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Propoxyphene and the Risk of Out-of-Hospital Death

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Abstract

Purpose—The opioid analgesic propoxyphene was withdrawn from the U.S. market in 2010, motivated by concerns regarding fatality in overdose and adverse cardiac effects, including prolongation of the QT interval. These concerns were based on case reports, summary vital statistics, and surrogate endpoint studies.

Methods—Using the linked Tennessee Medicaid database (1992–2007), we conducted a retrospective cohort study that compared risk of sudden cardiac, medication toxicity, and total out-of-hospital death for propoxyphene users with that for comparable nonusers of any prescribed opioid analgesic and users of hydrocodone, an opioid with similar indications. Cohort members had 1,873,500 propoxyphene prescriptions, 1,873,500 matched nonuser control periods and 936,750 matched hydrocodone prescriptions.

Results—Current propoxyphene users had no increased risk for sudden cardiac death (versus nonusers: HR = 1.00 [0.81–1.23]; versus current hydrocodone users: HR = 0.91 [0.68–1.21]) but did have increased risk for medication toxicity deaths (versus nonusers: HR = 1.85 [1.07–3.19], $p = 0.027$; versus current hydrocodone users: HR = 2.10 [0.87–5.10], $p = 0.100$). Because toxicity deaths were a small proportion of study deaths, total out-of-hospital mortality differed by less than 10% between the study groups and was not significantly elevated for propoxyphene (versus nonusers: HR = 1.09 [0.95–1.25]; versus current hydrocodone users: HR = 1.06 [0.87–1.29]).

Conclusions—Our findings support the concern that propoxyphene has greater toxicity in overdose but do not provide evidence that it increases the risk of sudden cardiac death.

Propoxyphene, a μ -opioid agonist structurally related to methadone, was introduced in the U.S. in 1957 and became one of the most frequently prescribed opioid analgesics worldwide.¹ However, it is generally considered a weak analgesic. Indeed, it is unclear whether or not it has better efficacy than acetaminophen² with which it is nearly always prescribed. Thus, growing concerns regarding fatality in overdose^{3,4} and possible adverse cardiovascular effects^{5–7} led to the announcement of its withdrawal in the UK in 2005,⁸ the European Union in 2009⁹ and the U.S. in November of 2010.¹⁰

Fatality in overdose is a major concern for all opioid analgesics, given that patients often ingest supra-therapeutic doses either inadvertently or deliberately.^{11,12} There are two lines of evidence that propoxyphene might have greater overdose liability than other opioids. First, numerous reports from emergency departments and poison control centers suggested that patients with propoxyphene overdose more frequently had rapid deaths, often within

one hour.^{1;13–19} Second, a Scottish study found that the estimated ratio of fatal overdoses to total prescriptions written was greater for propoxyphene than for either codeine or dihydrocodeine, even though the corresponding ratio for overdose hospital admissions did not differ from that of the other opioids.⁴ Similar findings were reported from a U.K. study that compared the estimated ratio of fatal:nonfatal overdoses for propoxyphene, tricyclic antidepressants, and acetaminophen.³

The rapidity of death in many reported cases of propoxyphene overdose suggested a possible cardiovascular mechanism. A study of 222 patients presenting with overdose to a single intensive care unit found 41% had ECG abnormalities, including widening of the QRS complexes and various ventricular arrhythmias.²⁰ Experimental studies suggest propoxyphene blocks sodium channels, which could predispose to an increased risk for serious ventricular arrhythmias and sudden cardiac death.^{7;21–24} Following the withdrawal of propoxyphene from the European Union, the FDA required the manufacturer to study QT prolongation, a characteristic of many other drugs that cause serious ventricular arrhythmias and sudden cardiac death.^{25;26} The finding from the “thorough QT” study that propoxyphene prolonged QT in healthy volunteers led to its withdrawal in the U.S.¹⁰

The concerns regarding propoxyphene’s safety are primarily based on case reports, summary vital statistics data, and a study of a surrogate endpoint. However, these data sources have well known limitations.^{27;28} In 2009, we initiated a controlled epidemiologic study to better define propoxyphene’s safety relative to both nonusers of opioids and users of hydrocodone, another widely used low-potency opioid analgesic.²⁹ Given that the primary safety concerns were rapidly fatal cardiovascular effects, the study endpoint was out-of-hospital mortality. This was further classified as sudden cardiac deaths--most likely to be related to serious ventricular arrhythmias³⁰--and medication toxicity deaths, the primary concern that led to propoxyphene’s withdrawal from the European market.^{4;8;9} Although propoxyphene is no longer marketed, it nevertheless is important to determine if the signal regarding propoxyphene’s safety is confirmed in controlled studies with clinical outcomes.

