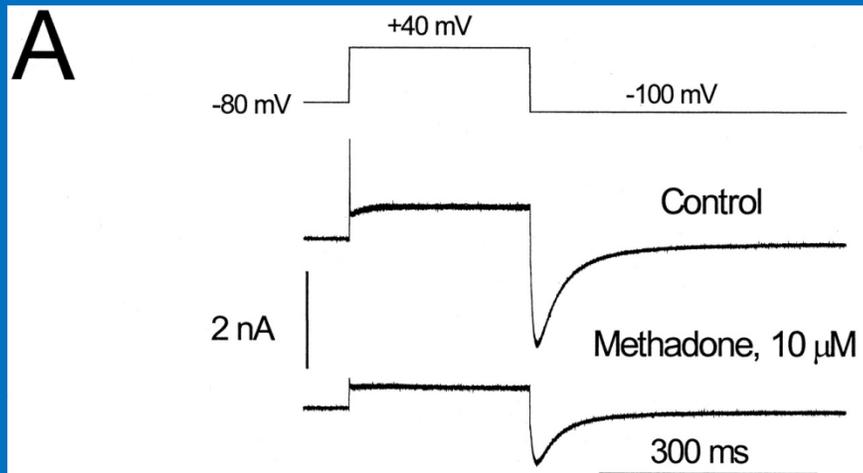
What is the evidence that
methadone prolongs the QT?

Etiology of QT prolongation and drug-induced TdP

- TdP invariably associated with blockade of the human-ether-a-go-go-related gene (hERG) associated potassium channel (I_{kr})
- cardiac action potential prolongation and QT prolongation



Blockade of IKr by methadone in HEK cells expressing human channel



Katchman, et al. *JPET* 2002; 303: 688-694)

IC₅₀ for I_hERG and C_{max} Comparison

Drug	IC ₅₀ for HERG Block	Maximum Plasma Conc. (C _{max}) ^a	Reference (C _{max})	Ratio: IC ₅₀ /C _{max}
LAAM	2.2 μM	1 μM	Henderson et al., 1977	2.2
Methadone	9.8 μM	3.6 μM	de Vos et al., 1995	2.7
EDDP	>50 μM	1 μM	de Vos et al., 1995	>50
Meperidine	75 μM	1.3 μM	Sprigge et al., 1982	58
Fentanyl	1.8 μM	30 nM	Ahonen et al., 2000	60
Buprenorphine	7.5 μM	36 nM	USP DI, 1999	208
Morphine	>1 mM	2.5 μM	Faura et al., 1996	>400
Codeine	>300 μM	0.66 μM	Band et al., 1994	>455

^a C_{max} values listed represent the upper limit of the range of values reported in the indicated references.

Katchman, et al. *JPET* 2002; 303: 688-694)

Oxycodone IC₅₀ 171 μM (or possibly ∞)

