

Emerging practices in pain and chemical dependency

Breakout session:
Methadone: cardiac toxicity

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Disclosure

- Speaker Board for:
 - Pfizer
 - Merck
 - Endo
 - Lilly
- Grant support
Orthopharma
- Other support
Grupo Ferrer (Spain)

History of methadone

- Developed in the 1930's in Germany as an alternative to morphine during WWII
- Was not widely utilized due to high incidence of side effects
- Spoil of war
- Rights purchased by Ely Lilly for \$1
- In 1947 approved in the US as analgesic and antitussive
- First known as “Dolphine”
 - “Dolor” = pain
 - “fin” = end
- Was widely used in the 40's and 50's. Several deaths reported in children/adults and fell into disuse in the 60's
- Track record of safety in the last 40 years
- Utilized as replacement therapy in heroin addicts in the 60's
- Increased use as analgesic in the last 10-15 years

What makes methadone different

- **Methadone has unique characteristics**
 - Variable half life (15-150 h)
 - Lipophilicity (tends to accumulate)
 - Hepatic metabolism (CYP 3A4 & 2D6, possible drug-drug interaction)
 - In the animal model shown to block N- methyl D-aspartate (NMDA) receptors and decrease tolerance to morphine and hyperalgesia
 - Reduce dose when switching to another opioid (cross-tolerance)
 - Cardiotoxicity?

Methadone

Other features of clinical relevance

- Unlike morphine there are no **hepatic** metabolites
- No dose adjustment is needed in patients with renal failure since there are no active metabolites
- Methadone is available in tablets, liquid and injectable forms. Parenteral routes include intravenous (i.v.) bolus dosing or continuous infusion

Oral Morphine to Methadone Conversion Ratios – One step approach using the following ratios

Morphine dose

30 - 90mg/24hr

91 – 300mg/24hr

>300mg/24hr

Morphine to methadone ratio

4:1

9:1

12:1

(Ripamonti et al. '98; Mercadante
et al. 99)

Public Health Advisory

- The FDA issued a public health advisory in November 2006 to provide patients and their caregivers and health care professionals with safety information to prevent serious complications from methadone use. The advisory stated: “Prescribing methadone is complex. Methadone should only be prescribed for patients with moderate to severe pain when their pain is not improved with other non-narcotic pain relievers. Pain relief from methadone lasts about 4 to 8 hours. However, methadone stays in the body

Public Health Advisory (continued)

- Much longer, from 8 to 59 hours after it is taken. As a result patients may feel the need for more pain relief before methadone is gone from the body. **Methadone may build up in the body to a toxic level if it is taken too often**, if the amount taken is too high, or if it is taken with certain other medications or supplements.”

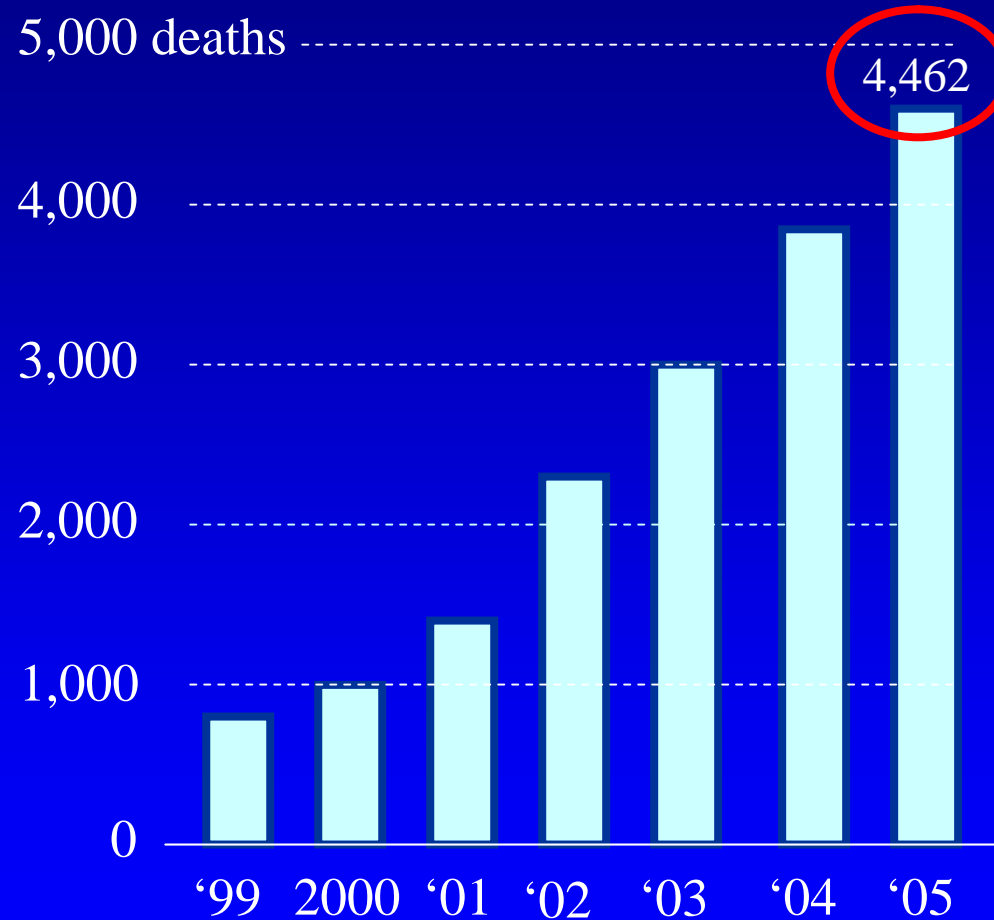
Why is Risk Assessment So Important?

Increasing Deaths From Opioid Analgesics

	1999	2002	% change
Opioid Analgesics	1942	4451	+129.2
Cocaine	2215	2569	+16.0
Heroin	858	1061	+23.7

Adapted from: Paulozzi LJ et al. *Pharmacoepidemiol Drug Safety*. 2006;15(9):618-627.