Methods

Design

We conducted a retrospective cohort study of Tennessee Medicaid enrollees for 1992 through 2007. Tennessee Medicaid files provided an efficient source of data for identifying the cohort, determining periods of probable exposure to medications, and ascertaining endpoints.^{27;31} The study Medicaid database, augmented with linkage to death certificates and a statewide hospital discharge database, included enrollment, pharmacy, hospital, outpatient, nursing home, and linked death certificate files.

The cohort included all Medicaid enrollees with at least 1 qualifying prescription for propoxyphene during the study period. Because the effects of propoxyphene on arrhythmias and poisonings most plausibly occur shortly following drug ingestion, study person-time was restricted to periods when the patient was most likely to be taking the medication. Thus, for each qualifying propoxyphene prescription, study person-time included up to 30 days (the maximum days of supply that can be dispensed in Tennessee Medicaid), beginning with the prescription fill date.

The cohort also had two control groups. The *nonuser controls* included persons with time periods during which there was no use of prescribed opioids. To reduce potential confounding, these periods were selected to assure a distribution of potential confounders comparable to that for the study propoxyphene prescriptions. We focused on specific time

periods rather than patients because a patient's health could change markedly during the 16 year study period. As for propoxyphene, each time period included in the analysis had a duration of up to 30 days.

The second control group included persons with hydrocodone prescriptions. The rationale for this active control was that an opioid class effect could influence the comparison of propoxyphene with nonuser controls. Hydrocodone is a low potency opioid with indications similar to those of propoxyphene²⁹ and there is no evidence of adverse cardiac effects. Study hydrocodone prescriptions consisted of a subset of all available prescriptions, selected to assure that the distribution of covariates at the time of the prescription fill was comparable with that for propoxyphene. For each qualifying hydrocodone prescription, study person-time included a period of up to 30 days.

Propoxyphene and hydrocodone are commonly prescribed episodically. Thus, a single person could have propoxyphene prescriptions, nonuser control periods, and hydrocodone prescriptions included in study person-time. Figure 1 depicts this for 5 hypothetical cohort members. Persons 1, 2, and 3 each contribute 4 time-periods to study person-time, consisting of propoxyphene prescriptions, nonuser control periods, and hydrocodone prescriptions, respectively. Person 4 has two propoxyphene prescriptions and 3 nonuser control periods included in study person-time. Person 5 contributes all three types of person-time.

Cohort and Study Person-Time

Because the cohort was designed to detect an increased risk for out-of-hospital deaths, it excluded seriously ill patients for whom such deaths might be expected as part of the disease process. Thus, all study person-time for the three groups had to satisfy several criteria (Table 1, criteria 1–8). Patients had to be 30 to 74 years of age at t_0 , the beginning of the time-period. The lower age limit was present because sudden death in children and young adults is very rare and may have a different etiology.³² The upper limit was present because in our experience the death-certificate-coded cause of death, an important element of our procedure for identifying sudden cardiac deaths, is less accurate for persons 75 and older.³⁰ They had to be enrolled in Medicaid (with pharmacy benefits) for at least 1 year and have medical care utilization during that year. Given that most study covariates are ascertained from medical care encounters, this assured some degree of medical surveillance. They could not be residing in a nursing home, have a life-threatening illness, or have been in the hospital in the past 30 days. In each of these circumstances, out-of-hospital death may not be unexpected. There could be no evidence of drug abuse, given that such persons would be more likely to have opioid toxicity unrelated to medical use. There could be no parenteral opioid administered at the time the prescription was filled because study data do not permit accurate quantification of the dose.

The last inclusion/exclusion criterion specified allowed use of other prescribed opioids (Table 1, criterion 9). For the propoxyphene and hydrocodone groups, there could be no filled prescription for the other opioid in the past 30 days because of potentially overlapping use. The nonuser controls could not have any filled prescription for an opioid analgesic, which assured the control period was free of recorded opioid use.

The time periods for both control groups ultimately included in study person-time were selected to assure that the distribution of study covariates at the beginning of the period (t_0) was comparable to that for the study propoxyphene prescriptions. The selection process used propensity scores, the conditional probability of a propoxyphene time period, given the study covariates.³³ The score was calculated from an extensive set of covariates that reflected patient status on t_0 and possibly were associated with both opioid use and the risk of death. It ultimately included nearly 200 covariates: demographic characteristics,

indicators of cardiovascular disease, psychiatric conditions and medications, neurologic disorders, frailty, other pro-arrhythmic medications, and intensity of medical care utilization (Appendix Table 1). The hydrocodone propensity score also included covariates, such as indication and past opioid use history, defined only for the study opioids (Appendix Table 2).

The propensity-score-based selection began by estimating the propensity scores for the propoxyphene prescriptions. There were two scores, one relative to potential nonuser control periods and the second relative to hydrocodone prescriptions qualifying for the study. For each control group, the appropriate score distribution in the propoxyphene prescriptions was divided into centiles. From each centile, we randomly selected a number of study control periods equal to 1/100 of the total control period sample size sought. For the nonuser controls, the sample size was equal to that of the study propoxyphene prescriptions. For hydrocodone, the sample size was one-half that for propoxyphene, the maximum possible given the number of potential hydrocodone prescriptions and the propensity score distributions.

