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Performance of Time-Dependent Propensity Scores: A Pharmacoepidemiology Case Study

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Abstract

Purpose—Pharmacoepidemiologic studies of acute effects of episodic exposures often must control for many time-dependent confounders. Marginal structural models permit this and provide unbiased estimates when confounders are on the causal pathway. However, if causal pathway confounding is minimal, analyses with time-dependent propensity scores, calculated for time-periods defined by individual drug prescriptions, may have better efficiency. We justify time-dependent propensity scores and compare the performance of these methods in a case study from a previous investigation of the risk of medication toxicity death in current users of propoxyphene and hydrocodone, with both substantial time-dependent confounding and a large number of covariates.

Methods—The cohort included Tennessee Medicaid enrollees who filled a qualifying study opioid prescription between 1992 and 2007. We identified 22 time-dependent covariates that accounted for most of the confounding in the original study. We compared analyses with all covariates in the regression model with those based on time-dependent propensity scores and those from marginal structural models.

Results—We identified 489,008 persons with 1,771,295 propoxyphene and 4,088,754 hydrocodone prescriptions. The unadjusted HR (propoxyphene:hydrocodone) was 0.70 (95% CI, 0.46–1.07). Estimates from inclusion of all covariates in the model, time-dependent propensity score analysis with inverse probability of treatment weighting, and marginal structural models were 1.63 (1.04–2.57), 1.65 (1.01–2.72), and 1.64 (0.83–3.27), respectively. Findings varied little with use of alternative propensity score methods, time origin, or techniques for marginal structural model estimation.

Conclusions—Time-dependent propensity scores may be useful for pharmacoepidemiologic studies with time-varying exposures when causal pathway confounding is limited.

Pharmacoepidemiologic studies of the acute effects of medications taken episodically require calculation of endpoint occurrence during periods of active drug use, or *current use*.^{1–5} To control for confounding, the study must account for covariate changes over time because their baseline values may not adequately capture medication use and other patient characteristics at the time of endpoint occurrence. Epidemiologists frequently manage such

potential confounding by including time-dependent covariates in a regression analysis. However, there are two important potential limitations of this approach.

First, traditional regression methods do not work well when the number of covariates is large relative to the number of endpoints. Second, the exposure may affect confounders, which occurs for variables that mediate an effect, or are on the “causal pathway”. For example, in HIV studies, CD4 counts are likely to be both a time-dependent confounder and altered by antiretroviral therapy, hence lying on the causal pathway between medication use and AIDS or its complications. When this occurs, standard methods to control for time-dependent confounders, such as regression analysis, produce biased estimates of the exposure effect.⁶

Marginal structural models, a generalization of inverse probability of treatment (IPT) weighting,^{7–9} can provide unbiased estimates when the number of endpoints is limited or there are time-dependent causal pathway confounders.^{6;10–12} For this reason, many consider them as the default analysis for time-dependent confounders. However, marginal structural model analyses may be inefficient. They divide follow-up into discrete time intervals and calculate a weight that is a product with terms for the current and all preceding intervals. As the number of intervals increases, the weights can take on extreme values, affecting the stability and precision of exposure effect estimates. Although stabilization and truncation of weights can improve efficiency,¹³ there is limited theory to guide their use.

If causal pathway confounding is absent or limited, time-dependent propensity scores may provide another approach for management of time-dependent confounding. They are a natural extension of the propensity score methods^{7–9} commonly employed for analyses with large numbers of covariates. Although time-dependent propensity scores have occasionally been used,^{4;14} little is known regarding their rationale and performance.

We address this question in the context of a prior investigation of the safety of propoxyphene,⁵ a low-potency opioid analgesic withdrawn from the market because of concerns regarding fatality in overdose^{15;16} and adverse cardiovascular effects.^{17–19} This example is characteristic of studies for which time-dependent propensity scores would be useful: an episodic exposure with risk linked to current drug use and substantial confounding by a large number of time-dependent covariates, but with little of this confounding thought to be due to factors on the causal pathway.

Here we present a brief theoretical rationale for the use of time-dependent propensity scores. We compare the time-dependent propensity score analyses to those with individual time-dependent covariates and to analyses from corresponding marginal structural models.

Methods

1. Time-Dependent Propensity Score

a. Setting—Following standard notation¹² we consider a scenario with treatment (exposure) variable A , outcome (endpoint) Y , and covariates (confounders) L (Figure 1)*.

For every possible treatment history , $Y_t^{\bar{a}}$ is the potential (possibly counterfactual) outcome that would have occurred had a subject received treatment history .

b. Justification: Conditional estimates—For an analysis with time-invariant covariates, if there is no unmeasured confounding, then for every possible a

$$Y^a \perp A|L,$$

the conditional exchangeability (also known as strongly ignorable treatment assignment or no unmeasured confounding) assumption. Intuitively, treatment assignment contains no information with regard to the outcome beyond that in the covariates. Thus, conditioning on L consistently estimates the conditional treatment effect. For binary treatments, the propensity score is

$$p(L) = \Pr[A=1|L].$$

Then

$$Y^a \perp A|p(L)$$

so long as $0 < p(L) < 1$ (the positivity assumption),⁸ and thus conditioning on the propensity score also will consistently estimate the conditional treatment effect.

In the time-dependent covariate setting, the conditional exchangeability assumption is:

$$Y_t^{\bar{a}_t} \perp A_t|\bar{A}_{t-1}, \bar{L}_t.$$

It is well known that if there is causal pathway confounding (treatment at time $t-1$ affects the covariates at time t [Figure 1-a]) then conditioning on the treatment and covariate histories does not consistently estimate conditional treatment effects.¹² To do so, one must further assume that treatment does not affect future covariate values (Figure 1-b).

