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The Impact of the Withdrawal of Propoxyphene from the U. S. Market

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Background

- **Timeline and Clinical Profile**
  - Propoxyphene - originally developed by Eli Lilly & Co[1,2]
  - Approved on August 16, 1957[1,2]
  - Indicated for the relief of mild to moderate pain[1,2]
  - Brand names: Darvon® and Darvocet®[1,2]
  - Most dispensed outpatient prescription from 1967 – 1969[3,4]
  - Assigned to schedule IV drug status on March 14, 1977[5]
  - First petition to ban propoxyphene - November 1978 by Public Citizen, a public advocacy group because:[2]
    - Concern about issues of narcotic abuse
    - In 1977, 2nd leading agent (after barbiturates) implicated in deaths in the U.S. caused by prescriptions
  - Petitions to remove propoxyphene were rejected by FDA[1,2]
  - In 1979, Eli Lilly published a paper that indicated cardiac conduction delays with propoxyphene use in dogs[6]
  - Further studies showed propoxyphene increased CNS depression in the elderly[7]
  - In 1991 propoxyphene appeared on the original *Beers* list (list of medications that are generally considered inappropriate when given to the elderly)[8]
  - From 1997 – 1999, propoxyphene was the single most implicated drug in suicide in Wales and England[9]
  - 1998 study found propoxyphene associated with an 80% increase in the risk of hip fractures in the elderly[10]

Background

- In 2005, the United Kingdom announced its phased withdrawal of propoxyphene based on the well known risk of overdose and the poorly established efficacy [11]
- In 2006, Public Citizen petitions the FDA for the second time to remove propoxyphene from the market citing:[11]
  - Poor efficacy
  - Potential addiction profile
  - Placement on *Beers* list
  - Cardiotoxic metabolite implicated in over 2000 accidental propoxyphene-related deaths from 1981-1999 according to DAWN (Drug Abuse Warning Network)
- FDA advisory committee recommended withdrawal of propoxyphene on January 30,2009 [11,12]
- FDA rejected the advisory committee recommendation on July 6,2009 and ordered Xanodyne (current manufacturer) to change product labeling and medication guides regarding safety pertaining to overdose & CNS depression and to conduct further studies to connect drug to heart problems.[12]
- European Medicines Agency issued 15 month phased withdrawal on June 25, 2009 due to concern of fatal toxicity and overdose.[11]
- On August 6, 2009, in a letter to the Commissioner of the FDA, Dr. Margaret Hamburg of the advocacy group petitioned once more for the 2006 petition to be reconsidered.[13]
- On November 19, 2010, the FDA released a press announcement stating that Xanodyne has voluntarily agreed to withdraw their brand versions of propoxyphene (Darvon® & Darvocet®) at their request and generic companies being asked to follow suit.[14]

Objectives

To determine the clinical and economic impact of the withdrawal of propoxyphene from the U.S. market. Using a proprietary data set we:

- Determined the prescription products that patients were switched to following withdrawal of propoxyphene.
- Determined the cost of the prescription products that patients were switched to.

Study Design

- Using a pharmacy claims database, investigators will analyze the impact of the withdrawal of propoxyphene products
- The procedure will be to first determine baseline propoxyphene usage and economic parameters via a query of databases to determine all pharmacy claims for these products between November 19, 2009 and November 19, 2010
- The next step will be to determine alternative drugs used for pain management in place of propoxyphene from November 20, 2010 through November 19, 2011 with identification numbers only.
- The information gathered from database queries will include the number of prescriptions for each drug, number of patients taking each product, number of doses dispensed per prescription, and economic data for each drug.

Predicted Outcomes

- In regards to pain relief, the potency of propoxyphene is the same as aspirin or acetaminophen.
- Taking into account all of the alternatives to propoxyphene, literature would suggest that acetaminophen would be the safest, most economic and most prevalent option for the majority of patients. While this may bet rue, there is the possibility and speculation that the contrary will be apparent in our results from our database study.

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