For each study opioid prescription or nonuser control period, the study person-time could terminate prior to 30 days. This occurred with a filled prescription for any opioid analgesic (which assured that all opioid use was known at t_0), the end of the study, failure to meet study eligibility criteria, or death.

Endpoints

The primary study endpoints were sudden cardiac death and death from medication toxicity. We also analyzed total study mortality to guard against differential misclassification of cause of death according to opioid use status.

Sudden cardiac death: clinical definition—Sudden cardiac death is defined as a sudden pulseless condition (arrest) that is immediately fatal (or rarely resuscitated with death in 48 hours) that is consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.^{34–37} Previous studies suggest that up to 85% of such deaths are provoked by a ventricular tachyarrhythmia.^{34;35} Thus, if propoxyphene is proarrhythmic, the incidence of sudden cardiac death should be increased among users, particularly in a cohort that excludes terminal patients for whom out-of-hospital deaths from serious illnesses would not be unexpected.

Sudden cardiac death: study ascertainment—We utilized a previously developed case definition to identify sudden cardiac deaths based on information present in the computerized study files.³⁰ The definition required an underlying cause of death code consistent with sudden cardiac death, no evidence of a terminal hospital/nursing home stay, and no terminal medical procedures inconsistent with unresuscitated cardiac arrest. We conducted a validation study in the propoxyphene and hydrocodone groups of the study population and found a positive predictive value of 90%.³⁸

Medication toxicity deaths—Medication toxicity deaths were those with an external cause of death code indicating either medication poisoning (unintentional, intent undetermined, intentional) and or an adverse medication effect. Landen and colleagues reviewed such deaths for New Mexico and found a positive predictive value of >90%.³⁹ Intentional poisonings were included because suicide liability was a primary concern for propoxyphene.^{4;8;9} Toxicity deaths were not restricted to those for which an opioid was

identified as the responsible drug because a large proportion of deaths related to opioid toxicity are coded as due to an unspecified drug.⁴⁰

Statistical Analysis

The primary analysis focused on current use of study opioids, which should correspond to the time of greatest risk for both proarrhythmic effects^{10,20} and opioid toxicity.⁴¹ Because the study opioids often are prescribed for less than the 30 days included in study person-time, we defined current use as the period from the filling of the prescription through the end of the dispensed days of supply (edited to resolve infrequent inconsistencies with quantity dispensed). A sensitivity analyses assessed the effect of including the study person-time following current use.

The analysis estimated the cumulative incidence, or risk, of death during up to 30 days of current study opioid use or for a comparable period for nonuser controls. The unadjusted cumulative incidence was calculated by dividing the number of deaths by number of person-years at risk. The relative risk of death between groups defined by opioid use status, adjusted for patient characteristics, was calculated with the hazard ratio (HR) from Cox regression models. The units for this analysis were the time periods included in the study followup. A single person could contribute multiple study opioid prescriptions as well as nonuser control periods to the analysis (Figure 1). However, for each person, these time periods were non-overlapping and the endpoint (death) occurred only once. Thus, statistical independence assumptions were not violated.⁴²

The regression models included age, sex, and propensity score decile. Separate models were fitted for the pairwise comparisons between the study groups, each with the appropriate propensity score (e.g., propoxyphene vs nonuser control, propoxyphene vs hydrocodone, and hydrocodone vs nonuser control). The distributions of these propensity scores within the three study groups were very comparable by virtue of the selection process (Appendix Table 3).

We included an analysis according to dose of study opioid. Dose was calculated by dividing the total dose dispensed by days of supply; if these were inconsistent with recommended daily doses the dose was considered missing. The analysis grouped study opioid users according to dose percentiles (<25th, 25th–89th, 90th) and compared propoxyphene use within each category to hydrocodone use.

All analyses were done with SAS version 9.3. All p-values are two-sided. The Vanderbilt Committee for the Protection of Human Subjects and the Tennessee Bureau of Medicaid and Department of Health approved the study. The study was funded by federal agencies, which had no role in study conduct or reporting. The listed authors were entirely responsible for study design, data analysis, manuscript preparation, and publication decisions; no other persons were involved. The first manuscript draft was written by the primary author, who vouches for the data and the analysis.

Results

The study cohort included 549,537 Medicaid enrollees. Cohort members had a total of 1,873,500 qualifying propoxyphene prescriptions, an equal number of nonuser control periods and 936,750 qualifying hydrocodone prescriptions. The median number of qualifying opioid prescriptions per cohort member was 2, with an interquartile range of 1–4 for hydrocodone versus 1–6 for propoxyphene (Appendix Table 4).