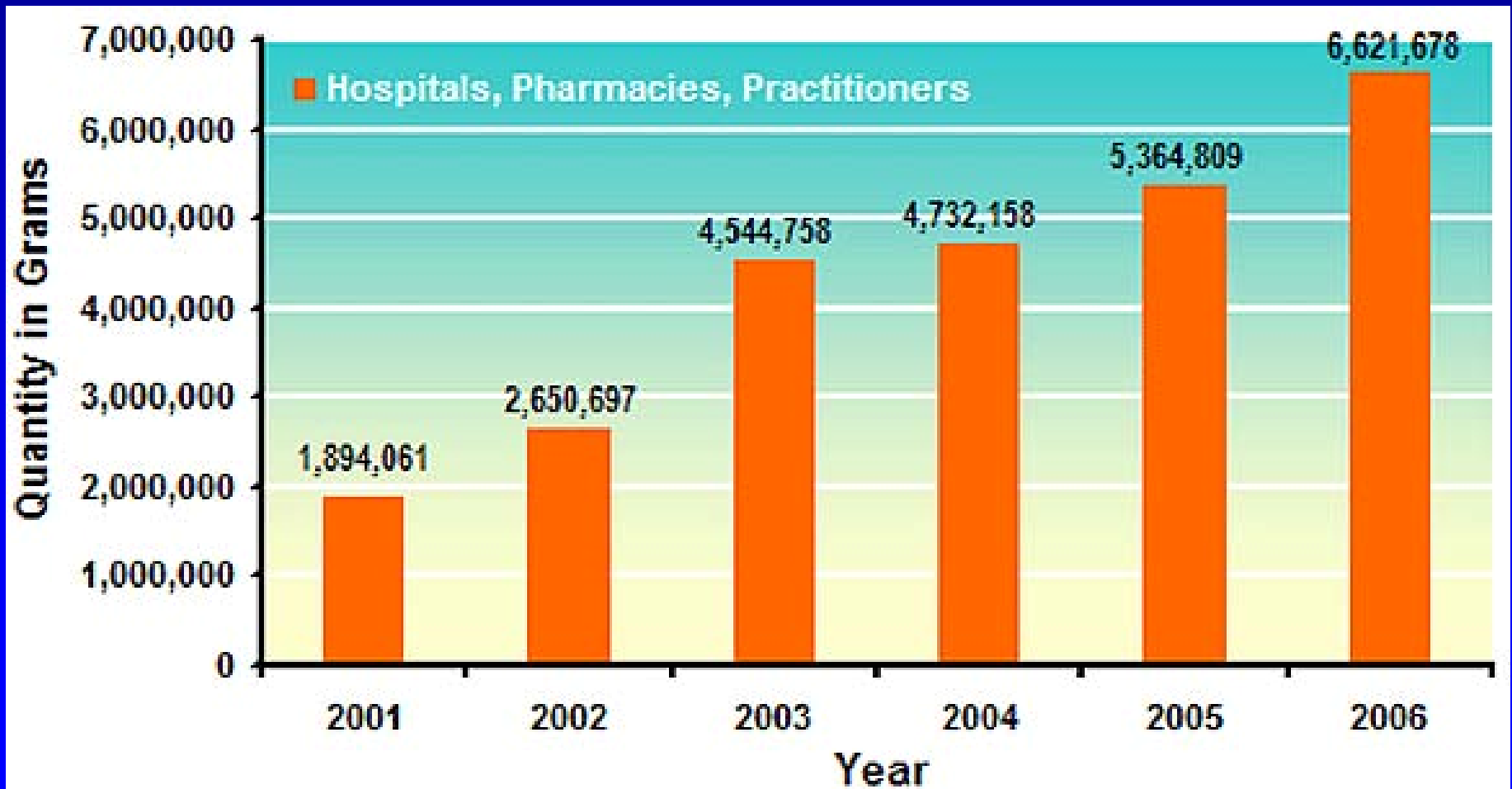
Methadone related deaths



Source: National Center for Health Statistics

Increases in legitimate distribution of methadone to hospitals, pharmacies, and practitioners, 2001-2006

(<http://www.usdoj.gov/ndic/pubs25/25930/index.htm>)

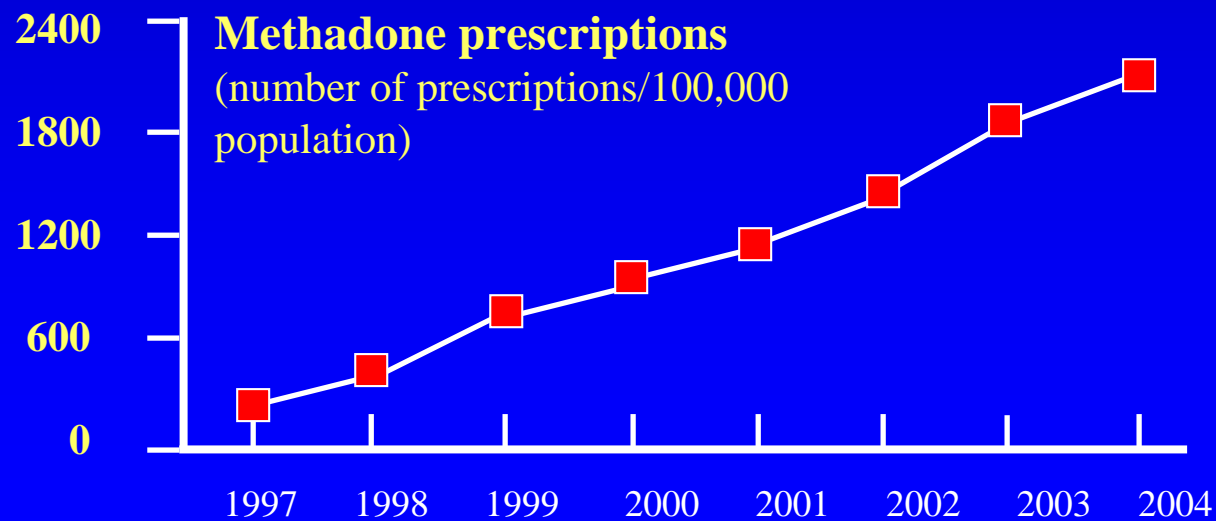
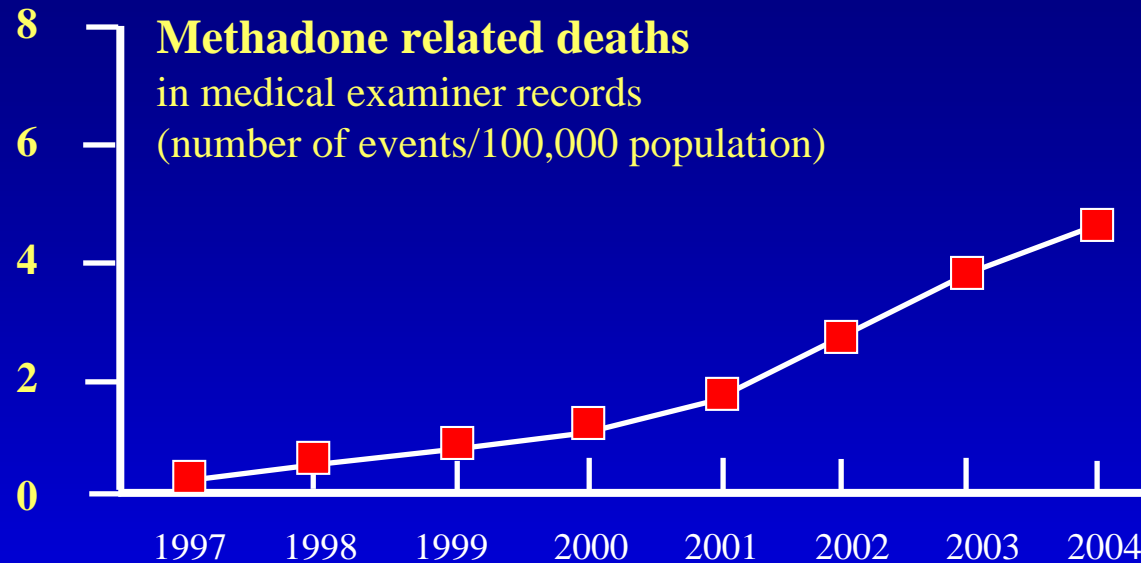


Legitimate Distribution of Methadone to Businesses (in Grams) and Percent of Change, 2001-2006

(<http://www.usdoj.gov/ndic/pubs25/25930/index.htm>)