Fanoë et al. *BJCP* 2009

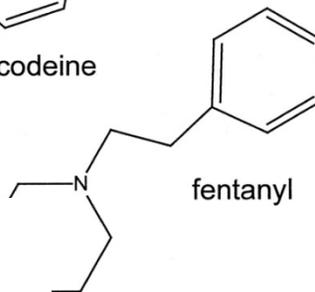
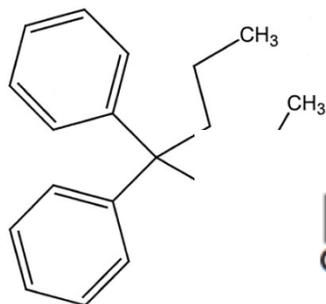
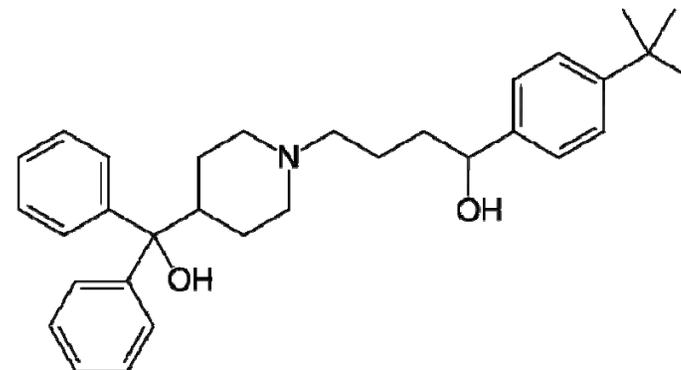
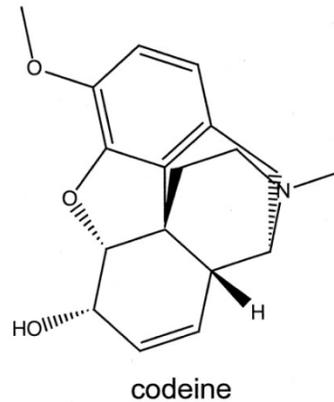
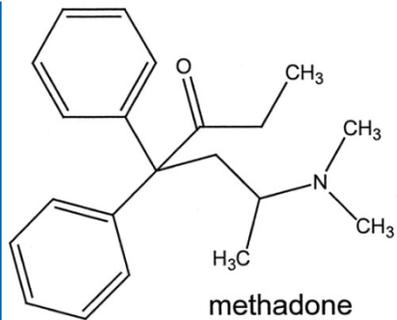
Appendix 1 Study drugs and anti-HERG activities

Drug name	1st year marketed (17)	ETCP _{un-bound} (nM)	IC ₅₀ (μM)	Ratio ^a	log ¹⁰ (ratio)	Cases	Non-cases
1. Nifedipine	1975	7.7	275	0.00003	-4.6	94	20 437
2. Nitrendipine	1985	3.02	10	0.00030	-3.5	3	610
3. Amiodarone	1962	0.5	1	0.00050	-3.3	271	10 467
4. Cetirizine	1987	56	108	0.00052	-3.3	18	5 217
5. Diphenhydramine	1946	34	30	0.00113	-2.9	37	3 296
6. Erythromycin	1952	170	72.2	0.00235	-2.6	54	12 173
7. Loratadine	1988	0.45	0.173	0.00260	-2.6	58	4 265
8. Ciprofloxacin	1987	5 281	966	0.00547	-2.3	72	14 936
9. Chlorpheniramine	1968	11	1.6	0.00688	-2.2	13	3 915
10. Amitriptyline	1961	41	4.66	0.00880	-2.1	92	7 301
11. Fluoxetine	1986	29	3.1	0.00935	-2.0	203	45 834
12. Risperidone	1993	1.81	0.15	0.0121	-1.9	143	12 254
13. Diltiazem	1973	122	10	0.0122	-1.9	145	11 282
14. Terfenadine	1982	0.29	0.02	0.0145	-1.8	200	5 162
15. Ebastine	1990	5.1	0.3	0.0170	-1.8	2	112
16. Mefloquine	1986	95.2	5.6	0.0170	-1.8	12	8 399
17.							
18.							
19.							
20. Pimozide	1969	0.43	0.015	0.0287	-1.5	22	482
21. Imipramine	1958	106	3.4	0.0312	-1.5	21	3 576
22. Tedisamil	-	80	2.5	0.0320	-1.5	0	1
23. Mibefradil	1997	12	0.35	0.0343	-1.5	95	2 370
24. Clarithromycin	1990	1 206	32.9	0.0367	-1.4	115	11 473