Generalizing the time-invariant result and assuming conditional exchangeability, positivity, and no causal pathway confounding:

$$Y_t^{\bar{a}_t} \perp A_t|p(\bar{A}_{t-1}, \bar{L}_t),$$

*To reduce notational complexity, subscripts indicating subjects are omitted. Upper case letters denote random variables, lower case their observed values. $\bar{a}_t$ denotes the treatment history ($a_0, a_1, \dots, a_t$) through time t with similar notation for the history of other variables. The orthogonal symbol $\perp$ denotes independence; the vertical bar $|$ conditioning, $\Pr[\]$ probability.

where $p(t-1, L_t)$ is the time-dependent propensity score. That is, if conditioning on the time-dependent prior treatment and covariates produces consistent conditional estimates, then, given positivity, so does conditioning on the time-dependent propensity score. The Appendix (§1) illustrates this reasoning for the specific case of the piecewise exponential distribution.

c. Justification: Marginal estimates—Marginal structural models can consistently estimate the marginal effect of A_t in the most general case in which Y_t is influenced by the entire treatment and covariate history and the covariates are affected by prior treatment (Figure 1-a).^{6,12} Absent causal pathway confounding (Figure 1-b), we can obtain consistent conditional estimates as described above (§1-a). As shown in the Appendix (§2), the time-dependent propensity score IPT-weighted mean estimates the marginal mean of potential outcome Y_t^{at} whereas the mean calculated with marginal structural model weights estimates that for potential outcome $Y_t^{\overline{at}}$. Even in the absence of causal pathway confounding, these are not necessarily equal. However, if we further assume that the entire effect of the treatment is mediated by A_t (Figure 1-c), the marginal mean of potential outcome $Y_t^{\overline{at}}$ is equal to that for Y_t^{at} . Thus, a time-dependent propensity score analysis with IPT weights and a marginal structural model will estimate the same marginal treatment effect (Appendix §2).

d. Censoring—Many pharmacoepidemiologic studies consider a time-to-event outcome with right censoring. To consistently estimate treatment effects, the time-to-event and censoring variables must be independent, conditional on the treatment and covariates. Thus, to condition on propensity scores, even in the time-invariant case, such independence must be present when the covariates are replaced by the propensity score. For IPT weighting, independence must hold in the pseudo population created by the weighting.

e. Time periods—Studies with time-dependent covariates require definition of the minimum period into which time is divided. In many automated database studies, this is the person-day, given that the date for medical care encounters typically is available. This may be inappropriate for time-dependent propensity scores. The positivity assumption requires that for every person and time-period combination, the probability of either treatment be non-zero[†]. However, when treatment is determined from prescriptions, it cannot change throughout the interval defined by the prescription, requiring a fixed propensity score during this interval, even though other covariates might change. Thus, the prescription interval is a natural time period for the analysis.

f. Time origin—Time-to-event analyses with right-censored data require definition of a time origin.¹¹ The analysis risk sets consist of all persons alive and uncensored at a time relative to that origin. The time variable typically corresponds to a study subject's time on followup, or a *person-relative time origin*. However, for many pharmacoepidemiologic studies, a time variable that begins with the prescription, or *prescription-relative time origin*, may be appropriate.¹¹ The risk set for day one includes day one for all study prescriptions and so on. This time origin best reflects a hazard that varies according to time since the

[†]See Daniel *et al*¹² §4.2.7 for a generalization for non-binary treatments.

filling of the most recent prescription, which may better represent patient risk for episodically used medications with no carry-over effect.

2. Propoxyphene Example

a. Prior study—We conducted a cohort study of Tennessee Medicaid enrollees between the ages of 30 and 74 and found that current users of propoxyphene had greater risk of death from medication toxicity than did current users of hydrocodone, another widely used low-potency opioid analgesic.⁵ Cohort members had a highly variable number of periods of current use of study drugs, often separated by intervals of non-use. Risk for death from medication toxicity was most plausibly altered by the drugs only during these periods. Because such risk was affected by numerous factors such as patient frailty that in turn were strongly associated with study opioid use, the analysis ultimately included 206 covariates, many of which were likely to change during followup. We hypothesized that causal pathway confounding was minimal, given that the effects of both study opioids are thought to be acute and it was unlikely, although certainly not impossible, that these materially affected future levels of key covariates. However, given the number of medication toxicity deaths, all covariates could not be included in the regression models. Thus, we managed confounding by propensity-score matching propoxyphene and hydrocodone prescriptions.

b. Present study: Cohort and followup—The present study included the full cohort from which the matched cohort for the prior study was selected, with minor changes in drug exposure definition (Appendix §3) to facilitate the marginal structural model analyses. A cohort member's followup consisted of a series of time periods corresponding to the current use of study opioids implied by study prescriptions (Figure 2). Other person-time was not considered, which assumes that periods of time off study opioids did not affect the risk of medication toxicity death.⁵

c. Present study: covariates—The present analyses included a subset of 22 of the original 206 covariates (Appendix Table 1) that were strongly related to the risk of medication toxicity death and accounted for most of the confounding. All covariates were defined for an interval (generally 365 days) just preceding the prescription.

3. Analyses

a. Time-dependent propensity score calculation—The propensity score, the probability that prescription t for subject i is for propoxyphene ($a_{it} = 1$), given the covariates (l_{it}), was estimated from the logistic regression model[‡]

$$\text{logit}\{\Pr[a_{it}=1|l_{it}]\}=\alpha_0+\alpha_1 * l_{it},$$

[‡]The notation for the remainder of the Methods, shown in Figure 2, allows for time-to-event data and right censoring. It does not distinguish between random variables and observed values. Thus, instead of $\Pr[A_{it} = a_{it}]$ to denote the probability that the exposure random variable for time period A_{it} takes on its observed value a_{it} , we write $\Pr[a_{it}]$.

with the prescription as the unit of analysis. The distributions of the propensity score in the hydrocodone and propoxyphene groups (Figure 3) overlapped (range: 0.02 to 0.79). We calculated time-dependent stabilized IPT weights²⁰ from the propensity score as:

$$w_{it}^* = Pr[a_{it}] / Pr[a_{it} | l_{it}]$$

where the numerator was estimated as the marginal frequency of the treatment group.

b. Prescription-relative time origin analyses—In the prescription-relative analyses (Models 1–5), the unit of analysis is the prescription (each prescription considered as an individual observation), which is equivalent to a prescription-relative time origin.¹¹ We assumed a proportional hazards model for the risk of medication toxicity death during the period of current use defined by the prescription (Figure 2, s_{it} days). Thus, for subject i , prescription t the hazard of medication toxicity death on day s in $(0, s_{it}]$ given study opioid a_{it} and covariates l_{it} was

$$\lambda(s | a_{it}, l_{it}) = \lambda_0(s) * \exp(\beta_1 * a_{it} + \beta_2 * l_{it})$$

with

$\lambda_0(s)$ the baseline hazard;

β_1 log of the hazard ratio (HR) for current use of propoxyphene versus hydrocodone[§];

β_2 vector of log HRs for the covariates.