Study covariates as of the beginning of study time periods were highly comparable (Table 2). Study opioid prescriptions were predominantly for females (73%) with a mean age of 52 years. The prevalence of diagnosed/treated cardiovascular/metabolic disease was elevated: 42% had a diagnosis of hypertension, 22% diabetes, and 6% heart failure. Concurrent use of psychotropic medications was frequent, with current use of a heterocyclic antidepressant, benzodiazepine, or musculoskeletal relaxant for 16%, 25%, and 42% respectively. Other comorbidity and medical care utilization indicated a high-risk patient population: 28% had recent beta-agonist use, 17% had diagnosed chronic obstructive pulmonary disease, 4% had a prescription for home oxygen, and 5% had had a cardiovascular hospitalization within the past year.

The most common indication for the study opioids was back (16%) and other musculoskeletal (26%) pain (Table 3). Other common indications were trauma (11%), surgical procedures (10%), and infections (7%). The qualifying study opioid prescriptions had a mean days of supply of 12 and 13 days for hydrocodone and propoxyphene, respectively. More than 95% of the study opioid prescriptions were a combination of the opioid with acetaminophen and 95% of the propoxyphene prescriptions were for the napsylate compound. The median dose (interquartile range) for study prescriptions was 15 (10–22.5) mg for hydrocodone and 300 (200–400) mg for propoxyphene (propoxyphene napsylate equivalents). During the year preceding the qualifying study opioid prescription, cohort members had filled prescriptions for opioid analgesics (study as well as other opioids) with slightly more than 100 days of dispensed supply.

Study followup included 59,930 person-years of current propoxyphene use during which there were 334 out-of-hospital deaths, or 55.7 deaths per 10,000 person-years (Table 4). Of these deaths, 146 were sudden cardiac deaths, 27 were medication toxicity deaths, and 161 were deaths from other causes. When compared to the nonuser control group, there was no significantly increased risk of either total study mortality (HR = 1.09[0.95–1.25]) or sudden cardiac death (HR = 1.00 [0.81–1.23]). Similarly, current hydrocodone use was not associated with either increased risk of total study mortality (HR = 1.06 [0.88–1.28]) or sudden cardiac death (HR = 1.14 [0.87–1.49]). Thus, when current users of propoxyphene were compared with current users of hydrocodone (Table 4, Figure 2), the former had no increased significantly risk for either total study mortality (HR = 1.06 [0.87–1.29]) or sudden cardiac death (HR = 0.91 [0.68–1.21]).

Current propoxyphene users had increased risk of death due to medication toxicity (Table 4). The HR relative to nonuser controls was 1.85 (1.07–3.19), which was statistically significant ($p = 0.027$), and that relative to current hydrocodone users was 2.10 (0.87–5.10), which was of borderline statistical significance ($p = 0.100$).

We also examined the risk for the combined endpoint of sudden cardiac or medication toxicity death. There was no significant increased risk for propoxyphene relative to either control group (Table 4).

We performed multiple sensitivity analyses that tested several study assumptions (Table 5). The HRs for total study mortality in propoxyphene versus hydrocodone users did not vary materially from those of the primary analysis. We also considered subgroups of the cohort for which propoxyphene might confer increased risk (Table 5). These included the first study prescription (persons susceptible to propoxyphene's adverse effects), prescriptions in the earlier years of the study (when propoxyphene use was more common), and groups according to opioid dose. None of the HRs were statistically significant.

Discussion

Is the absence of an observed increased risk for sudden cardiac death in study propoxyphene users inconsistent with the pronounced QT prolongation reported in the recent FDA-mandated study? In that study, healthy volunteers given daily doses of 600mg (the maximum recommended clinical dose, twice the median dose in our cohort) and 900mg had respective QTc increases of 29.8 and 38.2 milliseconds,¹⁰ a degree of prolongation often associated with proarrhythmic effects.^{25:26} However, the relation between medication QT prolongation and arrhythmic potential is complex.^{25:26} For example, amiodarone has a lower incidence of torsades de pointes than would be predicted by the magnitude of its QT prolongation.^{25:26} Indeed, we are aware of only one published case report in propoxyphene users of torsades de pointes or related arrhythmias,⁴³ despite its having been marketed for more than 50 years and prescribed for tens of millions of patients worldwide.

Endpoint misclassification may have reduced the observed propoxyphene HRs for sudden cardiac deaths. These deaths were identified with a computer definition based on both the underlying cause of death and pattern of terminal medical care. The definition was designed to be specific. Its positive predictive values in the sample used to develop the definition was 86%.³⁰ Subsequently, we found positive predictive values of 88% in a validation sample³⁰ and 90% in a separate sample of users of study opioids.³⁸ However, the development study suggested that as many as 25% of sudden cardiac deaths could be misclassified as other deaths.³⁰ If such misclassification was more frequent for study propoxyphene users, a true increased risk for sudden cardiac death could be obscured. Nevertheless, our finding of no significant increased risk for either the combined endpoint of sudden cardiac and medication toxicity deaths or total out-of-hospital mortality suggests that such misclassification does not explain the study findings.