25. Cibenzoline	1985	976	23	0.0424	-1.4	13	214
26. Phenytoin	1938	4 360	100	0.0436	-1.4	118	14 578
27. Bepiridil	1981	33	0.6	0.0550	-1.3	59	125
28. Fexofenadine	1996	345	5	0.0690	-1.2	24	2 224
29. Grepafloxacin	1997	2 087	27	0.0773	-1.1	6	287
30. Desipramine	1962	108	1.39	0.0777	-1.1	41	2 111
31. Ketoconazole	1981	177	1.9	0.0932	-1.0	9	4 734
32. Sertindole	1996	1.59	0.014	0.114	-0.9	20	266
33. Erythromycin i.v.	1952	8 516	72.2	0.118	-0.9	75	1 671
34. Domperidone	1978	19	0.16	0.119	-0.9	12	1 216
35. Haloperidol	1959	3.6	0.027	0.133	-0.9	247	7 864
36. Procainamide	1950	54 186	310	0.175	-0.8	101	2 652
37. Sematilide	-	4 449	25	0.178	-0.7	0	0
38. Flecaïnide	1982	753	3.91	0.193	-0.7	332	1 894
39. Sotalol	1974	14 733	74	0.199	-0.7	337	1 477
40. Astemizole	1983	0.26	0.0009	0.289	-0.5	68	1 974
41. Dofetilide	1999	2	0.005	0.400	-0.4	68	676
42. Disopyramide	1969	742	1.8	0.412	-0.4	110	1 843
43. Terfenadine & CYP3A4-inhibitor	1982	9	0.02	0.450	-0.3	60	264
44. Propafenone	1979	241	0.44	0.548	-0.3	97	1 146
45. Verapamil	1963	81	0.14	0.579	-0.2	332	10 788
46. Azimilide	1999	70	0.1	0.700	-0.2	0	0
47. Aprindine	1973	239	0.23	1.04	0.0	1	164
48. Cisapride	1988	4.9	0.002	2.45	0.4	596	6 278
49. Almokalant	-	150	0.05	3.00	0.5	0	0
50. Terodiline	1986	12	0.004	3.00	0.5	66	1 160
51. Sparfloxacin	1993	1 766	0.23	7.68	0.9	10	420
52. Quinidine	1918	3 237	0.3	10.8	1.0	181	3 399
53. Ibutilide	1996	140	0.01	14.0	1.1	154	27
54. Thioridazine	1958	979	0.033	29.7	1.5	152	3 520
>1 drug						421	4 581
Total						5 591	278 835

