

Statement of Sidney M. Wolfe, M.D.

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Hearing on Propoxyphene

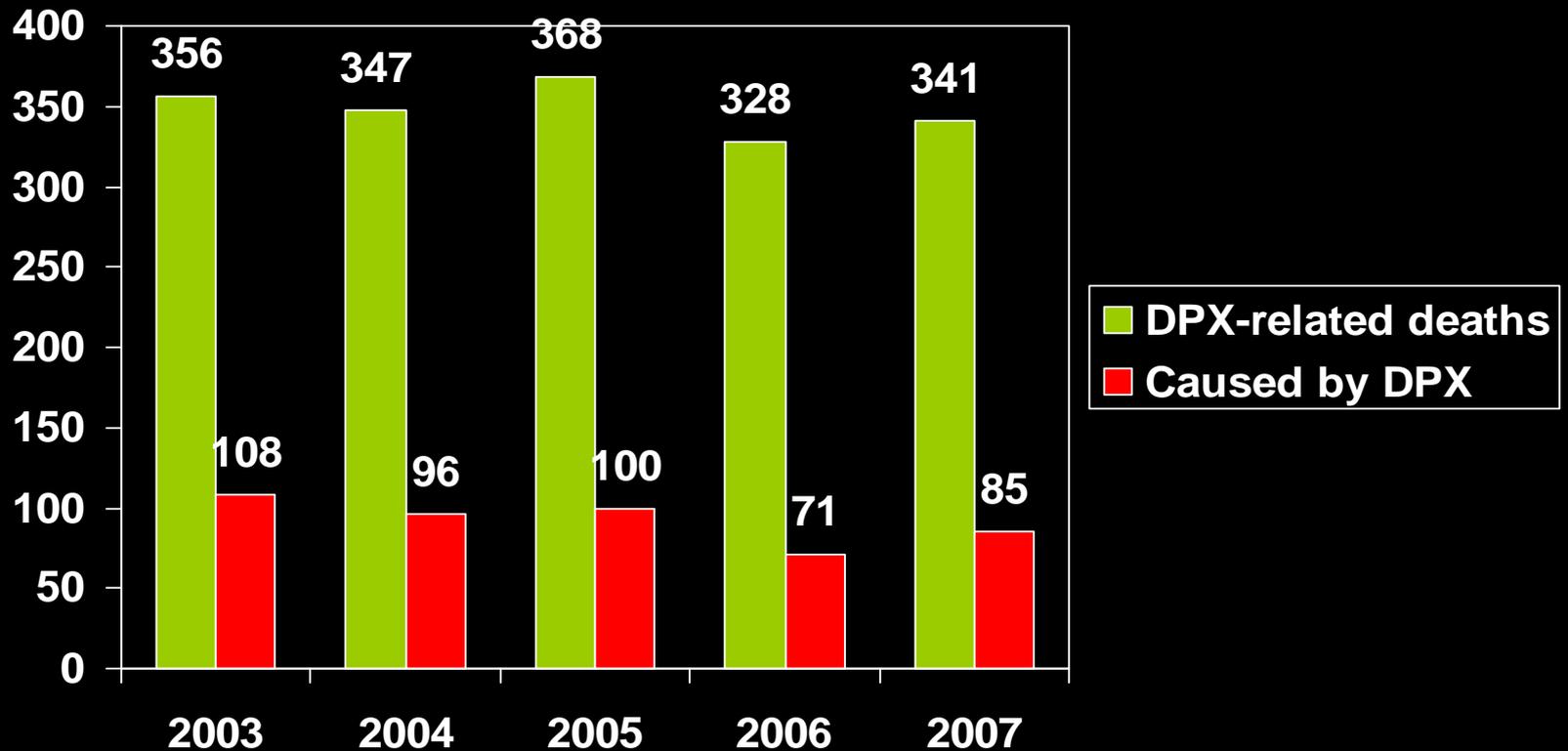
Before FDA's Anesthetic and Life Support
And Drug Safety and Risk Management
Advisory Committees

January 30, 2009

DAWN Propoxyphene(DPX)-related Deaths: 2006-2007

Year	2006	2007
Jurisdictions	114	168
DPX-related deaths	446	503
Type of death		
Suicide	90	101
Accident	278	323
Natural	4	9
Not det'd	73	66
Single drug	27	25
Multiple drugs	381	362

Florida Deaths Related to propoxyphene (DPX)



Source: Drugs Identified in Deceased Persons—2007

Report by the Florida Department of Law Enforcement

Details of 85 Florida DPX-Caused deaths: 2007

Type of Death	Accident	Suicide	Unspecified/ Natural
DPX as sole cause = 25	17	5	3
DPX+other drug(s) = 60	49	11	0
Total = 85	66	16	3

Source: Drugs Identified in Deceased Persons:2007 Data obtained from the Florida Department of Law Enforcement

Do We Still Need Propoxyphene?