Exposure to study opioids was determined from records of prescriptions filled at the pharmacy. Computerized pharmacy records are an excellent source of medication data because they are not subject to information bias³¹ and have high concordance with patient self-reports of medication use.^{44–46} The study opioids are not available over-the-counter and, given that they are controlled substances, they generally are not distributed to physicians as samples. However, some exposure misclassification is possible, as patients may fail to take prescribed opioids or obtain them from other persons, which may have attenuated the observed HRs.

We utilized two specific strategies to minimize confounding. First, there were two distinct control groups. Current use of propoxyphene was compared to periods of nonuse of any prescription opioid as well as to current use of hydrocodone, an opioid with indications similar to those of propoxyphene. Second, by use of propensity scores, the person-time for these control groups was selected in a manner that balanced the distributions of nearly 200 covariates across the study groups. The consistency of the findings between the control groups suggests this strategy reduced confounding.

Study power was limited by the size of the control groups. Although we considered inclusion of more control person-time, this would have reduced comparability of the study groups with regard to potential confounders. Although the measured factors could have been included in regression models, we were concerned that concomitant differences in unmeasured factors and the challenge of constructing regression models that adequately captured covariate interactions/nonlinear effects would lead to uncontrolled confounding.

Propoxyphene users had an approximately two-fold increased risk for deaths due to medication toxicity, which is consistent with numerous reports from emergency departments and poison control centers^{1:13–19} and population-based studies utilizing summary statistical

data.^{3,4} However, because these deaths accounted for only 8% of total deaths in the propoxyphene group, there were no significant differences in overall mortality.

In conclusion, for the study cohort, current use of propoxyphene was not associated with an increased risk for sudden cardiac death, either relative to comparable hydrocodone users or nonuser controls. Propoxyphene users did have an increased risk for medication toxicity deaths, but these were a small proportion of study deaths. Thus, risk for overall out-of-hospital mortality differed by less than 10% between the study groups and was not significantly elevated for propoxyphene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Reference List

1. Obafunwa JO, Busuttill A, Al-Oqleh AMAH. Dextropropoxyphene-related deaths - a problem that persists? *Int J Leg Med.* 1994; 106:315–318.
2. Li-Wan-Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ.* 1997; 315:1565–1571. [PubMed: 9437273]
3. Hawton K, Simkin S, Deeks J. Co-proxamol and suicide; a study of national mortality statistics and local non-fatal self poisonings. *BMJ.* 2003; 326:1006–1008. [PubMed: 12742920]
4. Afshari R, Good AM, Maxwell SRJ, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol.* 2005; 60:444–447.
5. Afshari R, Maxwell S, Dawson A, Bateman DN. ECG Abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *Clin Toxicol.* 2005; 43:255–259.
6. Heaney RM. Left bundle branch block associated with propoxyphene hydrochloride poisoning. *Ann Emerg Med.* 1983; 12:780–782. [PubMed: 6650949]
7. Whitcomb DC, Gilliam FR, Starmer CF, Grant AO. Marked QRS complex abnormalities and sodium channel blockade by propoxyphene reversed with lidocaine. *J Clin Invest.* 1989; 84:1629–1636. [PubMed: 2553778]
8. Committee on the Safety of Medicines of the United Kingdom. Overdose risk prompts UK withdrawal of propoxyphene combination. *J Pain Palliative Care Pharmacotherapy.* 2006; 20:49–50.
9. Bateman ND, Sandilands EA. European medicines evaluation agency bans dextropropoxyphene: A landmark decision for clinical toxicology? *Clin Toxicol.* 2009; 47:783.
10. FDA News Release. Xanodyne agrees to withdraw propoxyphene from the U.S. market. FDA. 2010:888-INFO-FDA.
11. Paulozzi L, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med.* 2006; 31:506–511. [PubMed: 17169712]
12. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med.* 2010; 363:1981–1985. [PubMed: 21083382]
13. Hudson P, Barringer M, McBay AJ. Fatal poisoning with propoxyphene: Report from 100 consecutive cases. *South Med J.* 1977; 70:938–942. [PubMed: 887979]