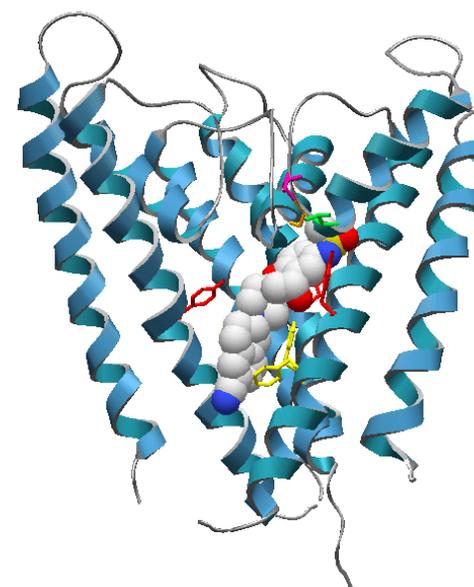
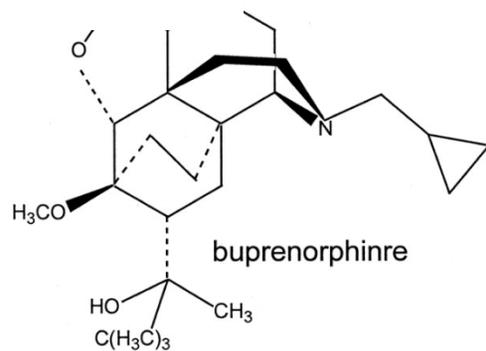
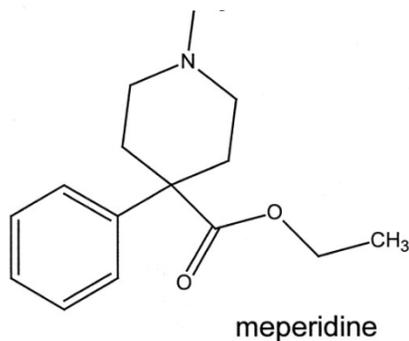
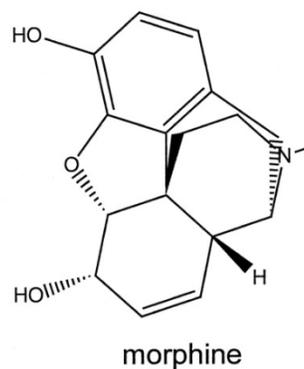
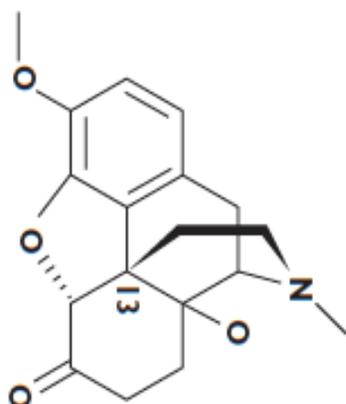
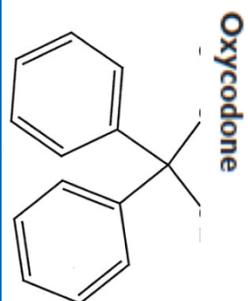
^aETCP_{unbound}/IC₅₀