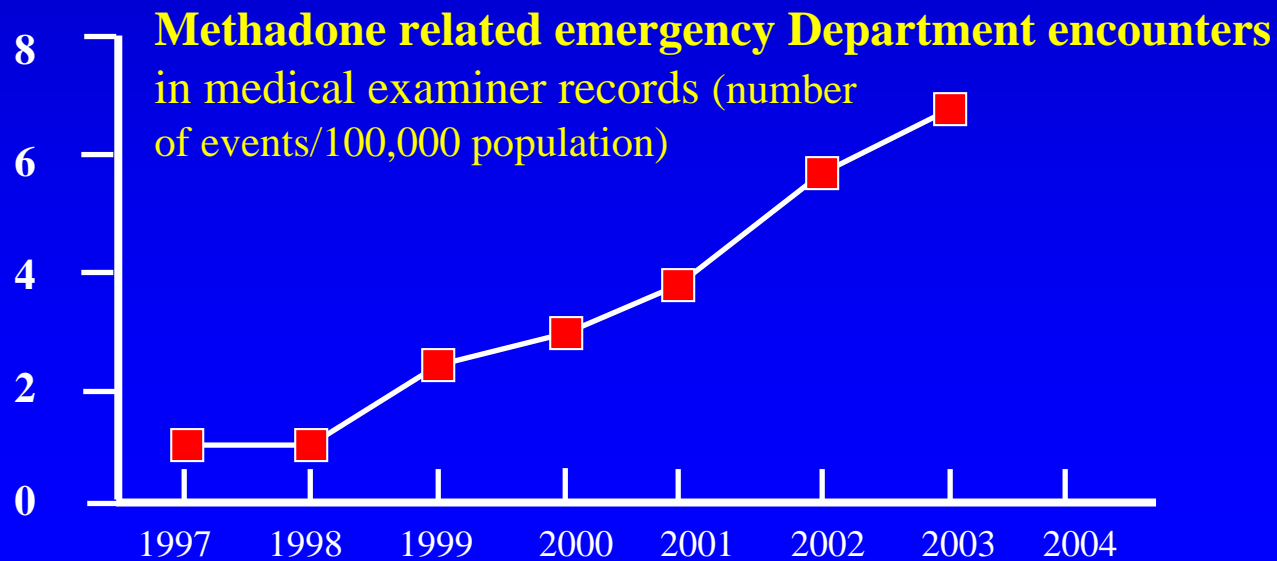
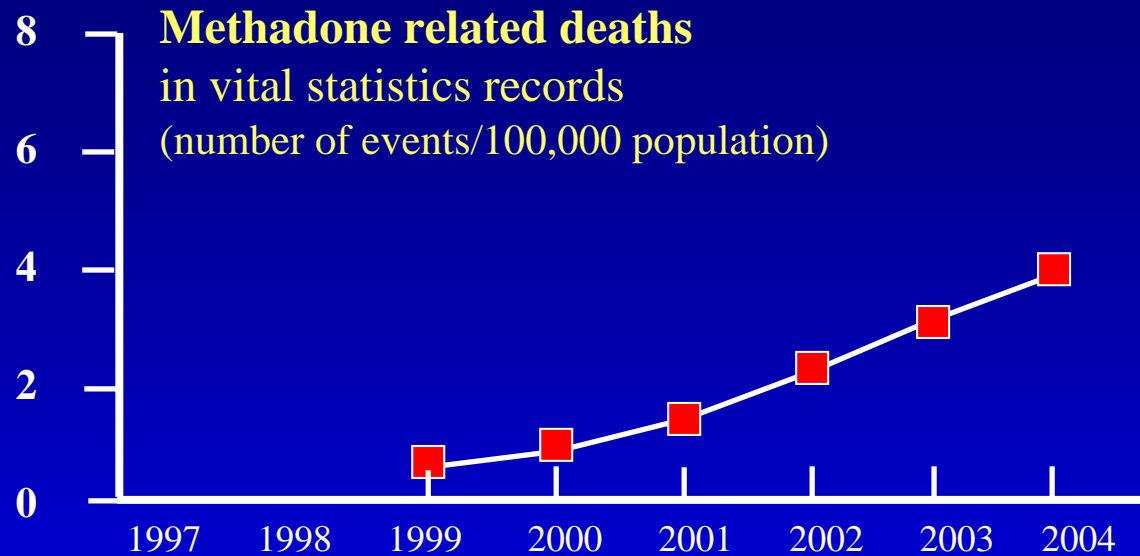
Year	Practitioners	Pharmacies	Hospitals
2001	6,260	1,660,432	225,368
2002	10,381	2,328,287	310,027
2003	15,113	3,274,059	393,957
2004	35,466	4,228,660	466,028
2005	43,199	4,810,467	509,138
2006	51,046	5,986,488	584,144
Percent of Change 2001-2006	715	261	159

Surveillance of methadone-related adverse drug events using multiple public health data sources



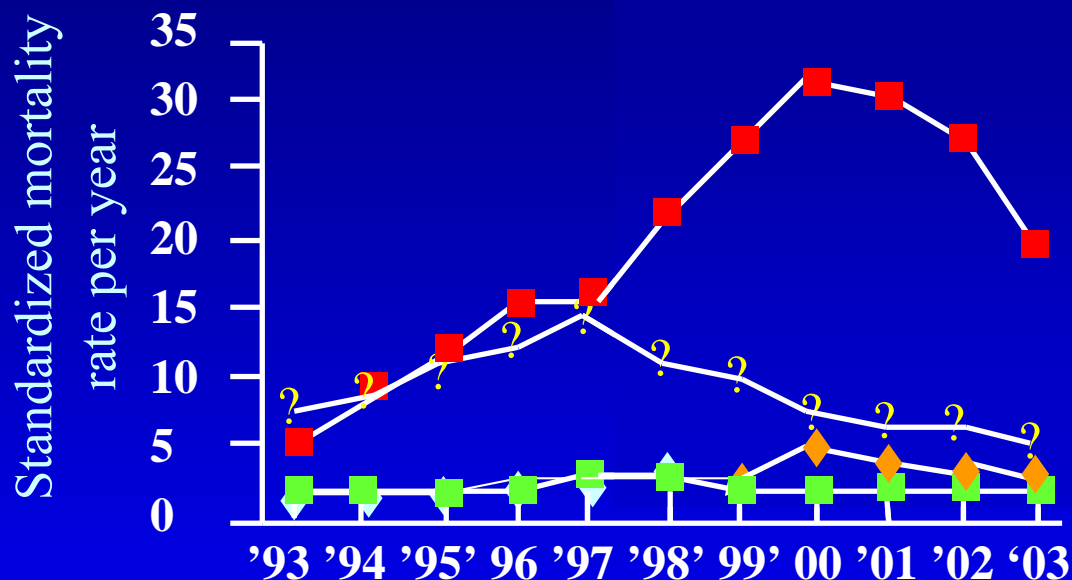
Sims et al., J Biomed Inform 2007 (modified)

Surveillance of methadone-related adverse drug events using multiple public health data sources



Sims et al., J Biomed Inform 2007 (modified)

Decrease in Methadone Deaths in England and Wales 1997-2003



? Methadone male

■ Methadone female

■ Heroin/Morphine male

◆ Heroine/Morphine female

Morgan OW., J Pub Health, 2006 (modified)

What are the underlying mechanisms that may lead to increased deaths?

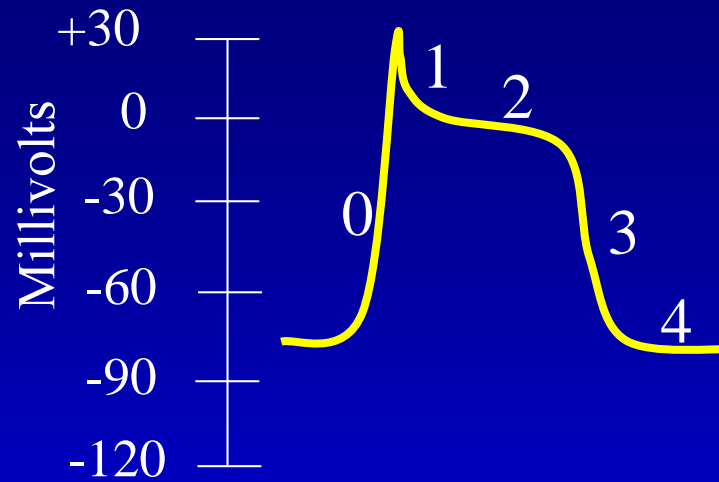
- QTc prolongation (Ventricular arrhythmia, Torsades de Pointes)?
- Syncope?
- What to do?
- Sleep Apnea?