The univariate analysis (Model 1) included only a term for a_{it} ; the analysis with individual covariates (Model 2) also included terms for l_{it} . The propensity-score-weighted analysis (Model 3) included only a_{it} and was fit with IPT weights w_{it}^* . The propensity score stratified analysis (Model 4) modeled the hazard of a medication death for a prescription with treatment a_{it} in stratum m as

$$\lambda_m(s | a_{it}) = \lambda_{m0}(s) * \exp(\beta_1 * a_{it})$$

with a common β_1 across strata estimated by maximum partial likelihood (see Allison²¹ p. 180). For propensity score regression modeling (Model 5), the model included the treatment and l_{it} was replaced with indicator variables for propensity score deciles. The weighted analysis used robust variance estimation because a single time period could be included multiple times.^{21;22} This was unnecessary for the other analyses because the time periods for an individual did not overlap and each person had at most one outcome (see Westreich *et al*¹¹ and Allison²¹ pp. 246–247).

[§]The parameter β_1 technically differs between models: some represent marginal effects (e.g., Models 1, 3, and 4) and others conditional effects (e.g., Models 2 and 5).

c. Person-relative time origin analyses—In the person-relative analyses (Models 6–10, which correspond to Models 1–5 above) the time origin was the fill date of the first study prescription and the time variable corresponded to cumulative days of drug treatment (Figure 2). For example, a person with two prescriptions, each with 15 days of supply would have a total of 30 days of followup and the time variable would be included in the interval (0,30].

Thus, for person i and day s^* in $(0, s_{t_i}^*]$ during the entire period of followup (Figure 2), we assumed

$$\lambda(s^*|a_{it}, l_{it}) = \lambda_0(s^*) * \exp(\beta_1^* a_{it} + \beta_2^* l_{it}),$$

where t is the time period including day s^* and a_{it} and l_{it} indicate the respective time-dependent values of the treatment and covariates for period t . The analyses were as defined for the corresponding prescription-relative time origin analyses, except that the risk sets differed and the propensity score and related variables were time-dependent.

d. Marginal structural models—For these analyses (Models 11–14), we modeled the hazard for person i on day s of followup (s^* in $(0, s_{t_i}^*]$, Figure 2) as

$$\lambda(s^*|a_{it}, l_{i1}) = \lambda_0(s^*) * \exp(\beta_1^* a_{it} + \beta_2^* l_{i1}).$$

The model was fit with time-dependent weights w_{it} calculated for each prescription fill (Appendix, §4). These inverse probability of treatment and censoring (IPTC) weights informally represent the time-dependent probability of the observed treatment and censoring history.^{6;10–12} The outcome model included the baseline covariates because the IPTC weights were stabilized by inclusion of these covariates in the numerator model for the weights (Appendix §4 and Daniel *et al*¹², §4.2.2–§4.2.4) to reduce variability.^{6;10–12;23} However, the estimates are no longer marginal, but rather conditional on baseline covariates. Given the wide range of the IPTC weights (Appendix Table 2), these were truncated at the 1st and 99th percentiles (Models 11,13,14) and at the 5th and 95th percentiles in a sensitivity analysis (Model 12).

We estimated β_1 from proportional hazards with time-dependent weights (Models 11,12).²³ We also included sensitivity analyses that used a common discrete time approximation methods^{6;10–12;21;24} appropriate for time periods with either variable (Model 13) or fixed (Model 14) length (Appendix §5).

e. Statistical software—All analyses were performed with SAS 9.2. The analysis programs are included in the Appendix (§6).

Results

Cohort Characteristics

The study cohort included 489,008 persons with 1,771,295 qualifying propoxyphene and 4,088,754 hydrocodone prescriptions. At the time of the prescription fill, cohort members with hydrocodone prescriptions had markedly different characteristics than did those with propoxyphene prescriptions (Table 1). Hydrocodone was more likely to be prescribed to males, younger patients, and during a later calendar year. These patients were also more likely to be taking psychoactive medications, particularly higher doses of benzodiazepines, and to have had prior medical care indicating an injury. After IPT weighting, the characteristics were highly comparable (Table 1), which suggests the propensity score was properly formulated.^{7;8}

The study included 139,395 person-years of hydrocodone current use and 57,778 person-years of propoxyphene current use, with 94 and 28 medication toxicity deaths, respectively^{**}. The unadjusted incidence of such deaths was greater in the hydrocodone group (6.7 per 10,000 person-years) than in the propoxyphene group (4.8 per 10,000). However, analysis according to propoxyphene propensity score deciles revealed strong confounding (Figure 4), with rates of death in the lowest decile more than 30 times those in the highest decile. Within each decile, the rates for propoxyphene were generally greater than those for hydrocodone.

Time-Dependent Propensity Score Analyses

In the prescription-relative time origin analysis, the univariate HR for propoxyphene was 0.70 (0.46–1.07) (Table 2), indicating a non-significant protective effect for propoxyphene. However, the HR with all of the covariates in the model was 1.63 (1.04–2.57), indicating increased risk. The IPT-weighted analysis had a point estimate (HR = 1.65 [1.01–2.72]) nearly identical to the individual covariate analysis, although the 95% confidence interval (CI) was slightly wider. Both stratification by propensity score deciles and inclusion of these in the regression model led to slightly higher point estimates (1.72 [1.09–2.69] and 1.73 [1.10–2.71] respectively), but with confidence interval widths more comparable to that from the individual covariate analysis.