Methadone Ratio ETCP/IC₅₀ 0.04-0.22

De Bruin EHJ 2005



Terfenadine and evil bi-phenyl structure



Drug Induced QT prolongation and TdP

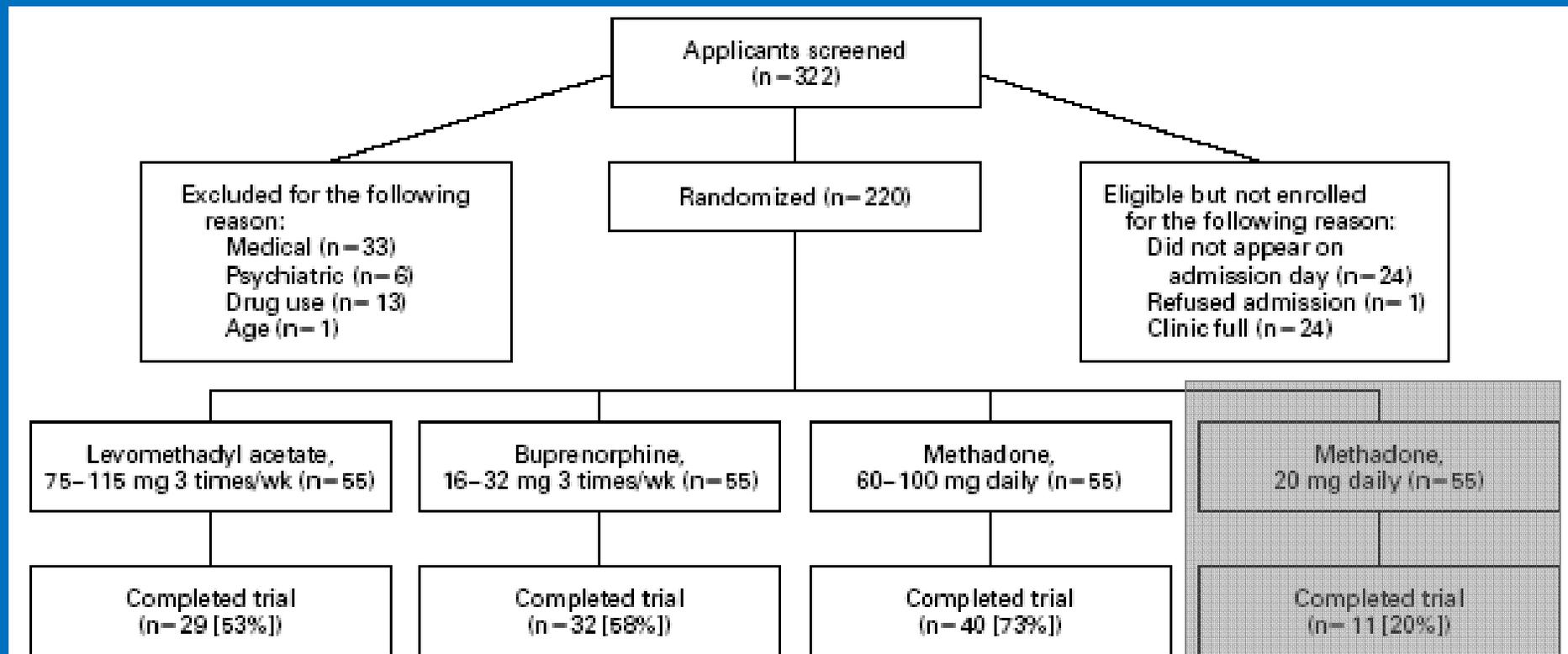
- Induction of TdP is multifactorial
- hERG blocking drug *plus*
 - **hERG mutation (0.1-1% of population)**
 - Pre-existing QTc >450 ms associated with SCD
 - Electrolyte disturbances- **↓ K⁺, ↓ Mg²⁺**
 - Female gender
 - Inhibition of drug metabolism (CYP3A4 and 2B6)
 - Cardiac Ischemia
 - Congestive heart failure
 - Liver disease- e.g. cirrhosis
 - Anorexia Nervosa