14. Wetli CV, Bednarczyk LR. Deaths related to propoxyphene overdose: A ten-year assessment. *South Med J*. 1980; 73:1205–1209. [PubMed: 7414379]
15. Jonasson B, Jonasson U, Saldeen T. The manner of death among fatalities where dextropropoxyphene caused or contributed to death. *Forensic Sci Int*. 1998; 96:181–187. [PubMed: 9854833]
16. Jonasson U, Jonasson B, Saldeen T. Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings. *Forensic Sci Int*. 1999; 103:125–132. [PubMed: 10481265]
17. Man CY. Overdose of dologesic with a fatal outcome: a case report. *Hong Kong J Emerg Med*. 2001; 8:207–211.
18. Hawton K, Simkin S, Gunson K, et al. A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol*. 2004; 59:207–212.
19. Jang DH, Hoffman RS, Nelson LS, Chu J, Bhanot K, Bagley W. Fatal outcome of a propoxyphene/acetaminophen (Darvocet) overdose: Should it still be used in the United States? *Ann Emerg Med*. 2011; 57:421–422. [PubMed: 21453827]
20. Madsen PS, Strom J, Reiz S, Sorensen MB. Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand*. 1984; 28:661–665. [PubMed: 6524282]
21. Holland DR, Steinberg MI. Electrophysiologic properties of propoxyphene and norpropoxyphene in canine cardiac conducting tissues in vitro and in vivo. *Toxicol Appl Pharmacol*. 1979; 47:123–133. [PubMed: 425111]
22. Wu C, Fry CH, Henry J. The mode of action of several opioids on cardiac muscle. *Experimental Physiology*. 1997; 82:261–272. [PubMed: 9129940]
23. Amsterdam EA, Rendig SV, Henderson GL, Mason DT. Depression of myocardial contractile function by propoxyphene and norpropoxyphene. *J Cardiovasc Pharmacol*. 1981; 3:129–138. [PubMed: 6160342]
24. Seyler DE, Borowitz JL, Maickel RP. Calcium channel blockade by certain opioids. *Fundam Appl Toxicol*. 1983; 3:536–542. [PubMed: 6662295]
25. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004; 350:1013–1022. [PubMed: 14999113]
26. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacological Reviews*. 2010; 62:760–781. [PubMed: 21079043]
27. Ray WA. Population-based studies of adverse drug effects. *N Engl J Med*. 2003; 349:1592–1594. [PubMed: 14573730]
28. Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? *Ann Intern Med*. 1996; 125:605–613. [PubMed: 8815760]
29. Von Korff M, Saunders K, Ray GT, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain*. 2008; 24:521–527. [PubMed: 18574361]
30. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf*. 2010; 19:563–572. [PubMed: 20029823]
31. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. *Am J Epidemiol*. 1989; 129:837–849. [PubMed: 2646920]
32. Liberthson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med*. 1996; 334:1039–1044. [PubMed: 8598843]
33. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006; 98:253–259. [PubMed: 16611199]
34. Marcus FI, Cobb LA, Edwards JE, et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol*. 1988; 61:8–15. [PubMed: 3337021]
35. Hinkle LE, Thaler HT. Clinical classification of cardiac deaths. *Circulation*. 1982; 65:457–464. [PubMed: 7055867]
36. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med*. 1994; 330:1852–1857. [PubMed: 8196728]

37. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA*. 1998; 279:23–28. [PubMed: 9424039]
38. Kawai VK, Murray KT, Stein CM, et al. Validation of a computer case definition for sudden cardiac death in opioid users. *BMC Research Notes*. 2012; 5:473. [PubMed: 22938531]
39. Landen MG, Castle S, Nolte KB, et al. Methodological issues in the surveillance of poisoning, illicit drug overdose, and heroin overdose deaths in New Mexico. *Am J Epidemiol*. 2011; 157:273–278. [PubMed: 12543628]
40. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. *Pharmacoepidemiol Drug Saf*. 2008; 17:997–1005. [PubMed: 18512264]
41. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med*. 2010; 152:85–92. [PubMed: 20083827]
42. Arnold, SF. *Mathematical statistics*. Prentice-Hall; 1990. p. 157
43. Adler A, Viskin S, Bhuiyan ZA, Eisenberg E, Rosso R. Propoxyphene-induced torsades de pointes. *Heart Rhythm*. 2011; 8:1952–1954. [PubMed: 21763256]
44. Landry JA, Smyer MA, Tubman JG, Lago DJ, Roberts J, Simonson W. Validation of two methods of data collection of self-reported medicine use among the elderly. *Gerontologist*. 1988; 28:672–676. [PubMed: 3229653]
45. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol*. 1995; 142:1103–1110. [PubMed: 7485055]
46. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. *J Am Geriatr Soc*. 1991; 39:1079–1084. [PubMed: 1753045]
47. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. *Am J Epidemiol*. 2003; 158:915–920. [PubMed: 14585769]
48. Donner, A.; Klar, N. *Design and analysis of cluster randomization trials in health research*. 1. London: Arnold; 2000.

Person

Time →

Figure 1.
Illustration of the inclusion of time periods in study person-time for 5 hypothetical cohort members.

Figure 2.

Cumulative incidence of total study mortality and sudden cardiac death (SCD) for current users of propoxyphene and hydrocodone. Hazard ratios (HRs) and 95% confidence intervals adjusted for age, gender, and propensity score decile.