Electrocardiographic Alterations in Multiple Drug Abusers

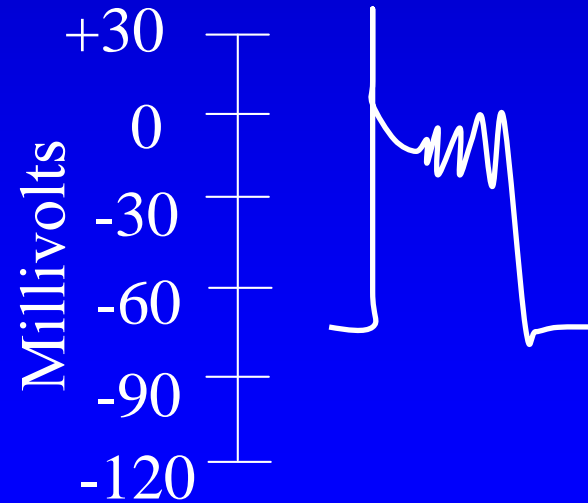
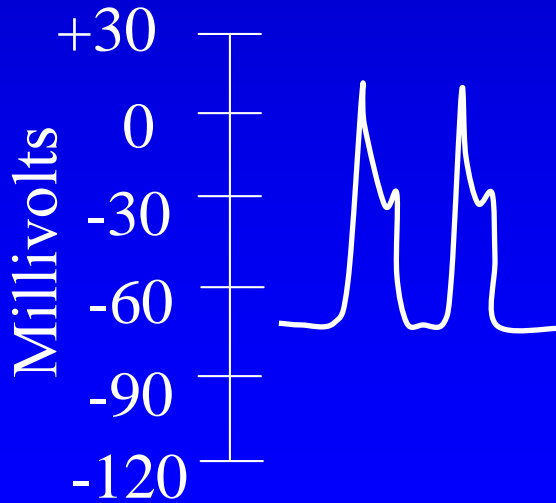
• Repolarization abnormalities	N	%
1. QTc prolongation	14	(34)
2. Prominent U wave	13	(31)
3. Abnormal T waves	12	(29)
• Arrhythmias		
1. Bradyarrhythmias	13	(31)
2. Premature Systoles	3	(7)
• Conduction Defects		
1. First Degree Heart Block	2	(4)
2. Abnormal Left axis deviation	2	(4)