In vivo evidence for QT prolongation due to methadone

- 26 case reports or series reporting QTc prolongation
- 1 RCT

Prospective Randomized Data

- 220 individuals in 17 week RCT comparing LAAM, Methadone and Buprenorphine
 - Johnson, et al. *NEJM* 2002:
 - Low dose Methadone group- not included due to 80% attrition rate



Results-Group Analysis

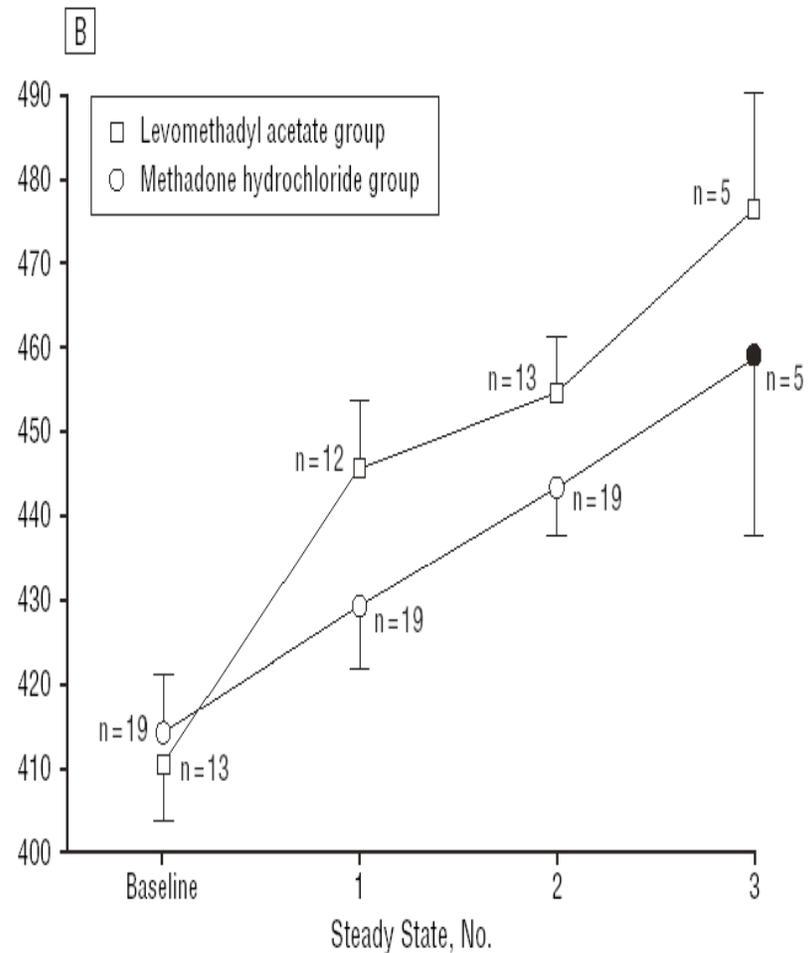
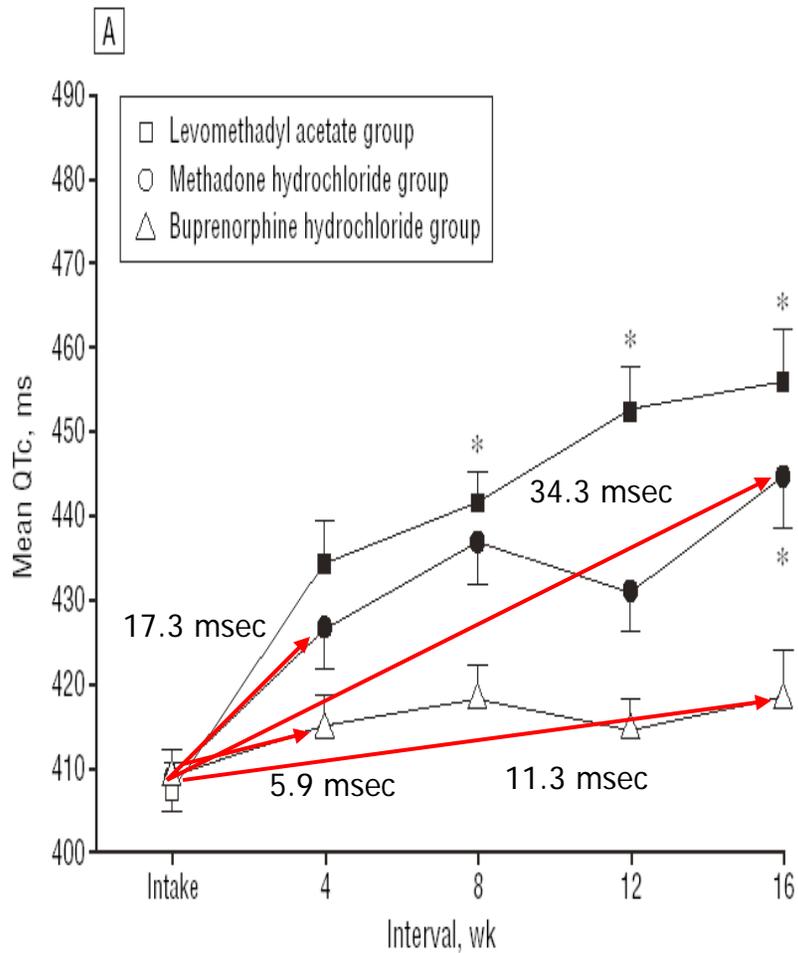
- Odds ratio for reaching pre-specified criteria of $>470/490$ msec^{1/2} (normal pre-drug QTc)

	<u>OR</u>	<u>95% CI</u>	<u>p-value</u>
LAAM vs. Methadone:	1.81	0.76 – 4.34	0.182
LAAM vs. Buprenorphine:	24.53	3.16 – 190.28	0.002
Methadone vs. Buprenorphine:	13.55	1.77 – 103.91	0.012

- mean QTc change ≥ 200 msec

- 12% of Methadone group
- 2% of Buprenorphine group
- O.R. 8.4 (95% CI 1.9-36.4, $p < .001$)

Unexpected Findings



RED FLAG

- 6 of 52 patients (11.5%) with a QTc >500
- 0% in Buprenorphine
 - QTc >500 associated with 4-fold risk for SCD in LQTS Registry compared to QTc 450

Relationship between QTc and TdP with d-Sotalol

On-Therapy QTc (ms)	Incidence of TdP	Change Baseline (ms)	Incidence of TdP
<500	1.3%(1787)	<65	1.6% (1516)
500-525	3.4%(236)	65-80	3.2% (158)
525-550	5.6%(125)	80-100	4.1% (146)
>550	10.8%(157)	100-130	5.2% (115)
() # patients assessed		>130	7.1% (99)

From BETAPACE®(sotalol hydrochloride) Package Insert- Berlex Laboratories 2001

What is the evidence that
methadone causes TdP?