Table 1

Inclusion/exclusion criteria for propoxyphene prescriptions that qualified for the study. The date of the prescription fill is t_0 .

<i>Applies to all three study groups</i>	
1. Age	Age 30–74 years at t_0 .
2. Enrollment	Enrolled with full pharmacy benefits on t_0 and the preceding 365 days.
3. Medical care	At least one filled prescription as well as two encounters with a diagnosis in the 365 days preceding t_0 .
4. Institution	Not residing in a nursing home or other residential institution on t_0 or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge.
5. Serious illness	No evidence of illness on t_0 or the preceding 365 days for which an out-of-hospital death might be expected. Exclusion diseases were cancer, HIV, renal/liver/respiratory failure, organ transplant, degenerative musculoskeletal disorders (e.g., multiple sclerosis), potentially lethal congenital anomalies or childhood conditions, or other evidence of end-stage illness.
6. Recent hospitalization	Not in the hospital on t_0 or the preceding 29 days.
7. Drug abuse	No recorded evidence of drug abuse (except for alcohol/tobacco).
8. Parenteral opioid	a. None within 1 day of prescription fill.
<i>Different criterion for each group</i>	
9. Other opioids	a. <i>Propoxyphene</i> : No prescription for hydrocodone in past 30 days; b. <i>Nonuser control</i> : No prescription for any opioid in past 30 days; c. <i>Hydrocodone</i> : No prescription for propoxyphene in past 30 days.

Table 2

Characteristics of qualifying study opioid prescriptions and matched nonuser control periods.

	Nonuser Control	Hydrocodone	Propoxyphene
Time periods in analysis, N	1,873,500	936,750	1,873,500
<i>Demographic characteristics</i>			
Calendar year baseline	1999.6	1999.6	1999.6
Age at baseline, years	52.4	52.1	52.5
Sex female	73.3%	73.0%	73.4%
White race	77.0%	76.7%	76.8%
Medicaid enrollment disabled	61.9%	61.5%	61.7%
<i>Cardiovascular/metabolic</i>			
Angiotensin converting enzyme inhibitor/receptor blocker	31.6%	31.6%	31.7%
Beta blocker	21.1%	21.2%	21.1%
Calcium channel blocker	26.2%	25.9%	26.2%
Digoxin	5.4%	5.2%	5.5%
Loop diuretic	22.2%	21.9%	22.2%
Other diuretic	26.1%	26.1%	26.2%
Insulin	9.4%	9.2%	9.4%
Oral hypoglycemic	15.8%	15.8%	15.7%
Statin	23.0%	23.2%	23.0%
Coronary heart disease	7.2%	7.0%	7.1%
Congestive heart failure	6.5%	6.4%	6.5%
Cerebrovascular disease	4.6%	4.5%	4.6%
Hypertension	42.0%	41.7%	42.0%
Diabetes	22.0%	21.9%	22.0%
Diabetes complication	7.8%	7.8%	7.9%
<i>Psychoactive medications</i>			
Heterocyclic antidepressant, prior use	14.3%	14.4%	14.2%
Heterocyclic antidepressant, use on t0	15.6%	15.5%	15.6%
Benzodiazepine, prior use	16.7%	16.6%	16.7%
Benzodiazepine, use on t0	24.6%	24.3%	24.5%
Selective serotonin reuptake inhibitor	28.1%	28.2%	27.8%
Trazodone	13.0%	13.1%	12.9%
Bipolar disorder medication	10.1%	10.1%	10.0%
Musculoskeletal relaxant	42.3%	42.3%	42.0%
<i>Other comorbidity</i>			
Beta agonist	27.8%	27.7%	27.6%
Other bronchodilator	16.5%	16.3%	16.4%

	Nonuser Control	Hydrocodone	Propoxyphene
Chronic obstructive pulmonary disease	17.5%	17.3%	17.4%
Asthma	9.5%	9.5%	9.4%
Home oxygen	4.4%	4.4%	4.4%
Unintentional fall	6.2%	6.2%	6.2%
Wheelchair or walker	3.7%	3.6%	3.7%
Incontinence	2.0%	1.9%	1.9%
<i>Medical care utilization</i>			
Cardiovascular hospitalization past year	5.3%	5.2%	5.3%
Other hospitalization past year	12.6%	12.7%	12.6%
Emergency department visit past 30 days	10.4%	10.7%	10.5%

Table 3

Indication, days of supply, dose and prior opioid use for qualifying study opioid prescriptions.