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Propoxyphene

- Propoxyphene (DPX) is a low affinity mu receptor agonist that may cause more respiratory depression, but only modest pain relief.
- The DPX oxidation product, norpropoxyphene (NPX), accumulates in the heart, is cardiotoxic, and this toxicity is not reversed by Naloxone

Safety Issues

- The industry response to Public Citizen's petition states the petition "does not raise any new safety issues that have not already been considered by the FDA." That statement is clearly untrue
- When DP was first approved over 50 years ago, methods for direct quantification of NPX did not yet exist, genetic polymorphism was unrecognized, while the hERG and SCN5A channels were yet to be identified

Death from DPX

- In England and Wales in 1997-1999, 18% of drug-related suicides involved DPX, constituting 5% of all suicides in that country.
- Death from DPX overdose may occur rapidly, the lethal dose can be relatively low, and the effects are potentiated by alcohol and other CNS depressants.
- The majority of DPX-related deaths occur before hospital treatment can be received.

Propoxyphene Metabolism

- First step in metabolism is oxidation by CYP3A4 to form norpropoxyphene
- Norpropoxyphene
 - Is cardiotoxic (binding to both SCN5A and hERG channels)
 - Is longer acting than the parent compound
 - Has effects that are not reversed by opiate antagonists

CYP3A4 Polymorphisms

- CYP3A4 is the major CYP enzyme catalyzing DPX metabolism.
- The variability in pharmacodynamic and pain relieving effectiveness of DPX is likely due to inter-subject variability in hepatic CYP3A4 expression and/or drug-drug interactions.

Dangers of CYP3A4 Inhibition

- Propoxyphene is a competitive inhibitor of CYP3A4, and many other drugs also fall into this class including:
 - Calcium channel blocking agents
 - Macrolide Antibiotics
 - Isoniazid
 - Proton pump inhibitors
- If carbamazepine break down is slowed, toxic levels may accumulate

Dangers of CYP2D6 inhibition

- Clear evidence suggests DPX also inhibits CYP2D6
- This opens up the possibility for other types of drug interactions
- Most beta blockers are metabolized by CYP2D6 – a report of bradycardia in a user of metoprolol suggest that symptomatic drug interactions are occurring

EKG Changes and DPX

- Norpropoxyphene accumulates in cardiac tissue and its effects ARE NOT reversed by naloxone.
- NPX may block both the I_{Na} and also I_K currents.
 - Blockade of the main sodium channel causes conduction delay
 - Blockade of hERG (slow rapid depolarizing K channel) may cause QT interval prolongation leading to torsades des pointes and sudden death. There are genetically determined polymorphic forms of hERG that may increase such toxicity

QRS prolongation

- QRS is significantly prolonged in DPX overdose
- Prolongation is dose dependent.
- These findings have clinical relevance to the management of patients with
- DPX poisoning; heart block must be anticipated

Increased Toxicity With EtOH

- When DP is co-administered with EtOH, first pass hepatic metabolism is decreased, which means that DP concentrations increase
- EtOH is frequently present in DPX deaths
 - In the UK a study of 123 suicides by DPX overdose, alcohol was found to be involved in 58.5% of the cases and these individuals generally had lower DPX blood drug levels, and consumed fewer tablets.

Why Propoxyphene Should be Banned

It is a dangerous drug: Large amounts of DPX are rapidly absorbed from the GI tract very quickly, making attempted suicide difficult to treat.

Even modest amounts of this drug might cause lethal cardiac arrhythmias in individuals with undiagnosed hERG genetic polymorphism.

Use of DPX can lead to dangerous levels of antibiotics and anticonvulsants

222 Consecutive patients admitted to one Danish ICU with DPX intoxication

- 107 (48%) heart failure
- 12 (15%) asystole
- 21 (9%) bradycardia
- 91 (41%) abnormal ECG
 - 43(19%) QRS>120ms
 - 19 (8%) ventric. arrhyth.

222 Consecutive patients admitted to one Danish ICU with DPX intoxication

- 100 (44%) acute respiratory failure
- 22 (10%) convulsions
- 163 (73%) stupor or coma

222 Consecutive patients admitted to one Danish ICU with DPX intoxication (cont'd)

- 17 (8%) died
- 9 deaths (53%) heart fail.
- 13 deaths (76%) cardiovascular causes
- all heart failure deaths > 55 y/o
- all brain damage deaths < 39 y/o

Pills/day	Type of Subject	Duration of Drug Use	Maximum Blood Concentration ($\mu\text{g/l}$)	
			DXP	NPX
3 (HCl)	Cancer patient	60 days	746 (2)	3010
3 (HCl)	Cancer patient	14 days	275 (2)	750
3 (HCl)	Normal vol.	4 days	241 (2)	.600
6 (HCl)	Normal vol.	4 days	849 (2)	1240
9 (N)	Addict	28 days	519 (3)	3830
11 (N)	Addict	42 days	567 (3)	4940
11 (N)	Addict	84 days	513 (6)	5070
12 (N)	Addict	84 days	424 (6)	1830
12 (HCl)	Cancer patient	365 days	866 (2)	3230

Retail Prescriptions for Propoxyphene: Millions