In vivo evidence for TdP due to methadone

- 15 case reports or series reporting TdP
 - 17 episodes of TdP in high dose methadone
 - Krantz *Annals of Intern Med* 2002
 - FDA MedWatch system, 43 cases of torsade de pointes associated with methadone; 8% were fatal and most involved doses of methadone exceeding 100 mg/day.
 - Pearson & Woosley *Pharmacoepidemiol Drug Saf.* 2005
 - One series showing recurrent TdP after re-challenge in patients with implanted defibrillators
 - Patel *Am J Cardiol*, 2008

ICD implant for methadone-induced TdP and continued methadone Rx

Patient	Age (yrs)/ Gender	Methadone Dose (mg)	Continuing Methadone Therapy	QTc Interval (ms) at Baseline	QTc Interval (ms) on Methadone	EF (%)	Type of ICD	Follow-Up (mo)	ICD Firings	Hospitalizations	Alive
1	40/F	260	0	450	660	68	Single	23	0	0	+
2	43/F	200	+	392	680	63	Single	15	0	0	+
3	46/F	92.5	+	460	540	75	Dual	48	5	4	+
4	Three of six had QTc of 450 or greater prior to methadone										
5	51/F	70	+	N/A	643	39	Dual	15	0	0	+
6	51/M	200	+	420	510	60	Dual	90	2	2	+
7	53/M	600	+	427	540	50	Dual	7	2	2	+
8	55/M	90	+	N/A	690	61	Dual	12	0	0	0

EF = ejection fraction; N/A = not available.

Other contributory toxic effects

- Methadone associated with sleep apnea
 - 30% had central sleep apnea vs 0% BMI matched controls
 - Higher waking PaCO₂
 - Wang Chest 2005
- Sleep apnea associated with significant QT prolongation
 - Gillis Sleep 1991

Increased Risk for Mortality

- Disproportionate incidence during first 14 days or in subjects not prescribed methadone
 - Caplehorn *Drug Alcohol Rev* 1998;17,9-17
 - http://www.dpt.samhsa.gov/medications/methadone_mortality2003/methadone_mortality-13.aspx
- May represent increased respiratory suppression and/or
- TdP more common in early Rx with AAD due to lack of induced, compensatory IKs
 - Roden *Circ* 2007

Increased Risk for Mortality

- Benzodiazepines frequently found in blood
 - Increased respiratory depression and/or
 - Benzodiazepines block IKs, may reduce repolarization reserve and trigger greater QT prolongation during stress or if the QT is prolonged
 - Seebohm Molecular Pharm 2003

Prevention of Torsade de Pointes in Hospital Settings

A Scientific Statement From the American Heart Association
and the American College of Cardiology Foundation

3. The risk-benefit ratio should be assessed for each individual to determine whether the potential therapeutic benefit of a drug outweighs the risk for TdP.
4. After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include an increase in QT_c from predrug baseline of 60 ms, marked QT_c interval prolongation >500 ms, T-U wave distortion that becomes more exaggerated in the beat after a pause, visible (macroscopic) T-wave alternans, new-onset ventricular ectopy, couplets and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.

