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Mortality Rates Among Substance Use Disorder Participants in Clinical Trials: Pooled Analysis of Twenty-Two Clinical Trials Within the National Drug Abuse Treatment Clinical Trials Network☆,☆☆

Robert Lindblad, M.D. [a], Lian Hu, Ph.D., M.P.H. [a], Neal Oden, Ph.D. [a], Paul Wakim, Ph.D. [b], Carmen Rosa, M.S. [c], Paul VanVeldhuisen, Ph.D. [a]

[a] The Emmes Corporation, Rockville, MD, United States
[b] Clinical Center, National Institutes of Health, Bethesda, MD, United States
[c] Center for the Clinical Trials Network, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, United States

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ABSTRACT

Background: Most substance use disorders (SUD) treatment clinical trials are too short and small to reliably estimate the incidence of rare events like death.
Objective: The aim of this study is to estimate the overall mortality rates among a SUD treatment-seeking population by pooling participants from multiple clinical trials conducted through the National Institute on Drug Abuse (NIDA)-sponsored National Drug Abuse Treatment Clinical Trials Network (CTN).
Participants: Drug and or alcohol users (N = 9866) who sought treatment and participated in one of the twenty-two CTN trials.
Measurements: Data were collected through randomized clinical trials in national community treatment programs for SUD. Pooled analysis was performed to assess age- and gender-standardized mortality rate(s) (SM rate(s)), and mortality ratio(s) (SM ratio(s)) of CTN trial participants compared to the U.S. general population.
Results: The age- and gender-SM rate among CTN trials participants was 1403 (95% CI: 862–2074) per 100,000 person years (PY) compared to 542 (95% CI: 541–543) per 100,000 PY among the U.S. general population in 2005. By gender, age-adjusted SM ratio for female CTN trial participants was over five times (SM ratio = 5.35, 95% CI: 3.31–8.19)), and for male CTN trial participants, it was over three times (SM ratio = 3.39, 95% CI: 2.25–4.90) higher than their gender comparable peers in the U.S. general population.
Conclusions: Age and gender-standardized mortality rates and ratios among NIDA CTN SUD treatment-seeking clinical trial participants are higher than the age and gender comparable U.S. general population. The overall mortality rates of CTN trial participants are similar to in-treatment mortality reported in large U.S. and non-U.S. cohorts of opioid users. Future analysis with additional CTN trial participants and risk times will improve the stability of estimates, especially within subgroups based on primary substance of abuse. These SUD mortality rates can be used to facilitate safety monitoring within SUD clinical trials.

1. Introduction

Substance use is a serious public health problem in the U.S. associated with high rates of pre-mature deaths and high costs in health care and societal economics (Fenoglio, Parel, & Kopp, 2003; ONDCP, 2012; United Nations Office on Drugs and Crime, 2012). Mortality in SUD populations has been mainly investigated in prospective cohort studies (Arendt, Munk-Jorgensen, Sher, & Jensen, 2011; Degenhardt, Bucello, et al., 2011; Degenhardt, Singleton, et al., 2011). A meta-analysis of 58 cohort studies across many countries among opioid dependent or regular users reported a pooled all-cause mortality rate of 2090 (95% CI: 1930–2260) deaths per 100,000 person-years (PY) and a pooled age- and gender-standardized mortality ratio (SM ratio) of 14.66 (95% CI: 12.82–16.50) compared to the general population (Degenhardt, Bucello, et al., 2011). Another systematic review that included seven cohort studies with problematic or dependent cocaine users suggests that crude mortality rates are highly variable across individual studies and countries, ranging from 530 (95% CI: 100–1580) to 6610 (95% CI: 5210–7110) per 100,000 PY (Degenhardt, Bucello, et al., 2011; Tyndall et al., 2001). Factors such as country of the study, SUD subpopulations (drug injectors versus non-injectors), cohort sizes, follow-up stages,

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and treatment phases (in-treatment versus post-treatment) likely contribute to the variability in mortality rates reported in the literature. In addition, mortality rates reported in the above meta-analysis were derived from longitudinal follow-up studies and may have limited generalizability to SUD patients who seek treatment primarily in community treatment programs through SUD treatment clinical trials. To our knowledge, there have been no reports estimating mortality in SUD treatment-seeking clinical trial participants.

The National Institute on Drug Abuse (NIDA)-sponsored National Drug Abuse Treatment Clinical Trials Network (CTN) was established in 1999. Through February 2012, twenty-three clinical trials involving pharmacological and/or psychosocial/behavioral interventions have been completed among SUD populations (Tai et al., 2010; Wells, Saxon, Calsyn, Jackson, & Donovan, 2010). Participants enrolled in CTN research studies are self-identified substance users with a confirmed SUD diagnosis and seeking treatment at a community treatment program (CTP), with research trials typically having short follow-up (average six months) and sample sizes of a few hundred participants. When these trials are analyzed individually, it leads to imprecise estimates of rare events like death. The public availability of participant-level information from these individual CTN trials allows for pooling of data and provides more precise estimates of the overall mortality among SUD clinical trial participants. In addition to highlighting the issue of mortality in substance use populations, as studied in the CTN, the primary goal of estimating mortality in SUD clinical trials is to provide a reference to facilitate safety monitoring of SUD clinical trial interventions in the future.

The main objective of the current analysis is to estimate the overall mortality rates by pooling CTN clinical trial data and then compare these rates to the U.S. general population.

