Estimating Prescription Painkiller Mortality in the United States

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PAA 2015

Background

Over the past two decades, prescription painkiller abuse has emerged as an epidemic responsible for an alarming amount of premature mortality (CDC 2012; Warner et al. 2011; Rossen et al. 2013). Drug overdoses have overtaken transport accidents as the number one accidental cause of death in the United States (CDC 2014), and an increasing number of these drug overdoses can be attributed to prescription painkillers. In fact, prescription painkiller overdoses now account for more deaths than both heroin and cocaine overdoses (Palouzzi 2006).

The majority of studies assessing prescription painkiller mortality have only looked at deaths directly attributable to drug abuse as defined by the CDC (2012). However, there are a number of other causes of death that can result from prescription painkiller abuse including liver failure and various injuries. Major prospective cohort studies, such as CPS-I and CPS-II, do not include questions on substance abuse, so they cannot be used to estimate of the effect of drug abuse all cause mortality. Even if we had a large sample prospective cohort study with prescription painkiller abuse questions and linked mortality data, we would still suffer from self-report biases, which are especially abundant when dealing such a sensitive issue.

Perhaps our best current estimates of all-cause prescription painkiller mortality come from retrospective cohort studies. Degenhardt et al. provided a systematic review of

58 such studies assessing mortality among dependent users of heroin and other opioids (2010). Overall, these retrospective cohort studies have found significant increases in mortality rates across a range of causes among drug users. The majority of studies followed up with individuals that were hospitalized or sought treatment for drug abuse. Unfortunately, this is a self-selected population and is not a representative sample. Additionally, only 6 of these studies were conducted in the United States, and all of them studied heroin users. More recently, Veldhuizen and Callaghan conducted a larger retrospective cohort study among people previously hospitalized with opioid-related conditions in Northern California (2011). This study improves upon previous attempts, but again suffers from selection issues, and cannot definitively separate prescription painkiller users from heroin users. Additionally, none of the aforementioned studies has been able to break down prescription painkiller mortality by state, age, and year.

As an alternative to cohort studies and cross-sectional surveys, vital statistics can provide a rich source of data to indirectly evaluate the impact of behaviors on mortality. Previous efforts have been made to evaluate the effect of a risk factor on all-cause mortality using vital statistics in the context of smoking. Specifically, lung cancer has been used as an indicator of smoking, and its relationship with other causes of death has been used to estimate the effect of smoking on all causes of death (Peto et al. 1992; Preston et al. 2010; Fenelon and Preston 2012). A similar approach is used here for estimating the effect of prescription painkiller abuse on all cause mortality.

Methods

The first step in this analysis is to calculate the number of deaths directly attributable to prescription painkiller abuse. It is important to note here that the distinction between "direct" and "indirect" is not clear. For the purposes of this paper, causes of death *directly* caused by prescription painkillers will refer to causes of death that meet the following criteria. First, the death's underlying cause must be attributable to drug abuse, as defined by the CDC (CDC 2012). Second, the multiple cause of death data must make no mention of any illicit drugs. Third, the multiple cause of death data must make at least one mention of a prescription painkiller. These deaths are primarily overdoses. Multiple cause of death data is taken from the NCHS (CDC 2012). I use these prescription painkiller deaths as an indicator of the damage done by prescription painkiller abuse, since any variation in prescription painkiller mortality is entirely reflective of changes in prescription painkiller abuse. I then model the relationship between directly attributable prescription painkiller deaths and all other deaths to estimate the effect of prescription painkiller abuse on mortality for all causes.

I follow Preston, Glei, and Wilmoth (PGW) in the development of my model (2010). First, I use negative binomial regression to predict the log of the death rate for deaths not directly caused by prescription painkiller abuse as a function of the death rate from deaths directly caused by painkiller abuse:

$$\ln (M_O) = B_{PK}M_{PK} + B_AX_A + B_sX_s + B_T X_T + e, \qquad (1)$$

where M_O is the death rate for all other deaths, and M_{PK} is the direct prescription painkiller death rate in each state-year-age group. X_A ,$X_{S,}$, and X_T are dummies for each age group, state, and year, respectively. The original PGW paper included an interaction term for year and lung cancer death rate and age and lung cancer death rate. These terms were excluded in this context, because we are only dealing with a 6 year period, and age interaction terms were insignificant when included in the model. Population for each state-year-age group is specified as a statistical offset. The model is estimated separately for men and women. Five year age groups from 20-24 to 55-59 will be included, as this is where prescription abuse most strongly influences mortality patterns. Only non-Hispanic whites are included in this analysis. Years 1999-2004 are used since they have publicly available state identifiers.