Summary

- Methadone is increasingly prescribed for chronic pain
- Mortality rising out of proportion to prescriptions
 - Uniquely potent hERG blocker
 - Undeniable proarrhythmic effect
- Buprenorphine, ER oxycodone, and ER morphine have few QT consequences and appear to have less morbidity

Consensus Recommendations

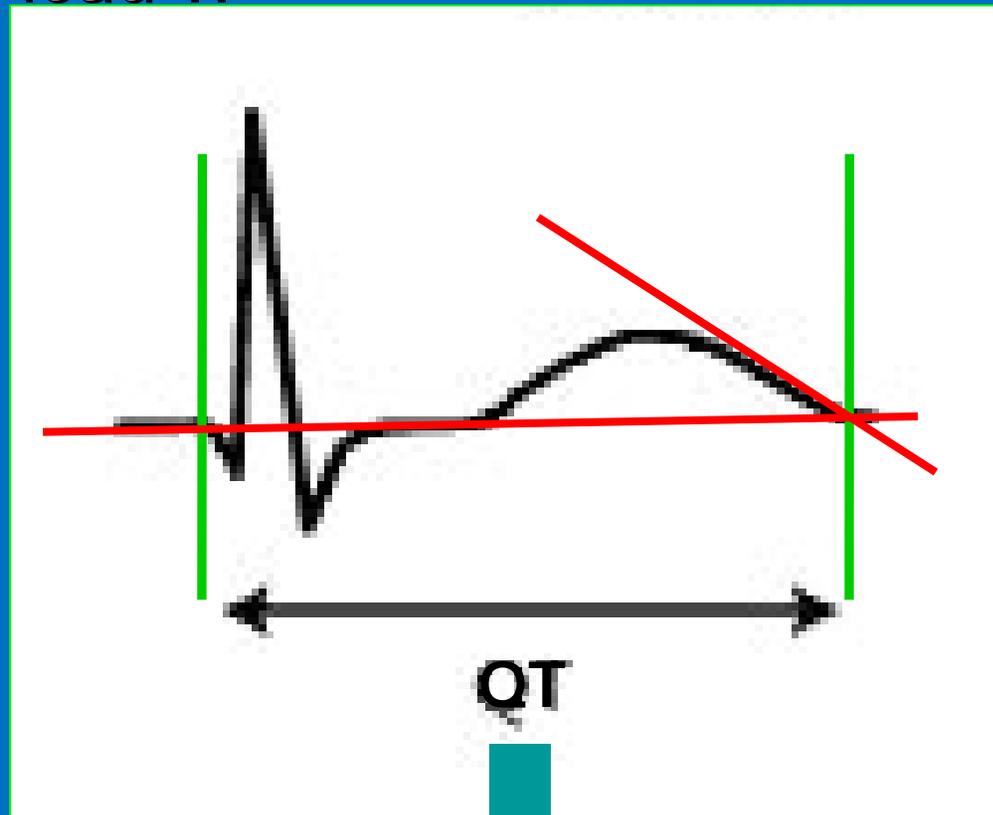
- Check baseline QTc prior to therapy; discuss history of cardiac disease
- If QTc <450, induce after discussion
- Repeat QTc at one month, or if dose >100 mg/day
- QTc >500, consider dose reduction, alternative therapy
- Avoid hypokalemia, drugs that block CYP3A4, drugs that prolong QTc
 - <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>
- Syncope merits consideration of cardiology consultation

What would I do?

- Do not exceed doses >100 mg/day
- AVOID benzodiazepines
- CONSIDER the possibility that methadone may exacerbate untreated sleep apnea

Measuring the QT

- QT interval describes the duration of depolarization and repolarization
- Limb lead II



$$QTc = QT / \sqrt{RR}$$

QT Interval Normal Ranges

Suggested QTc Values for Diagnosing QT Prolongation

QTc Values (msec) By Gender

	Men	Women
Normal	<430	<450
Prolonged (top 1%)	>450	>470
Study Criteria	>470	>490

QTc = QT/ \sqrt{RR} ; Adapted from Moss, A J. Am J Cardiol 1993; 72:23B-25B

From the Long QT Syndrome (LQTS) Registry

Questions ?