Stimmel et al., 1973

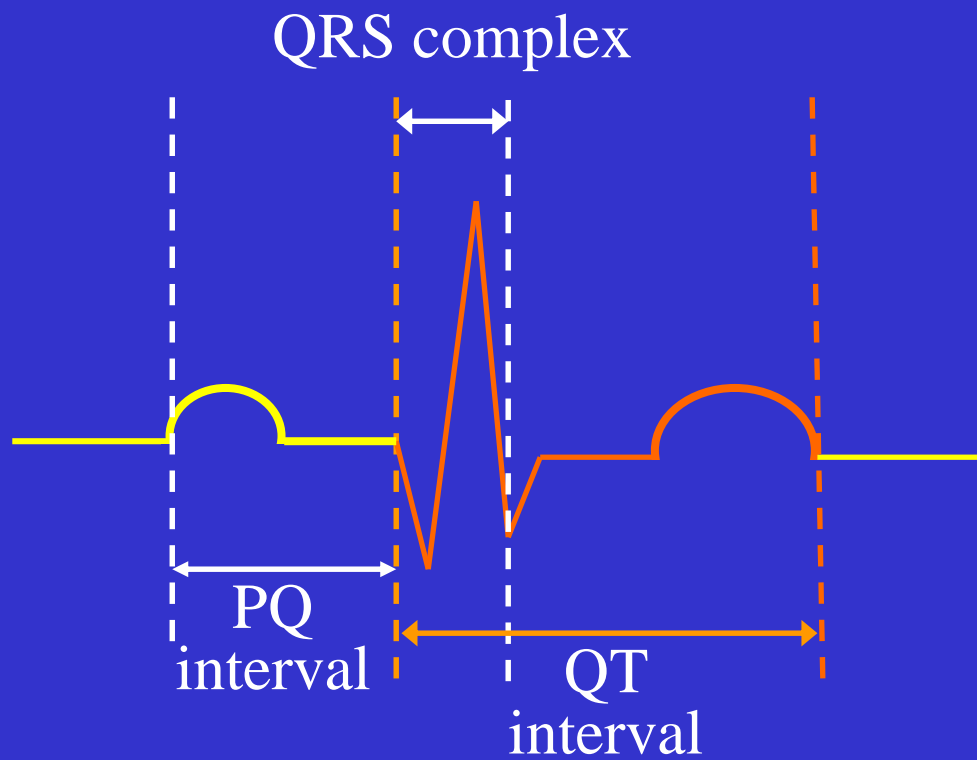
Action Potential



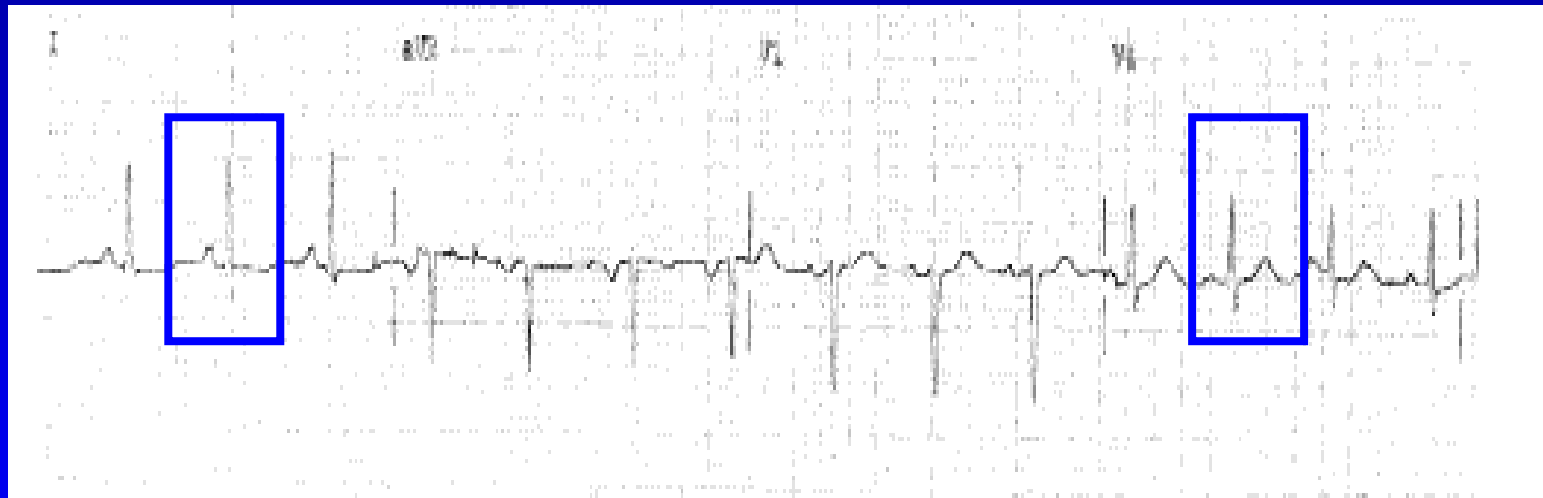
Action Potential



Schematic representation of an ECG

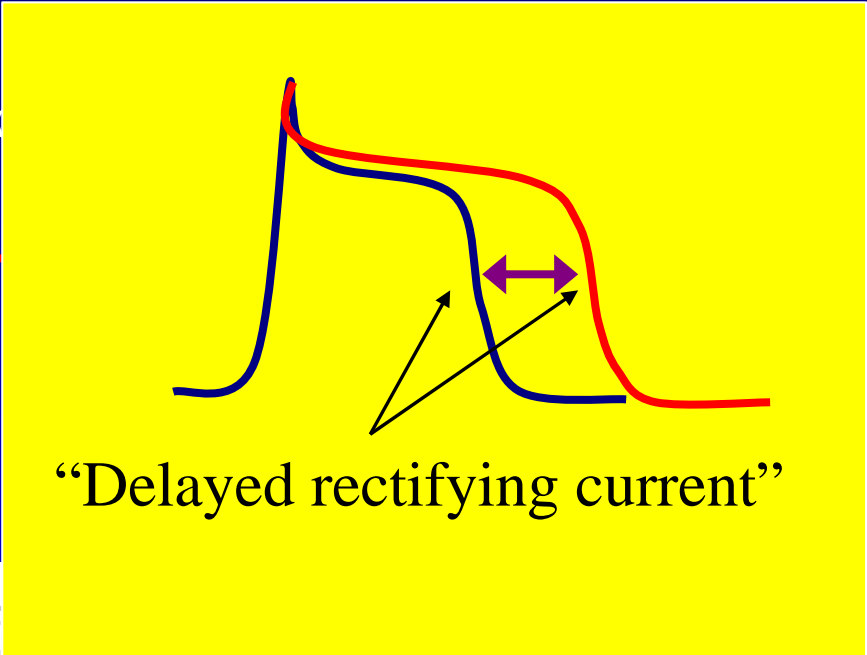


Normal sinus rhythm with normal QTc interval

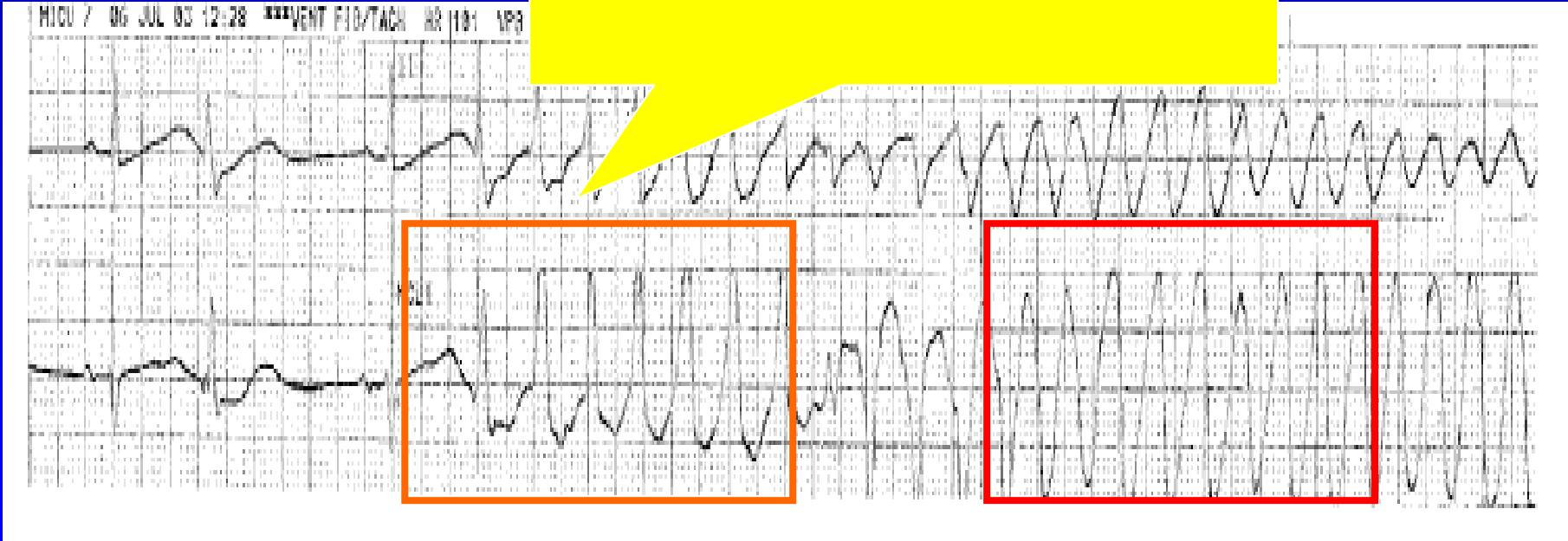


A telemetry strip in

intes (TdP)

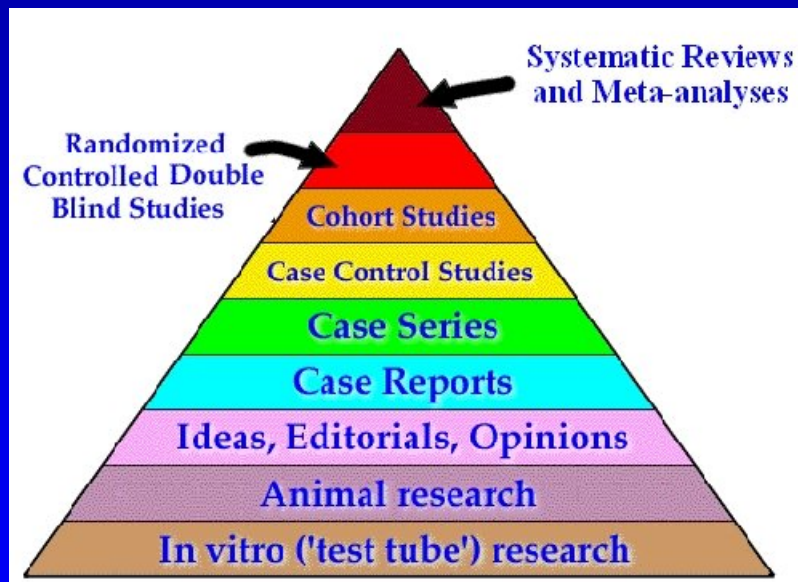


“Delayed rectifying current”



What is the evidence?