The proportion of deaths attributable to prescription painkillers is found by comparing the actual number of deaths to the number of deaths that would be expected if there were no prescription painkiller abuse and thus no direct prescription painkiller deaths. Following PGW, this is estimated with the following formula:

$$A_O=1 - e\hat{}(-B'_{PK}(M_{PK}-\lambda^N{}_L)) \qquad (2)$$

Where B'_{PK} is the coefficient from the regression, M_{PK} is the observed direct prescription painkiller death rate, and $\lambda^N{}_L$ is the expected rate among non-users. Unlike lung cancer's relationship with smoking, we know non-drug users cannot die from prescription painkillers, so this value is 0.

Finally, after calculating A_O, the overall attributable fraction for deaths from prescription painkillers is the following:

$$A = (D_{PK}+A_O D_O)/D \qquad (3)$$

Where D_{PK} represents observed number of deaths directly caused by prescription painkiller abuse, D represents the observed number of deaths from all causes, and D_O is the number of deaths from all causes other than direct prescription painkiller deaths. The number of deaths attributed to prescription painkiller abuse can then be calculated by state, year, and age.

Results

Equation 1 yields a coefficient for the direct prescription painkiller death rate of .587 ($p<.0001$) for women and .30494 ($p<.0001$) for men. The exponential of these coefficients represents the proportional increase in the death rate for all other causes associated with a 1 per 1,000 increase in the direct prescription painkiller death rate. Using equations 2 and 3, I then estimate prescription painkiller attributable deaths by year, age, and state for men and women. Across the entire population, our estimates of prescription painkiller deaths increase by 44% for men and by 54% for women when accounting for all causes of death. The breakdown by state, year, and age can be seen below. Tables 1A and 1B are sorted by the crude prescription painkiller death rate. For both men and women, West Virginia and New Mexico have the highest prescription painkiller death rate. Tables 2A and 2B show that, as expected, the prescription painkiller death rate increased dramatically from 1999-2004. Finally, Tables 3A and 3B show that the prescription painkiller death rate peaks at ages 45-49 for both men and women.

Table 1A Prescription Drug Induced Mortality by Year for Men

Year	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
1999	196605	7834	11034.38	8.81	0.06
2000	202147	7962	11327.05	8.95	0.06
2001	209043	8892	12796.08	10.02	0.06
2002	214578	10785	15580.29	12.11	0.07
2003	217755	11949	17383.14	13.45	0.08
2004	216845	12525	18208.48	14.00	0.08

Table 1B Prescription Drug Induced Mortality by Year for Women

Year	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
1999	110028	3871	5863.53	4.68	0.05
2000	112970	4182	6388.12	5.05	0.06
2001	117676	4874	7489.65	5.86	0.06
2002	120213	6242	9629.54	7.48	0.08
2003	122050	6962	10845.03	8.39	0.09
2004	121688	7710	12044.61	9.26	0.10

Table 2A Prescription Drug Induced Mortality by State for Men in 2004

State	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
WV	2203	184	288.19	30.16	0.13
NM	1796	171	265.32	30.14	0.15
LA	3501	310	454.79	27.71	0.13
OK	3317	229	359.14	23.28	0.11
NV	2243	154	243.37	22.24	0.11
FL	14828	1087	1643.65	22.07	0.11
UT	1598	192	263.50	21.87	0.16
KY	4551	298	450.94	21.40	0.10
TN	6006	356	552.83	20.59	0.09
AZ	4779	356	537.65	20.27	0.11
PA	9891	831	1139.18	19.70	0.12
MS	2311	114	176.11	18.11	0.08
WA	4390	381	548.22	18.10	0.12
SC	3311	160	248.11	15.41	0.07
MI	7366	485	682.79	15.04	0.09
OH	9139	559	801.18	14.89	0.09
WY	470	27	39.85	14.68	0.08
MD	3137	214	294.56	14.64	0.09
CA	23313	1496	2236.67	14.52	0.10
DE	608	36	49.06	14.27	0.08
ME	1126	76	98.96	13.99	0.09
NC	6312	339	485.99	13.60	0.08
RI	823	51	72.12	13.57	0.09
MA	4735	299	406.92	12.96	0.09
IN	5150	281	393.30	12.89	0.08
CO	3527	216	308.81	12.73	0.09
GA	6073	281	423.95	12.67	0.07
AL	4018	143	217.41	12.19	0.05
OR	3012	145	220.40	12.04	0.07
VT	476	30	40.31	11.91	0.08
AR	2646	96	143.55	11.87	0.05
MT	739	39	54.85	11.72	0.07
MO	4809	219	314.24	11.69	0.07
KS	2141	105	151.63	11.44	0.07
TX	17287	739	1075.38	10.41	0.06
NJ	5381	273	373.39	10.19	0.07
VA	4586	236	318.06	10.01	0.07
NH	944	53	68.09	9.69	0.07
CT	2332	111	150.71	9.23	0.06
IL	8231	378	512.93	9.18	0.06
WI	3745	183	246.52	8.92	0.07
ID	1097	36	51.23	7.17	0.05
MN	3102	125	171.39	6.68	0.06
NY	11580	336	500.30	6.35	0.04
NE	1182	30	43.66	5.02	0.04
IA	2152	48	65.93	4.40	0.03
SD	491	10	14.52	3.96	0.03
ND	390	7	8.84	2.72	0.02