Person-relative time origin analyses had generally similar findings (Table 2). Point estimates after adjustment for either the individual covariates or the time-dependent propensity score were slightly higher than those from the prescription-relative analysis. The IPT-weighted analysis HR was closest to that from the individual covariate analysis, but the CI was slightly wider.

Marginal Structural Model Analyses

The marginal structural model estimate (HR = 1.64 [0.83–3.27]) was virtually identical to the prescription-relative analyses that included individual covariates in the regression model

^{**}The prior study had 27 medication toxicity deaths in the propoxyphene group; the additional death in the present study resulted from the one day extension of the period of current use.

or that was IPT-weighted (Table 2). However, the 95% confidence interval was substantially wider and included 1. Truncating the weights at the 5th and 95th percentiles did not materially alter this finding, nor did use of a discrete time approximation with variable-length time periods. The estimate from the discrete time approximation with fixed-length time periods was slightly lower.

Discussion

In our case study, time-dependent propensity score analysis results were quite comparable to those from analyses with time-dependent covariates in a regression model. This was true for both prescription-relative and person-relative time origins. These analyses had point estimates close to those from marginal structural model analyses (although no formal tests of significance were performed). This suggests that causal pathway confounding was minimal, informally justifying the time-dependent propensity score approach for the study dataset.

The setting for the propoxyphene marginal structural model analyses differs from that of many previously published studies,^{6,10–12} which typically analyzed the effects of long-term treatments on chronic diseases, such as antiretroviral therapy efficacy for HIV. Once initiated, treatment was assumed to persist,¹¹ limiting variation in weights. In contrast, we studied an acute drug treatment for which disease risk was most plausibly altered only during periods of active medication use. Thus, we formulated marginal structural models that ignored person-time off drug and had weights that permitted treatment to change with each new time period. The outcome model allowed variable-length time periods, reflecting the common circumstance in which prescriptions define different periods of probable drug treatment. This application of marginal structural models may be useful for other pharmacoepidemiologic studies.

Confidence intervals for the marginal structural model analyses were substantially wider than those for the other analyses, even after stabilizing and truncating the weights. This suggests that for pharmacoepidemiology applications with limited causal pathway confounding, the mean square error for marginal structural model estimates may be greater than those from time-dependent propensity score analyses. In addition, use of stabilized weights for marginal structural models requires including the baseline covariates in the model for the numerator of these weights in the outcome model, problematic for large numbers of baseline covariates. Indeed, the original cohort for this case study had 206 covariates, but only 122 medication toxicity deaths.⁵

The period of current drug use defined by a filled prescription, during which the exposure was fixed, was the shortest time interval for which covariate values were updated. Similarly, we used this period for calculation of weights in the marginal structural model analyses. This approach was necessary because the positivity assumption²⁵ requires that the probability of either treatment be non-zero for each study time period. However, if covariate changes within the prescription interval were important (for example, prescriptions issued for long time periods), then propensity-score-based analyses might be suboptimal. In our case study (as in many pharmacoepidemiologic studies), prescription intervals were short (ranging between 2 and 30 days) and covariate changes within the intervals infrequent.

We suggest the time origin be chosen according to the pattern of drug treatment and the hypothesized mechanism by which this affects the endpoint. In our example, study opioid use typically was episodic and toxicity was most plausibly related to current rather than past exposure. This argues for the prescription-relative time origin as risk sets will consist of comparable days relative to the prescription fill. However, for treatments that are less variable or have cumulative effects, a person-relative origin might be more appropriate, although in this circumstance causal pathway confounding might be more likely.

Because our findings come from a single case study, the extent to which they can be generalized to other circumstances is unknown. Although prior study of time-dependent propensity score analyses has been limited,²⁶ our findings suggest these methods are useful for pharmacoepidemiologic studies with large numbers of covariates and time periods, but minimal causal pathway confounding. For the data set studied, these analyses yielded point estimates very comparable to those from either inclusion of individual time-dependent covariates in regression models or from marginal structural model analyses. Further research to better define the reliability and utility of time-dependent propensity score analyses is needed.

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Appendix

1. Time-Dependent Propensity Score: Piecewise Exponential Approximation to Proportional Hazards

The justification for time-dependent propensity scores in Methods, §3-b reduced the time-dependent case to the time-invariant case. The piecewise exponential model provides a concrete illustration of this reasoning. As shown in Figure 2, followup for subject i is divided into t_i periods of length s_{it} such that a treatment (exposure) variable (a_{it}) and a set of covariates (l_{it}) are constant for the period and with an indicator variable for outcome (endpoint) occurrence (y_{it}). We assume that for each period the hazard, conditional on the treatment and covariates, is constant. For this model,²⁶ the hazard function

$$\log\{\lambda_{it}\} = \beta_{0t} + \beta_1 * a_{it} + \beta_2 * l_{it} \quad (1)$$

where β_{0t} is the log of the constant hazard for period t . Estimation of parameters for model (1) is known to be equivalent to estimation of those for a Poisson count variable model in an independent pseudo-population of $\sum t_i$ subjects, where each subject corresponds to a single time period.¹⁻³ In this model

$$\log\{E[y_{it}]\} = \log(s_{it}) + \beta_{0t} + \beta_1^* a_{it} + \beta_2^* l_{it} \quad (2)$$

In the original problem the y_{it} are neither Poisson (because they cannot take on values >1) nor independent (for each person, only the last can be 1). However, because the likelihoods for these models coincide,¹⁻³ solving (2) is equivalent to solving (1), a result that is the basis for Poisson regression for individual subjects with time-dependent covariates. The duality of these models allows us to transform a time-dependent covariate problem (1) into a time-invariant problem (2). Thus, if conditioning on the propensity score in model 2 will provide the same result as conditioning on the covariates, the same will occur for model 1.