	Hydrocodone	Propoxyphene
N	936,750	1,873,500
<i>Indication</i>		
Back pain	16.0%	16.0%
Other musculoskeletal pain	25.9%	26.4%
Abdominal pain	6.6%	6.5%
Headache	5.6%	5.4%
Other neurologic condition	0.9%	0.9%
Infection	7.2%	7.1%
Trauma	11.2%	10.8%
Surgery	9.6%	9.4%
Dental	1.4%	1.3%
Not found	15.8%	16.2%
Prescription days of supply, mean	11.8	13.1
Prescription daily dose, mg ^a		
Lower quartile	10	200
Median	15	300
Upper quartile	22.5	400
90th percentile	30	500
Study opioids, prior year, days of supply, mean	92.3	94.9
Non-study opioids, prior year, days of supply, mean	10.3	10.1

^aPropoxyphene HCL converted to napsylate equivalents, assuming 65mg HCL = 100mg napsylate. Weighted according to days of supply, essentially equivalent to person-time for current use.

Table 4

Occurrence of out-of-hospital death during current use of qualifying opioid prescriptions and matched nonuser control periods. There are two reference categories for the hazard ratios (HRs): the nonuser control periods and the qualifying hydrocodone prescriptions. CI denotes confidence interval.

	Nonuser Control	Hydrocodone	Propoxyphene
Person-years of study followup	119,282	26,397	59,930
All study deaths			
N	550	142	334
Rate/10 ⁴ person-years	46.1	52.7	55.7
HR (95% CI): nonuser control		1.06 (0.88–1.28)	1.09 (0.95–1.25)
HR (95% CI): hydrocodone			1.06 (0.87–1.29)
Sudden cardiac deaths			
N	260	71	146
Rate/10 ⁴ person-years	21.8	26.4	24.4
HR (95% CI): nonuser control		1.14 (0.87–1.49)	1.00 (0.81–1.23)
HR (95% CI): hydrocodone			0.91 (0.68–1.21)
Medication toxicity deaths ^a			
N	30	6	27
Rate/10 ⁴ person-years	2.5	2.2	4.5
HR (95% CI): nonuser control		0.97 (0.40–2.38)	1.85 (1.07–3.19)
HR (95% CI): hydrocodone			2.10 (0.87–5.10)
Sudden cardiac and medication toxicity deaths			
N	290	77	173
Rate/10 ⁴ person-years	24.3	28.6	28.9
HR (95% CI): nonuser control		1.11 (0.86–1.44)	1.07 (0.88–1.30)
HR (95% CI): hydrocodone			1.01 (0.77–1.32)
Other deaths			
N	260	65	161
Rate/10 ⁴ person-years	21.8	24.1	26.9
HR (95% CI): nonuser control		1.00 (0.76–1.32)	1.11 (0.91–1.36)
HR (95% CI): hydrocodone			1.12 (0.84–1.50)

^aThere were 79% of the toxicity deaths coded as either unintentional or undetermined intent. Results did not differ materially when the analysis was restricted to these, thus excluding deaths coded as intentional.

Table 5

Sensitivity analyses^a. Total study mortality hazard ratios (HRs) for comparison of propoxyphene versus hydrocodone. CI denotes confidence interval.

	HR	95% CI
1: Primary analysis	1.06	0.87–1.29
2: Current+recent use	0.94	0.82–1.09
3: Current use, restricted to new users	1.11	0.82–1.54
4: Controls for clustering by propensity score centile	1.06	0.86–1.31
5: Restricted to first study prescription	1.97	0.90–4.33
6: Restricted to prescriptions prior to 2004	1.01	0.81–1.25
7. Dose		
90th percentile or above	1.22	0.62–2.40
25th–89th percentile	0.98	0.71–1.35
Below 25th percentile	0.68	0.29–1.57

^aThe analyses are defined as follows:

1. Primary analysis compares current use of propoxyphene to current use of hydrocodone.
2. Recent use is cohort person time that extends from the day following the last day of supply to the end of the time period. For a propoxyphene prescription with 10 days of supply for which the full 30 day period was included in the study, the primary analysis was restricted to the first 10 days of current use. This analysis would include the subsequent 20 days of recent use.
3. New users of study opioids,⁴⁷ defined as cohort members with no use in the year prior to cohort entry, except for up to 30 days preceding t₀, which allowed patients entering the cohort from a hospital to have a post-discharge study opioid.
4. Same as primary analysis except robust sandwich variance estimation⁴⁸ to account for potential clustering by propensity score centile.
5. First prescription for specific opioid and none in the year preceding cohort entry. $p = 0.092$. No significant elevation for any of the cause-specific HRs. There were 30 total deaths in the propoxyphene group and 8 for hydrocodone.
6. Fill date prior to calendar 2004.
7. The dose categories are as defined in Table 3. Excludes 4% of propoxyphene and 2% of hydrocodone prescriptions for which we could not reliably calculate daily dose. The HRs compare the dose category for propoxyphene with the comparable category for hydrocodone. Because the propensity scores were not calculated for specific doses, the multivariate analysis controls for age, sex, and calendar year. The trend for dose response is not significant ($p=.284$).