The Evidence Pyramid



- Systematic reviews and meta-analysis (secondary clinical research)
- Randomized control trials (RCTs), quasi-experimental studies, correlational studies, case series (primary clinical research)
- In-vitro and animal studies (direct evidence)

Food and Drug Administration (FDA) spontaneous reporting system: QTc and TdP

Case	year reported	sex	Age	TdP	Dose mg/day	Route	possible contributing factors	Death as an outcome
1	1996	F	30	Y	NR	NR		N
2	1997	F	78	N	NR	NR	Cisapride	Y
3	1998	M	16	N	NR	NR	Cisapride, erythromycin	N
4	2000	M	48	N	NR	NR		N
5	2000	F	42	Y	700	PO	Levomethadyl	N
6	2000	F	55	Y	270	PO	Ondansetron	N
7	2000	M	50	Y	NR	NR		N
8	2000	F	42	Y	840	PO		N
9	2000	F	52	Y	650	PO	Domperidone, low Mg ⁺⁺	N
10	2000	F	42	Y	500	PO		N
11	2000	F	40	N	29	PO		Y
12	2000	F	35	N	NR	NR	Levofloxacin, cardiomyop, low K ⁺ , MI	N
13	2000	F	43	N	600	PO	Low K ⁺	N
14	2000	M	37	N	280	PO	Levomethadyl	N
15	2000	F	42	Y	800	PO		N
16	2001	M	38	N	1680*	IV		Y
17	2001	F	48	Y	1100	PO		N
18	2001	F	56	N	NR	NR	Gatifloxacin	N
19	2001	M	NR	Y	NR	N	Low K ⁺	N
20	2001	M	44	Y	75	PO		N
21	2001	F	39	Y	NR	NR		N
22	2001	F	44	Y	NR	NR		N
23	2001	F	72	N	NR	NR		N

Food and Drug Administration (FDA) spontaneous reporting system: QTc and TdP (continue)

Case	year reported	sex	Age	TdP mg/day	Dose	Route	possible contributing factors	Death as an outcome
24	2001	M	38	Y	110	PO		N
25	2001	NR	26	Y	240	IV	Ondansetron, tacrolimus	N
26	2001	M	44	Y	75	PO		N
27	2001	F	39	Y	90	PO	Levomethadyl	N
28	2001	M	46	N	NR	NR	Azithromycin, levofloxacin	N
29	2001	M	45	Y	NR	NR	Low K ⁺	N
30	2001	F	NR	Y	583	PO	Low K, low Mg ⁺⁺ , cardiom	N
31	2001	F	6	N	360	IV		Y
32	2002	F	41	Y	NR	NR	Levomethadyl, low Mg ⁺⁺	N
33	2002	F	35	Y	360	PO		N
34	2002	F	47	Y	NR	NR	Azithrom, droperi, MI	Y
35	2002	F	31	N	460	PO	Low Mg ⁺⁺	N
36	2002	M	NR	Y	NR	NR	LowK, low Mg ⁺⁺	N
37	2002	F	48	Y	NR	NR	Azithromycin, droperidol	N
38	2002	F	40	Y	100	PO	Low Mg ⁺⁺	N
39	2002	M	32	N	80	PO		N
40	2002	M	NR	Y	420	PO		N
41	2002	M	NR	N	45	PO	Low K ⁺	N
42	2002	F	33	N	680	PO		N
43	2002	F	45	Y	85	NR		N
44	2002	F	51	Y	90	NR		N

Food and Drug Administration (FDA) spontaneous reporting system: QTc and TdP
(continue)

Case	year reported	sex	Age	TdP	Dose	Route	possible contributing factors	Death as an outcome
45	2002	M	51	Y	110	NR		N
46	2002	M	47	Y	600	NR		N
47	2002	M	52	Y	550	NR		N
48	2002	F	41	Y	660	NR	Low K+	N
49	2002	M	52	Y	540	NR	Low K+	N
50	2002	F	55	Y	270	NR	Low K+	N
51	2002	F	47	Y	65	NR	Low K+	N
52	2002	M	50	Y	1000	NR	N	
53	2002	F	51	Y	90	NR	Low K+	N
54	2002	F	46	Y	126	NR	Low K+	N
55	2002	M	38	Y	300	NR		N

Prospective, Cross Sectional, and Retrospective Studies Reporting QTc Int Prol or TdP

QTc Prol	DD	% subj Prol	QTc ?ms n>500	RF	TdP	n	Dose	Evid	Indic	Reference
Yes	0>500	0	NR	Yes	No	41	NR	Pros	ST	Stimmel et al., 1973
Yes	Yes	NR	428	+/-	0>500	132	80a(30-150)	Pros	ST	Martell et al., 2003
Yes	0>500	5	429	+/-	No	118	80 (20-180)	Pros	ST	Krantz et al., 2005
Yes	Yes	07	431	+/-	No	160	80c (20-180)	Pros	ST	Martell et al., 2005
Yes	0>500	5	440	No	No	8	57 (10e90)	Pros	Pain	Fredheim, 2006
Yes	Yes	32	428	+/-	0>500	104	110 (20-1200)	CSec	Pain/ST	Cruciani et al., 2005
Yes	2>500	5	423	No	No	83	387 (10-600)	CSec	ST	Maremmani 2005
Yes	0>500	5	418	+/-	3>500	138	171 (40-290)	CSec	ST	Peles et al., 2007
Yes	Yes	9	422	+/-	8>500	179	145(10-430)	CSec	ST	Eap et al., 2007
Yes	Yes	32	NR	+/-	No	393	100 (50-235)	CSec	ST	Fanoe et al., 2007
Yes	0>500	8	457	+/-	NR	650	NR	CSec	ST	Chinello et al., 2007
Yes	Yes	NR	NR	No	No	47	17.8 20.6 mg/h	Ret	Pain	Kornick et al., 2003
Yes	N/A	NR	413	+/-	0>500	56	30 (2-480)	Ret	Pain	Reddy et al., 2004
Yes	27>500	NR	NR	+/-	13	5503 (ev)	410 (29-1680)	Ret	NR	Pearson et al., 2005
Yes	Yes	30	440	+/-	NR	167	100 (4-600)	Ret	ST	Ehret et al., 2006
No	1>500	7	413	+/-	23% >470 (m) and 490 (f)			Ret	ST	Skjervold et al., 2006
Yes	NR	NR	>490	+/-	23% >470 (m) and 490 (f)			DobBli	ST	Wedam et al., 2007
Yes	0>500	NR	NR	+/-	23% >470 (m) and 490 (f)	55	69±29	cont	ST	Athanasos et al., 2008
No	NR	0	NR	+/-	0>500	22		cont	ST	Wieneke et al., 2009

Disparity in Opinions on When to Recommend an ECG for Patients on Methadone

“Vigilant for doses >600 mg/day”	Walker et al., 2003
“Patients on high doses”	Almehmi et al., 2004
“Never necessary”	Krook et al., 2004
“Never necessary”	Martell et al., 2005
“Never necessary”	Maremmani et al., 2005
“OT-prolonging medications. Repeat ECG after	Sticherling et al., 2005
“Consider ECG before starting”	
“ECG screening in patients at risk, specially after starting CYP2A4 inhibitors or increase in dose”	Ehret et al., 2006
“ECG for patients on >120 mg/day ideally every patient at entering treatment”	Peles et al., 2007
“For HIV-infected patients receiving drugs with QTC prolongation potential”	Chinello et al., 2007
“ECG for high risk patients”	Krantz et al., 2007
“ECG in methadone users.with inhibitors of methadone metabolism”	Routhier et al., 2007
“An ECG is a convenient way with little cost to screen for an increased risk of TdP”	Ehret et al., 2007
“pretreatment ECG for all patients...follow-up ECG Within 30 days and annually “	Krantz et al., 2009

Effect of Methadone on QTc Duration (Case Series/Reports)

QTc ms Δ ms n>500 ms	RF	TdP	n	Dose mg/day (Range)	Indic	Reference
615±77 NR 17>500	+/-	Yes	17	397 (65-1,000)	Pain/ST	Krantz et al., 2002
NR	Yes	Yes	3	660-650-700	Pain	Walker et al., 2003
597 NR 4>500	Yes	3	4	(275-500)	NR	Gil et al., 2003
601 152 NR	Yes	No	1	80	ST	Schmittner et al., 2004
582	Yes	Yes	1	450	ST	Krantz, Garcia et al., 2005
NR	Yes	Yes	1	NR	ST	Krantz, Rowan et al., 2005
562+/-77 NR 4>500	+/-	Yes	5	268 (140-340)	Pain/ST	Sticherling et al., 2005
Fluc	No	No	1		Pain	Ower et al., 2005
542	Yes	No	1	100	ST	Rademacher et al., 2005
549	Yes	Yes	1	700	ST	Almehmi et al., 2004
NR	Yes	Yes	1	NR	ST	Lamont and Hunt, 2006
626	Yes	Yes	1	120	ST	Chatterjee and Burgi, 2006
517	Yes	Yes	1	145	ST	Routhier et al., 2007
510	Yes	No	1	50 (Maternal)	ST	Hussain and Ewer, 2007

Cruciani RA, J Pain Symp Manag, 2008 (modified)

Risk Factors for QTc Prolongation/TdP (cont...)