If there is causal pathway confounding, estimates conditional on the individual time-dependent covariates will not estimate the conditional treatment effect. By the results above, estimates based on time-dependent propensity score analyses will be similarly biased.

2. Marginal Estimates Via IPT Weighting: Analyses Based on Weights from Time-Dependent Propensity Scores Versus Those from Marginal Structural Models††

Conceptually, marginal structural models create pseudo-populations in which the treatment is sequentially randomized. This permits consistent estimation of the marginal mean of potential outcome $Y_t^{\overline{a_t}}$. In contrast, inverse weighting with the time-dependent propensity score creates a pseudo-population in which the randomization occurs at time t , which permits consistent estimation of the marginal mean of potential outcome $Y_t^{a_t}$ (see below). However, even in the absence of causal pathway confounding (scenario depicted in Figure 1-b) the effect of A_t on Y_t would be confounded by previous treatment history A_{t-1} in the pseudo-population generated by inverse time-dependent propensity score weighting. That is, since the previous treatment history A_{t-1} can affect the outcome Y_t independently of the current treatment A_t , the marginal mean of potential outcome $Y_t^{\overline{a_t}}$ is not necessarily equal to that for $Y_t^{a_t}$. Thus, we cannot establish equivalence between the two weighting methods for the scenario in Figure 1-b.

We can demonstrate this equivalence if the entire treatment effect is mediated by the current value of the treatment variable (Figure 1-c scenario). First, we show the inverse time-dependent propensity score weighted mean is equal to the marginal mean of potential outcome $Y_t^{a_t}$ assuming consistency, conditional exchangeability, and positivity. The inverse time-dependent propensity score weighted mean can be written as

$$E \left[\frac{I[A_t = a_t] Y_t}{f[A_t | \overline{A}_{t-1}, \overline{L}_t]} \right],$$

where $I(\cdot)$ is the indicator function and $f(\cdot)$ is the conditional probability mass function.

$$\begin{aligned}
&= E \left[\frac{I[A_t=a_t]Y_t^{a_t}}{f[A_t=a_t|\bar{A}_{t-1},\bar{L}_t]} \right] && \text{(consistency)} \\
&= E \left\{ E \left[\frac{I[A_t=a_t]Y_t^{a_t}}{f[A_t=a_t|\bar{A}_{t-1},\bar{L}_t]} \middle| \bar{A}_{t-1}, \bar{L}_t \right] \right\} && \text{(double expectation)} \\
&= E \left\{ E \left[\frac{I[A_t=a_t]}{f[A_t=a_t|\bar{A}_{t-1},\bar{L}_t]} \middle| \bar{A}_{t-1}, \bar{L}_t \right] E \left[Y_t^{a_t} \middle| \bar{A}_{t-1}, \bar{L}_t \right] \right\} && \text{(conditional exchangeability)} \\
&= E \left\{ E \left[\frac{f[A_t=a_t|\bar{A}_{t-1},\bar{L}_t]}{f[A_t=a_t|\bar{A}_{t-1},\bar{L}_t]} \right] E \left[Y_t^{a_t} \middle| \bar{A}_{t-1}, \bar{L}_t \right] \right\} \\
&= E \left\{ E \left[Y_t^{a_t} \middle| \bar{A}_{t-1}, \bar{L}_t \right] \right\} \\
&= E \left[Y_t^{a_t} \right].
\end{aligned}$$

If we further assume the potential outcome $Y_t^{\bar{a}_t}$ has the same marginal mean as the potential outcome $Y_t^{a_t}$, that is $E[Y_t^{\bar{a}_t}] = E[Y_t^{a_t}]$, then the two weighting procedures both estimate the marginal mean of potential outcome $Y_t^{\bar{a}_t}$.

3. Changes from Prior Study

Drug exposure

For the present study, there were minor changes in the definitions of drug exposure. In the prior study, current use began on the day the prescription was filled and terminated with the end of the days of supply.⁴ We reduced the number of prescriptions per person by combining contiguous prescriptions for study opioids, so long as the periods of current use overlapped, combined current use was no more than 30 days (Tennessee Medicaid generally has a maximum of 30 days of supply) and none of the covariates changed. This only affected the marginal structural model analyses, for which reducing the number of time periods per person led to more stable weights. We also extended the period of current use by 1 day for prescriptions for which this period was less than 30 days, which did not materially affect study findings. This permitted combining prescriptions with a 1 day separation between periods of current use (not uncommon for the study opioids), further reducing the number of prescriptions per person.

Covariates

The original study included 206 covariates. The present analysis included 22 covariates (Appendix Table 1) that accounted for most of the confounding. The prescription-relative propensity-scorestratified analysis based on the 206 covariates from the original study yielded an HR of 1.82, whereas that from the analysis based on the 22 covariates for the present study was 1.74.

Appendix Table 1

Study covariates, binary unless otherwise noted.

Covariate	Comparison
1. Age at prescription fill	Continuous, per year

Covariate	Comparison
2. Calendar year 1992 to 1995	Vs 2004–2007
3. Calendar year 1996 to 1999	Vs 2004–2007
4. Calendar year 2000 to 2003	Vs 2004–2007
5. Sex, female	Vs male
6. Residence standard metropolitan statistical area	Yes vs no
7. Medicaid enrollment uninsured	Yes vs no
8. Benzodiazepine, former (use past year but not past 90 days)	Vs no use past year
9. Benzodiazepine, recent (use past 90 days but not current use)	Vs no use past year
10. Benzodiazepine, current, <5mg diazepam equivalents**	Vs no use past year
11. Benzodiazepine, current, 6–9mg	Vs no use past year
12. Benzodiazepine, current, 10–19mg	Vs no use past year
13. Benzodiazepine, current, 20+mg	Vs no use past year
14. Selective serotonin reuptake inhibitor	Any past year vs none
15. Bipolar disorder medication	Any past year vs none
16. Emergency department visit prior 30 days	Yes vs no
17. Musculoskeletal relaxant	Any past year vs none
18. Unintentional fall	Any past year vs none
19. Emergency department visit for injury, 1–5 visits	Vs none past year
20. Emergency department visit for injury, 6 or more visits	Vs none past year
21. Outpatient visits for injury, 1–10 visits	Vs none past year
22. Outpatient visits for injury, 11 or more visits	Vs none past year