Table 2B Prescription Drug Induced Mortality by State for Women in 2004

State	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
NM	938	105	165.40	18.79	0.18
WV	1277	112	178.80	18.71	0.14
TN	3388	272	458.13	17.07	0.14
NV	1150	114	182.92	16.71	0.16
LA	1959	165	262.30	15.98	0.13
OK	1955	135	236.23	15.31	0.12
FL	7928	648	1038.70	13.95	0.13
KY	2600	172	272.80	12.94	0.10
AZ	2536	206	340.52	12.84	0.13
UT	882	106	154.31	12.81	0.17
WA	2657	252	384.86	12.70	0.14
MT	460	35	55.58	11.88	0.12
SC	1783	114	190.10	11.80	0.11
WY	265	20	31.71	11.68	0.12
AR	1543	80	138.91	11.48	0.09
OR	1768	131	209.70	11.45	0.12
MS	1185	65	111.27	11.44	0.09
NC	3439	254	401.07	11.22	0.12
GA	3487	212	337.30	10.08	0.10
PA	5571	390	579.14	10.02	0.10
DE	354	22	34.07	9.91	0.10
OH	5364	330	530.54	9.86	0.10
IN	3058	191	298.86	9.80	0.10
CA	12682	932	1486.53	9.65	0.12
MO	2768	164	256.30	9.54	0.09
MD	1877	126	188.81	9.38	0.10
CO	1980	146	219.59	9.05	0.11
ME	680	43	63.35	8.95	0.09
KS	1239	76	116.03	8.75	0.09
AL	2398	89	155.58	8.73	0.06
RI	478	29	46.24	8.70	0.10
MI	4150	261	389.48	8.58	0.09
NH	559	39	57.99	8.26	0.10
ID	576	39	56.69	7.94	0.10
SD	281	18	27.92	7.62	0.10
MA	2654	160	234.44	7.47	0.09
TX	9062	493	763.62	7.39	0.08
VA	2658	155	219.88	6.92	0.08
WI	2152	116	177.41	6.42	0.08
CT	1406	72	100.03	6.13	0.07
NJ	3090	123	181.63	4.96	0.06
IL	4478	177	256.80	4.60	0.06
MN	1747	82	117.76	4.59	0.07
VT	272	11	15.38	4.54	0.06
NE	661	25	38.00	4.37	0.06
IA	1195	41	59.02	3.94	0.05
NY	6887	158	254.24	3.23	0.04
ND	211	4	5.50	1.69	0.03

Table 3A Male Age Trends in Prescription Drug Induced Mortality

Age	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
20-24	61170	5169	6128.18	6.59	0.10
25-29	67435	6829	8011.46	7.39	0.12
30-34	55867	5767	6896.16	8.79	0.12
35-39	101379	9892	12503.69	11.81	0.12
40-44	156202	12458	17385.09	15.66	0.11
45-49	214344	10772	17235.26	16.67	0.08
50-54	271990	6290	11800.04	12.77	0.04
55-59	328586	2770	6369.55	8.50	0.02

Table 3B Female Age Trends in Prescription Drug Induced Mortality

Age	Total deaths	Deaths directly attributable to prescription painkillers	Total deaths attributable to prescription painkillers	Crude prescription painkiller death rate(per 100,000)	Proportion of all deaths attributable to prescription painkillers
20-24	19929	1691	1893.33	2.03	0.10
25-29	26501	2778	3150.55	2.91	0.12
30-34	26096	2807	3306.67	4.22	0.13
35-39	53431	5398	6860.13	6.48	0.13
40-44	86346	7420	10547.38	9.50	0.12
45-49	119750	6747	11101.52	10.74	0.09
50-54	160878	4458	8880.40	9.61	0.06
55-59	211694	2563	6714.02	8.96	0.03