- **Potential of commonly used medications in HIV/AIDS and chronic pain patients to produce QT prolongation**

Very probable: quinidine

Probable: pimozide, ziprasidone

Possible: clarithromycin, erythromycin, pentamidine, chlorpromazine, **haloperidol, olanzepine, risperidone, amitriptyline, desipramine, imipramine, sertraline, venlafaxine**

Improbable: fluconazole, levofloxacin, trimethopim-sulfamethoxazole, **fluoxetine, paroxetine, sumatriptan, zolmitriptan, methadone**

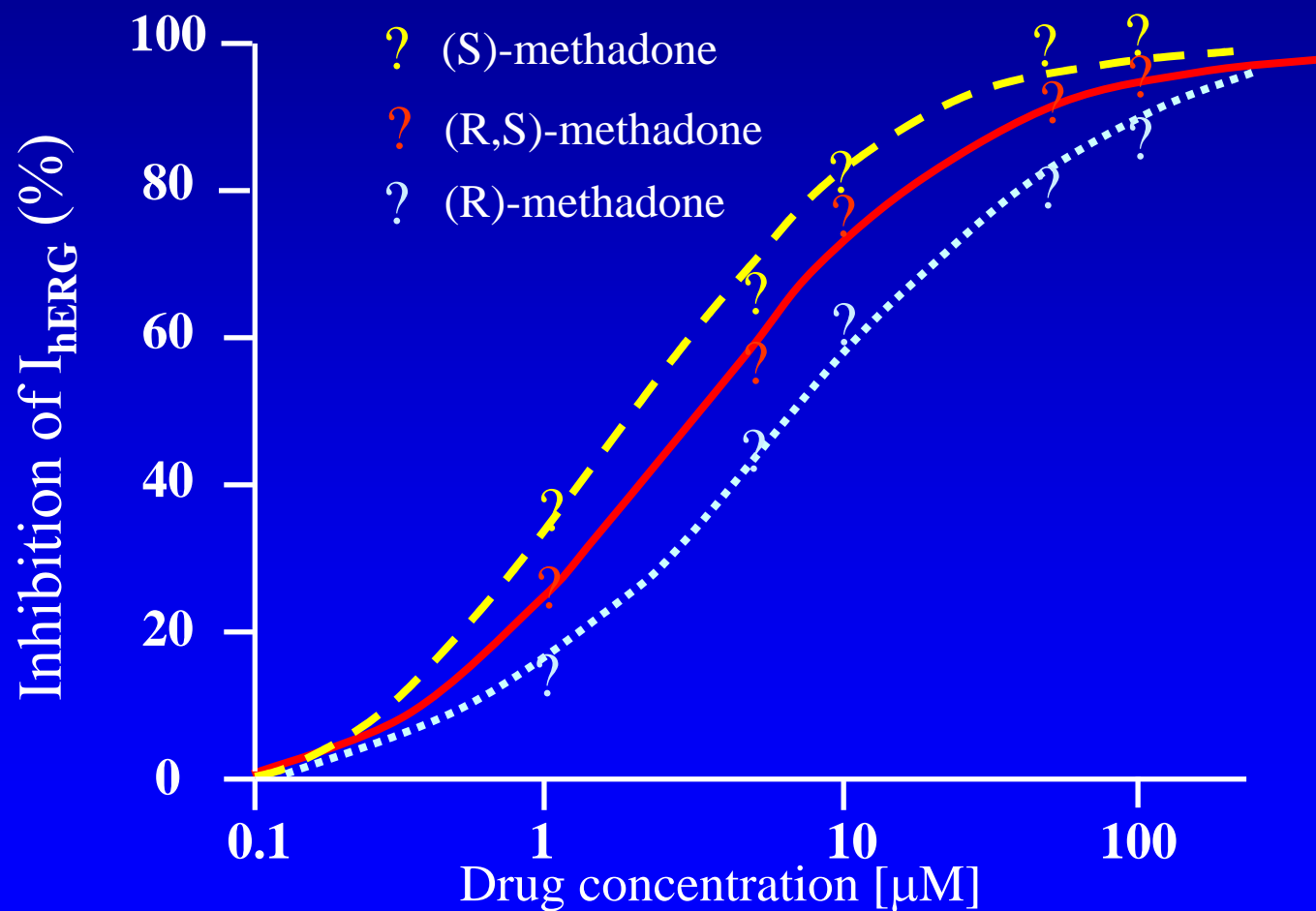
Very improbable: azithromycin, ciprofloxacin, clindamycin

- **Drugs associated with torsades de pointes**

Amiodarone, arsenic trioxide, bepridil, chlorpromazine, cisapride, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, mesoridazine, methadone, entamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine

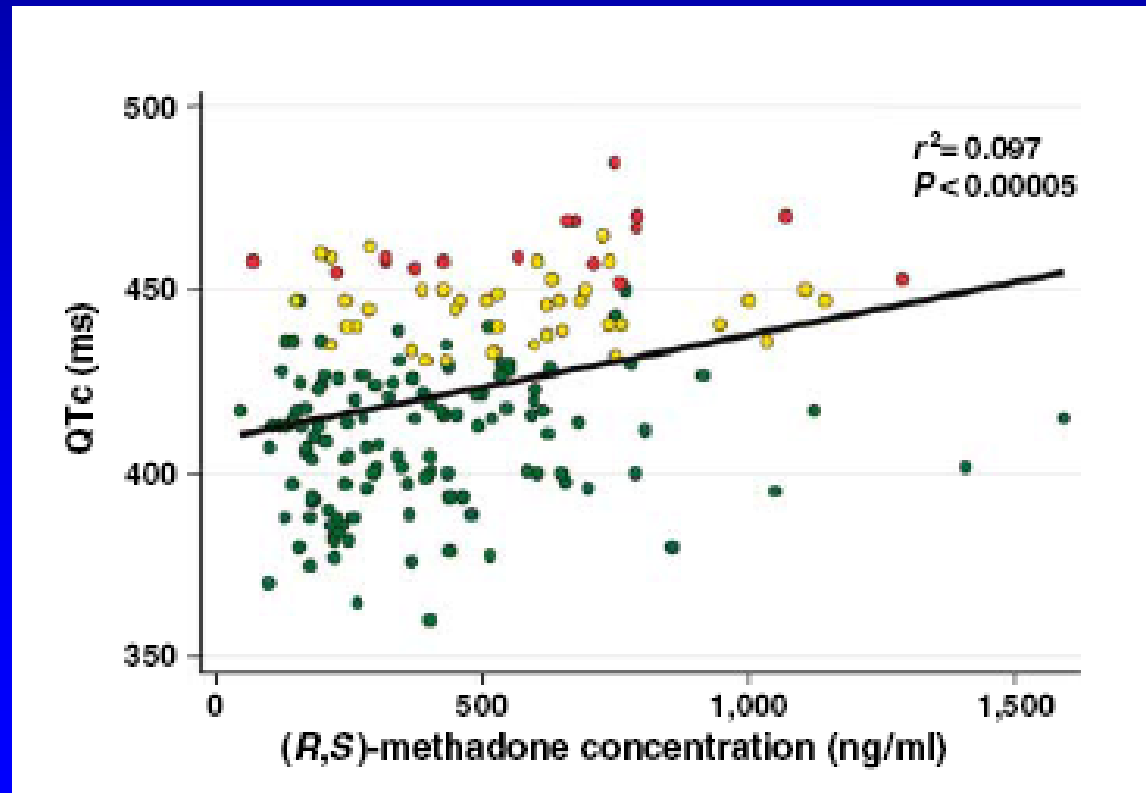
For full list of meds visit www.torsades.org