4: Marginal Structural Model Weights

Weight calculation

The time-dependent weights are the product of a treatment weight (denoted by superscript x) and a censoring weight (superscript c):

$$\begin{aligned}
 w_{it} &= w_{it}^x * w_{it}^c \\
 w_{it}^x &= \prod_{k=1}^t p_{ik}^x \\
 w_{it}^c &= \prod_{k=1}^t p_{ik}^c
 \end{aligned}$$

where the individual terms for the products are

$$\begin{aligned}
 p_{ik}^x &= \Pr[a_{ik} | \bar{a}_{ik-1}, l_{i1}] / \Pr[a_{ik} | \bar{a}_{ik-1}, \bar{l}_{ik}] \\
 p_{ik}^c &= \Pr[c_{ik}=0 | \bar{a}_{ik}, l_{i1}] / \Pr[c_{ik}=0 | \bar{a}_{ik}, \bar{l}_{ik}]
 \end{aligned}$$

where the bar notation denotes the history of the values of the time-varying treatment or covariate through the specified time period (see Figure 2 for notation). The models for the treatment weight numerator and denominator, respectively, were

$$\begin{aligned}\logit\{\Pr[a_{ik}=1]\} &= \alpha_0 + \alpha_1 * a_{ik-1} + \alpha_2 * l_{i1} \\ \logit\{\Pr[a_{ik}=1]\} &= \alpha_0 + \alpha_1 * a_{ik-1} + \alpha_2 * l_{ik}\end{aligned}$$

This modeled treatment probability for a time period as a function of treatment in the prior period and either the baseline covariates or the covariates in the current time period. (Throughout this section, for simplicity we denote all parameters with α , although these parameters clearly differ between models.) Given that much study opioid use was episodic, we hypothesized it was more strongly related to recent rather than remote history.

The models for the censoring weight numerator and denominator, respectively, were

$$\begin{aligned}\logit\{\Pr[c_{ik}=1]\} &= \alpha_0 + \alpha_1 * k + \alpha_2 * a_{ik} + \alpha_3 * l_{i1} \\ \logit\{\Pr[c_{ik}=1]\} &= \alpha_0 + \alpha_1 * k + \alpha_2 * a_{ik} + \alpha_3 * l_{ik}\end{aligned}$$

The term for the time period (k) was included because it was strongly related to the probability of censoring.

The distribution of the weights (excluding those for the first time period, which by definition were 1) is shown in Appendix Table 2. Given the extreme values, they were truncated at the 1st and 99th percentiles.

Appendix Table 2

Distribution of marginal structural model (MSM) weights (prior to truncation). Excludes weights for the first time period, which by definition are 1.

Percentile	MSM Treatment Weight	MSM Censoring Weight	MSM Weight
Minimum	0.000038572	0.000029843	0.000025259
1st	0.114841621	0.073919730	0.027046284
5th	0.318198241	0.206221984	0.118766570
10th	0.468472236	0.321313504	0.224852629
25th	0.737734956	0.574393955	0.500723452
50th	0.997192171	0.845243987	0.836161037
75th	1.191405556	0.982832114	1.067799465
90th	1.704992879	1.352723708	1.630875634
95th	2.491622884	2.049419746	2.551147684
99th	8.496094814	6.240454391	9.241844235
Maximum	467370.8417	1059.279845	140312.1591

5. Marginal Structural Models, Discrete Time Approximation

In the discrete time approximation, a data set is created with one observation for each time period of each subject. The probability of an outcome for subject i in period t (e.g., $y_{it} = 1$, see Figure 2), given that none has yet occurred is then modeled. The approximation is

accurate if this probability is low for each period, which is the case for medication toxicity deaths.

The most common discrete time approximation is the pooled logistic model. The distribution of y_{it} is assumed to be binomial and the model is:

$$\text{logit}\{\Pr[y_{it}=1]\}=\beta_{0t}+\beta_1*a_{it}+\beta_2*l_{1t}.$$

However, this assumes that the time periods are of equal length. As Alison⁵ notes (pp 248–249), applying this analysis to data for which the intervals are of unequal length can result in biased estimates if the probability of the outcome is related to the length of the interval. For the present study the risk of medication toxicity death is most plausibly associated with acute opioid exposure and thus should increase with increasing periods of exposure. Given that this can vary markedly for the study opioid prescriptions, we used a discrete time approximation that accounted for the days of opioid current use in each prescription. We can use the piecewise exponential approximation to proportional hazards and the equivalence of this to Poisson regression with independent count variables^{1–3} to solve

$$\log \{Pr[Y_{it}=1]\}=\log (s_{it})+\beta_{0t}+\beta_1*a_{it}+\beta_2*l_{1t}.$$

This discrete time approximation is a standard way of accounting for events whose occurrence is dependent on the length of a time interval (e.g., see Kalbfleisch and Prentice⁶ p.136).

These models are over-parameterized given that they include a term for the hazard during each time period. We followed two approaches to estimating these parameters. First, we simply estimated a single intercept term, the assumption of constant hazard. Second, we performed an additional analysis that included time period via 6 indicator variables: for time periods 1–10, 11–20, ..., and 61+. The results were essentially identical to those of the primary analysis with a single intercept term and thus are not presented.

In the discrete time approximation, the weighting creates a pseudo-population in which a single subject with an endpoint could be included multiple times. To account for this, robust variance estimation via generalized estimating equations was used. This utilized SAS Proc GENMOD with the statement

REPEATED SUBJECT=(cohort member study number)/TYPE=IND.