To evaluate the reliability of this estimation technique, I reran the analysis using individual causes of death as the dependent variable instead of all other causes of death. I chose three different types of causes of death: Injuries, liver-related deaths, and causes of death that we would not expect to be associated with prescription painkillers. Injuries are often related to prescription painkillers as prescription painkillers can cloud judgment and worsen sensory perception. Liver related deaths are expected to be associated with prescription painkillers, as acetaminophen is a major cause of liver failure in the United States and is often paired with prescription painkillers like hydrocodone and oxycodone (FDA 2009). I also chose several causes of death that have no known relationship to prescription painkillers. These causes included diabetes, colon cancer, skin cancer, and breast cancer for women and prostate cancer for men. Table 5 shows that our expectations are realized as all injuries and liver-related deaths have positive coefficients, and most of them are significant. Meanwhile, none of the unrelated causes of death have significant coefficients in either direction.

Table 5 Coefficients for Other Causes of Death

Type	Cause	Male	Female
Liver	Liver Cirrhosis	.827*	2.16*
	Liver Cancer	1.01*	1.56*
	Hepatitis	1.47*	2.75*
Injury	Fall	0.41	3.34*
	Drown	0.55	3.23*
	Transport Accidents	.877*	1.70*
	Suicide	1.346*	5.81*
Unrelated	Breast Cancer	x	0.38
	Prostate Cancer	0.39	x
	Colon Cancer	0.24	-0.24
	Skin Cancer	0.35	-0.21
	Diabetes	0.11	0.8

The exponential of the coefficients represents the proportional increase in the death rate for the individual cause associated with a 1 per 1,000 increase in the direct prescription painkiller death rate.
(*) if $p<0.05$

Conclusion

This is the first attempt to use vital statistics to indirectly estimate the effect of prescription drug abuse on all-cause mortality. Using the PGW method in the context of prescription painkiller abuse, I found that current estimates of prescription painkiller mortality are too low. I found a roughly 50% increase in the number of deaths attributable to prescription painkillers if we include all causes of death. In 2004, this accounted for 9% of all deaths for ages 20-60. I am also able to provide estimates by state, age, and year, which had been missing from the literature. Hopefully, these estimates can be used in future studies addressing the underlying causes of this epidemic. This research suggests that the prescription painkiller epidemic may be even more severe than we imagined.

References

Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2010 on CDC WONDER Online Database, released 2012. Data are from the Multiple Cause of Death Files, 1999-2010, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/ucd-icd10.html

Centers for Disease Control and Prevention (CDC. "CDC grand rounds: prescription drug overdoses-a US epidemic." *MMWR. Morbidity and mortality weekly report* 61.1 (2012): 10.Human Services, Centers for Disease Control and Prevention.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta‐analysis of cohort studies.*Addiction*, *106*(1), 32-51.

Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and Anesthetic and Life Support Drugs Advisory Committee meeting on June 29 and 30, 2009.

Fenelon, A., & Preston, S. H. (2012). Estimating smoking-attributable mortality in the United States. *Demography, 49(3),* 797–818.

Paulozzi, L. J. (2006). Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. *American journal of public health*, *96*(10), 1755.

Peto, R., Lopez, A. D., Boreham, J., Thun, M., & Heath, C. (1992). Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *The Lancet, 339(8804),* 1268–1278.

Preston, S., Glei, D., & Wilmoth, J. (2011). Contribution of Smoking to International Differences in Life Expectancy. In E. Crimmins, S. H. Preston, & B. Cohen (Eds.), *International Differences in Mortality at Older Ages: Dimensions and Sources* (pp. 105–131). Washington, D.C.: National Academies press.

Preston, S. H., Glei, D. A., & Wilmoth, J. R. (2010). A new method for estimating smoking- attributable mortality in high-income countries. *International Journal of Epidemiology, 39(2),* 430–438.

Rossen, L. M., Khan, D., & Warner, M. (2013). Trends and Geographic Patterns in Drug-Poisoning Death Rates in the US, 1999–2009. *American journal of preventive medicine*, *45*(6), e19-e25.

Warner, M., Chen, L. H., Makuc, D. M., Anderson, R. N., & Miniño, A. M. (2011). Drug poisoning deaths in the United States, 1980-2008. *NCHS data brief*, (81), 1-8.

Veldhuizen, S., & Callaghan, R. C. (2014). Cause-specific mortality among people previously hospitalized with opioid-related conditions: a retrospective cohort study. *Annals of epidemiology*, *24*(8), 620-624.