Inhibition of I_{hERG} currents by methadone and methadone stereoisomers

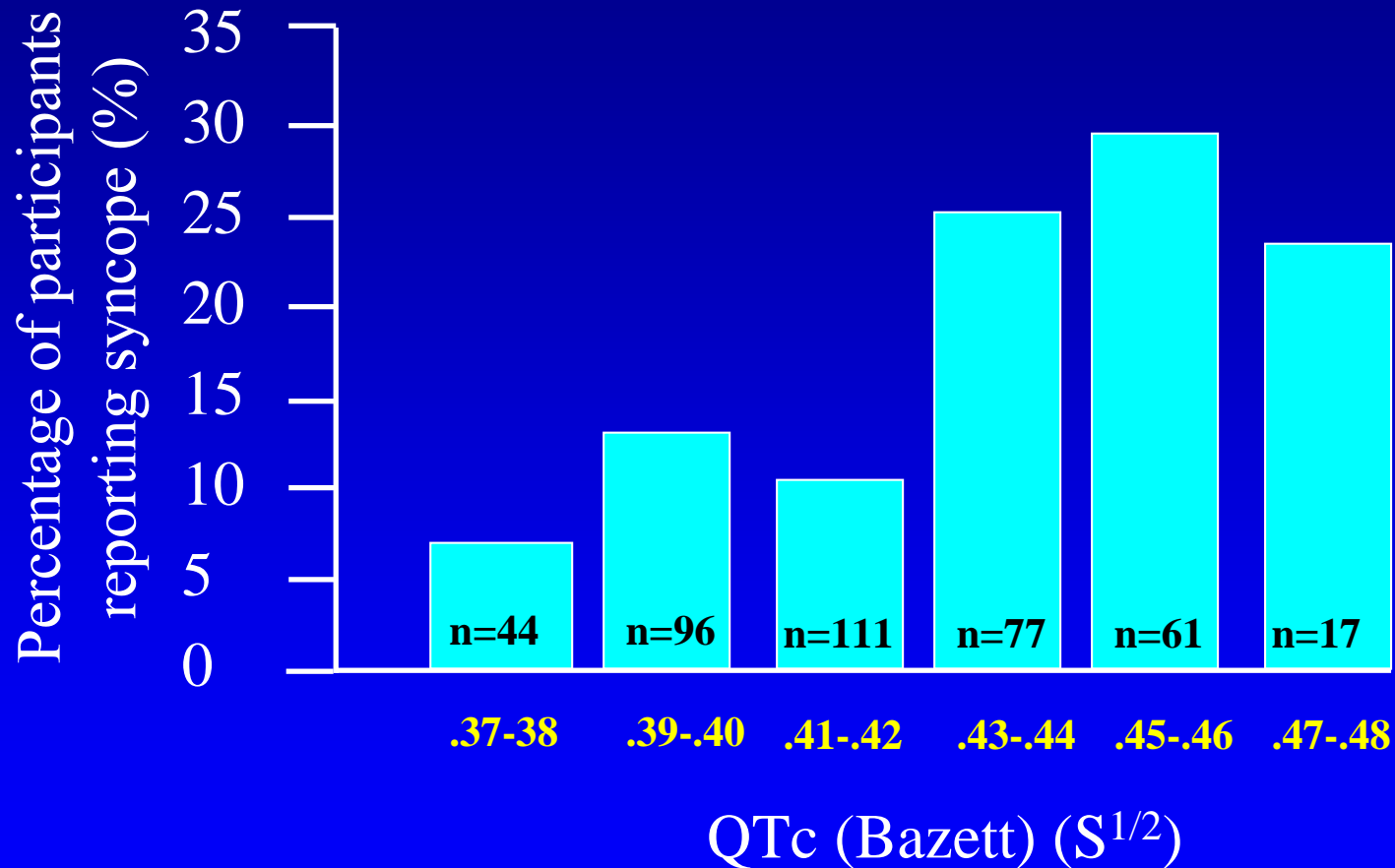


Dose response for methadone and QTc interval prolongation?

Variable results.



Methadone and syncope. Is it caused by QTc interval prolongation?



Fanoie et al., 2007

Does methadone metabolism impact
on the QTc interval duration?

Methadone metabolism and QTc interval duration

- CYP2B6 genotypes, and (R)- and (S)-methadone plasma concentrations were obtained for 179 patients receiving (R,S)-methadone
- The mean heart-rate-corrected QT (QTc) was higher in CYP2B6 slow metabolizers than in extensive metabolizers
- CYP2B6 slow metabolizer status was associated with an increased risk of prolonged QTc

Risk Factors for QTc Prolongation/TdP

- Elderly women
- Advanced heart disease
- Congenital and acquired long-QT syndromes
- Concomitant use of drugs with potential to prolong QTc
- Family history of sudden death
- Hypokalemia
- Hypomagnesemia
- **CYP 3A4, 2D6 inhibitors**
 - Potent inhibitors
 - Protease inhibitors: ritonavir, nelfinavir, indinavir
 - Macrolide antibiotics: erythromycin, clarithromycin, troleandomycin
 - Antifungal agents: ketokonazole, itraconazole
 - Less potent inhibitors: Saquinavir, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, clotrimazole

Case Presentation I

This is a 67 years old woman with Hx of HIV cardiomyopathy who is coming for a follow up visit, with a chief complain of pain in the lower extremities that worsened after her ID specialist placed her on antiretroviral medications. The pain is burning, constant, scores 5/10 at Baseline and increases with activity to 8-9/10 in a numeric scale 0-10.

The pain involves the entire feet and extends half the way up the shins. The pain is symmetrical and is accompanied by numbness and tingling. There is some discomfort to the touch. She was treated with TC's antidepressants, duloxetine, gabapentine, pregabalin and topiramate, but either she developed side effects or the medications did not help and they were discontinued. She underwent a trial with morphine sulfate and fentanyl patch that resulted in mild pain relief and severe side effects including severe sedation with frequent falls.

Case Presentation I

Based on the results with the other mediations you decide to do a trial with methadone.

Case Presentation I

What is the best course of action?

- Do we do an ECG at baseline?
- ECG is 450 ms. What do we do next?
- ECG is 488 ms. What now ?
- ECG is 500 ms? What is the best action.
- ECG is 536 ms. What is the next best action?
- ECG before starting methadone was 450 and 3 weeks after methadone 489 ms. Next course of action?

Summary

- **Methadone has unique properties** that makes it a useful opioid in the management of severe chronic pain especially when the patient has not done well on other opioid drugs
- **The long half life can lead to increased risk** for sedation and respiratory depression especially with rapid dose escalation
- Rapid titration guidelines for other opioids do not apply to methadone
- **Careful titration, close monitoring** and patient/family education is required
- Careful when combined with benzodiazepines(?)
- Have a low threshold for ECG
- All patients treated with >100 mg/day should have an ECG until better data become available
- Increase in the number of deaths associated with the use of methadone has been observed.