6: SAS Analysis Programs

```
/* ===== Analysis programs for Table 2
===== */
/* Each analysis is referred to by its number in the "Model" column of Table
```



```

2 */
/* Inputs */
/* Datasets
RxAnalysis08 Includes one observation for each study prescription
Observation variables listed below */
/* Variables
recip ID of individual cohort members
curdays Days of current use in prescription
lpyears log(curdays/365)
Ptime0 Person-relative time, first day of prescription
Ptime1 Person-relative time, last day of prescription
xanypois_cur Indicator variable for endpoint
tablopioid Exposure: 0 = hydrodocone, 1 = propoxyphene
&Reduced_Variables Covariate values for given prescription, e.g., lit
&Reduced_Variables_1 Covariate values for first prescription, e.g., li1
IPT_Weight Inverse probability of treatment weight for prescription
Rx_Decile Propensity score decile for prescription
Wit Marginal structural model weight, truncation 1/99 %
Wita " ", truncation 5/95 */
/* Formats
decilef Combines upper two deciles propensity score */
/* Macros
%PrintCoxParms Prints proportional hazards parameter estimates
%PrintGENMODParms1 Prints generalized linear model parameter estimates */
Title2 'Time-dependent propensity score';
Title3 '1. Prescription relative, Univariate';
ods select none;
proc phreg data=data.RxAnalysis08;
class tablopioid /descending;
model curdays*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_01;
run;
%PrintCoxParms(DataFile=data.RxTab02_01);
run;
Title3 '2. Prescription relative, Individual covariates ';
ods select none;
proc phreg data=data.RxAnalysis08;
class tablopioid /descending;
model curdays*xanypois_cur(0) = &Reduced_Variables tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_02;
run;
%PrintCoxParms(DataFile=data.RxTab02_02);
run;
Title3 '3. Prescription-relative, IPT weighting, robust variance';

```

```

ods select none;
proc phreg data=data.RxAnalysis08 covs(aggregate);
weight IPT_Weight;
ID Recip;
class tablopioid/descending;
model curdays*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=Data.RxTab02_03;
run;
%PrintCoxParms(DataFile=data.RxTab02_03);
run;
Title3 '4. Prescription-relative, Propensity score decile stratification ';
ods select none;
proc phreg data=data.RxAnalysis08;
format Rx_Decile decilef.;
strata Rx_Decile;
class tablopioid /descending;
model curdays*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=Data.RxTab02_04;
run;
%PrintCoxParms(DataFile=Data.RxTab02_04);
Title3 '5. Prescription-relative, Propensity score decile in model';
ods select none;
proc phreg data=data.RxAnalysis08;
format Rx_Decile decilef.;
class tablopioid Rx_Decile/descending;
model curdays*xanypois_cur(0) = Rx_Decile tablopioid /RL;
ods output ParameterEstimates=Data.RxTab02_05;
run;
%PrintCoxParms(DataFile=Data.RxTab02_05);
Title3 '6. Person-relative, Univariate';
ods select none;
proc phreg data=data.RxAnalysis08;
class tablopioid /descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_06;
run;
%PrintCoxParms(DataFile=data.RxTab02_06);
run;
Title3 '07. Person-relative, individual covariates in model';
ods select none;
proc phreg data=data.RxAnalysis08;
class tablopioid /descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = &Reduced_Variables tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_07;

```

```

run;
%PrintCoxParms(DataFile=data.RxTab02_07);
run;
Title3 '08. Person-relative, IPT weighting, robust variance';
ods select none;
proc phreg data=data.RxAnalysis08 covs(aggregate);
weight IPT_Weight;
ID Recip;
class tablopioid/descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=Data.RxTab02_08;
run;
%PrintCoxParms(DataFile=data.RxTab02_08);
run;
Title3 '09. Person-relative, Propensity score decile stratification ';
ods select none;
proc phreg data=data.RxAnalysis08;
format Rx_Decile decilef.;
Strata Rx_Decile;
class tablopioid/descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = tablopioid /RL;
ods output ParameterEstimates=Data.RxTab02_09;
run;
%PrintCoxParms(DataFile=data.RxTab02_09);
run;
Title3 '10. Person-relative, Propensity score decile in model';
ods select none;
proc phreg data=data.RxAnalysis08;
format Rx_Decile decilef.;
class tablopioid Rx_Decile/descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = Rx_Decile tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_10;
run;
%PrintCoxParms(DataFile=data.RxTab02_10);
run;
Title2 'Marginal Structural Models';
Title3 '11. Proportional hazards with time-dependent weights, robust
variance';
ods select none;
proc phreg data=data.RxAnalysis08 covs(aggregate);
weight Wit;
ID Recip;
class tablopioid /descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = &Reduced_Variables_1 tablopioid /RL;

```

```

ods output ParameterEstimates=data.RxTab02_11;
run;
%PrintCoxParms(DataFile=data.RxTab02_11);
run;
Title3 '12. Proportional hazards, time-dependent weights, robust variance,
5/95 trunc';
ods select none;
proc phreg data=data.RxAnalysis08 covs(aggregate);
weight Wita;
ID Recip;
class tablopioid /descending;
model (Ptime0,Ptime1)*xanypois_cur(0) = &Reduced_Variables_1 tablopioid /RL;
ods output ParameterEstimates=data.RxTab02_12;
run;
%PrintCoxParms(DataFile=data.RxTab02_12);
run;
Title3 '13. Discrete time approximation, variable length time period';
ods select all;
proc genmod data=data.rxanalysis08 descending;
weight Wit;
class recip tablopioid/descending;
model xanypois_cur = &Reduced_variables_1 tablopioid/dist=poisson link=log
offset=lpyears;
repeated subject=recip/sorted type=ind;
ods output ParameterEstimates=Data.RxTab02_13;
run;
%PrintGENMODParms1(DataFile=Data.RxTab02_13);
Title3 '14. Discrete time approximation, fixed length time period';
ods select all;
proc genmod data=data.RxAnalysis08 descending;
weight Wit;
class recip tablopioid/descending;
model xanypois_cur = &Reduced_variables_1 tablopioid/dist=binomial
link=logit;
repeated subject=recip/sorted type=ind;
ods output ParameterEstimates=Data.RxTab02_14;
run;
%PrintGENMODParms1(DataFile=Data.RxTab02_14);

```

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Figure 1.

Causal diagram for various time-dependent confounding scenarios. A is the treatment variable, L the covariates, and Y is the outcome. Three scenarios are presented a) most general case with *causal pathway confounding* in which the treatment can affect the future values of the covariates; b) no causal pathway confounding but past treatments can affect the outcome independent of A_t , and c) the entire causal effect of the treatment is mediated by A_t .

Figure 2.

Study time periods and variables. Followup is depicted for a single cohort member, person i , who has t_i study opioid prescriptions, each represented by a colored block. The numbers within the blocks denote the time periods, which are half open--e.g., $(0, s_{it}]$, may be of different lengths and separated by intervals of non-use of study opioids, which are not considered in the analysis. The variables for a single time period (denoted by t) are shown, along with the corresponding notation.

Figure 3.
Distribution of the propensity score in the propoxyphene and hydrocodone groups.

Figure 4.

Unadjusted incidence of medication toxicity deaths among current users of propoxyphene and hydrocodone, according to decile of the propoxyphene propensity score. PY denotes person-years of current use. In this and all other stratified analyses, the two highest propensity deciles were combined to assure at least 1 endpoint per stratum.

Table 1

Study covariates at the time of the prescription fill. Unless otherwise specified, all values are percentages. Covariates describing medical care reflect that received during the 365 days just preceding the prescription fill, unless otherwise stated. IPT denotes inverse probability of treatment.

	Unweighted		IPT Weighted	
	Hydrocodone	Propoxyphene	Hydrocodone	Propoxyphene
N of prescriptions *	4,088,754	1,771,295	-	-
Age, mean	47.9	52.5	49.3	49.2
Calendar year, mean	2001.8	1999.6	2001.1	2000.9
Sex, female	66.0%	73.5%	68.3%	68.4%
Residence, standard metropolitan statistical area	48.4%	47.1%	48.0%	48.3%
Medicaid enrollment uninsured	23.7%	22.6%	23.4%	23.7%
Benzodiazepine use				
None in past year	43.6%	51.2%	45.9%	46.6%
Former (use past year but not past 90 days)	10.0%	8.9%	9.7%	9.6%
Recent (use past 90 days but not current use)	8.6%	7.7%	8.3%	8.2%
Current, <5mg diazepam equivalents **	3.8%	5.5%	4.3%	4.3%
Current, 6–9mg	8.2%	8.5%	8.3%	8.2%
Current, 10–19mg	13.0%	10.5%	12.2%	11.9%
Current, 20+mg	12.8%	7.7%	11.3%	11.2%
Selective serotonin reuptake inhibitor	37.9%	27.6%	34.8%	35.1%
Bipolar disorder medication	17.2%	9.9%	15.0%	15.1%
Emergency department visit prior 30 days	15.4%	10.4%	13.9%	14.1%
Musculoskeletal relaxant	53.8%	41.6%	50.0%	49.7%
Unintentional fall	10.3%	6.1%	9.0%	9.1%
Emergency department visit for injury				
1–5 visits	29.2%	20.4%	26.5%	26.7%
6 or more visits	1.2%	0.4%	0.9%	0.9%
Outpatient visits for injury				
1–10 visits	41.7%	36.4%	40.1%	40.4%
11 or more visits	0.7%	0.4%	0.6%	0.6%

* There were 74,782 persons with only prescriptions for propoxyphene, 213,691 with only prescriptions for hydrocodone, and 200,535 with prescriptions for both.

** Benzodiazepine dose equivalents: Alprazolam (0.75 mg), Bromazepam (6 mg), Chlordiazepoxide (15 mg), Clonazepam (0.5 mg), Clorazepate (7.5 mg), Diazepam (4 mg), Estazolam (1 mg), Flurazepam (15 mg), Halazepam (60 mg), Lorazepam (1 mg) Oxazepam (30 mg), Quazepam (15 mg), Temazepam (7.5 mg), Triazolam (0.125 mg).

Table 2

Performance of analyses with time-dependent propensity scores relative to those with time-dependent individual covariates and marginal structural model analyses. IPT denotes inverse probability of treatment.

Model	Description	Hazard Ratio Estimate	95% Confidence Interval
<i>Time-Dependent Covariate Analyses: Propensity Score versus Individual Covariates</i>			
<i>Time Origin Prescription-Relative</i>			
1	Univariate	0.70	0.46–1.07
2	Individual covariates in regression model	1.63	1.04–2.57
3	Propensity score: IPT weighting	1.65	1.01–2.72
4	Propensity score: stratified by propensity score deciles	1.74	1.10–2.75
5	Propensity score: regression model includes propensity score deciles	1.73	1.10–2.71
<i>Time Origin Person-Relative</i>			
6	Univariate	0.71	0.47–1.09
7	Individual covariates in regression model	1.67	1.06–2.62
8	Propensity score: IPT weighting	1.69	1.03–2.77
9	Propensity score: stratified by propensity score deciles	1.77	1.12–2.78
10	Propensity score: regression model includes propensity score deciles	1.78	1.13–2.80
<i>Marginal Structural Model Analyses*</i>			
11	Weights truncated at 1st, 99th percentiles	1.64	0.83–3.27
12	Weights truncated at 5th, 95th percentiles	1.63	0.82–3.24
13	Discrete time approximation, variable prescription length allowed	1.64	0.84–3.20
14	Discrete time approximation, fixed prescription length assumed	1.56	0.80–3.04

* Unless otherwise specified, estimated with proportional hazards with time-dependent inverse probability of treatment and censoring weights truncated at the 1st and 99th percentiles.