2. Methods and materials

Of the completed twenty-three trials, twenty-two trials were included in this analysis. The excluded trial (NIDA-CTN-0029) only enrolled cigarette smokers with attention deficit hyperactivity disorder (ADHD) and specifically excluded individuals with current drug abuse or dependence. The target population of the remaining twenty-two trials was drug and or alcohol abuse or dependence individuals. De-identified data of 9866 randomized participants from these twenty-two multi-site clinical trials were retrieved from the NIDA Data Share (https://datashare.nida.nih.gov/). Data from various assessments collected on the case report forms of these trials were used to construct a database for analysis, which included adverse event (AE)/serious AE (SAE) forms, demographics, participant disposition, and questionnaires. In general, CTN trials recorded death events on AE, SAE, or special disposition case report forms (CRFs). The occurrence of a death could be discovered by study staff via reporting by family members, friends, hospital records, or newspaper obituaries. The causes of deaths recorded in CRFs were then uniformly MedDRA coded. Baseline primary substance of use was identified through the Addiction Severity Index-Lite (ASI-Lite) (McLellan, Luborsky, Woody, & O'Brien, 1980) for twenty out of the twenty-two trials. For the remaining two trials without the ASI-Lite assessment tool, a self-reported substance use instrument or a global substance use measure was used to identify primary substance use at the baseline. For the purposes of analysis, we collapsed the smaller primary substance of use subgroups of cannabis, alcohol, other drugs, and no problem into a single subgroup named "All Others". These primary substances of abuse had relatively low total risk times (from 83 to 570 PY), limiting our ability to examine differences in mortality, and further, none of included CTN trials specifically targeted these substances despite them being noted as a primary substance of use based on the ASI-Lite assessment.

Mortality rates were calculated as the number of observed deaths divided by cumulative time (days) at risk from all participants, and then standardized to 100,000 person-years (PY) (Porta, 2014; Zhang & Yu, 2008). Risk time for each participant was calculated as the days from randomization to death (if died) or the last available contact day (if completed the trial or were lost to follow-up). Death and demographic information for the U.S. general population was retrieved from the "Human Mortality Database" (http://www.mortality.org/). To compare the mortality of CTN trial participants to the U.S. general population, both direct standardization (age- and gender-standardize mortality rates, SM rates) and indirect standardization methods (standardized mortality ratio, SM ratio) were used. Average age (range: 13–78) and gender distributions of the U.S. general population of the year 2001–2010 were used as the reference population structure. Specifically, an age- and gender-SM ratio was computed as the ratio of the observed number of deaths over the expected number of deaths in the CTN sample, where the age and gender-specific mortality rate of the reference population (i.e., U.S. population) was applied to the target population (i.e., CTN sample) to yield the expected number (Last, 1983). Ninety-five percent confidence intervals (95% CIs) around SM ratio were estimated using Byar's approximation to Poisson-distributed deaths (Breslow & Day, 1987; Liddell, 1984; Sahai & Khurshid, 1993). An age- and gender-SM rate was calculated for both the CTN sample and the U.S. general population of the year 2005 by applying age- and gender-specific mortality rates of the target sample (i.e., CTN sample or U.S. population of the year 2005) to the age and gender profile-matched reference sample (i.e., average age and gender distributions of U.S. populations of the year 2001 to 2010). 95% CIs of SM rates were estimated assuming a Gamma distribution of the rate by an exact method exploiting the relationship between the chi-squared and cumulative Poisson distributions (Fay & Feuer, 1997; Zhang & Yu, 2008).

An advantage to pooling multiple trials together is to reduce the sampling error and improve the stability of estimates. In the pooled analysis, between-trial heterogeneity (i.e., random trial effect) was investigated by an extended proportional hazard (PH) Cox regression model (i.e., frailty model), assuming that the between-trial variance follows a normal distribution with zero mean and variance σ^2 (Simmonds et al., 2005). In the Cox PH model, a participant either had a death event, or was censored at loss to follow-up (LTFU) or study completion date. For a LTFU participant, the censoring day was the last contact day before the participant was lost.

Both unadjusted (crude) and adjusted survival curves of the pooled CTN sample were calculated using the Cox PH model. The corrected group prognosis method (Chang, Gelman, & Pagano, 1982; Ghali et al., 2001), a method analogous to direct standardization, was applied to generating the adjusted survival curves. The reference population for the adjusted survival curves was the U.S. population of Year 2005, approximately the mid-time point when CTN trial participants were recruited (2001–2010).

SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) was used to perform all analyses.

3. Results

3.1. Demographics and mortalities of pooled CTN trials

Table 1 characterizes the analysis population pooled across the 22 CTN trials. Mean age of the 9866 participants randomized in these 22 trials was 37.1 years old. The majority of the study population was male (58.2%), white (52.2%), and non-Hispanic origin (82.6%). There were 23.5% African Americans/black. Primary substance of use at baseline was illicit or licit opioids among 26.3% participants, multi-drug/or combined drug/substance and alcohol among 24.0% participants, stimulant among 17.6% participants and all others among 31.1% participants which included alcohol among 14.1% participants, cannabis in 11.3%, other drugs among 2.1%, and no-primary drug/alcohol problem in 3.6% participants. A total of 49 deaths (0.5%) were reported over 4730 PY of risk time in the 9866 CTN participants for an overall pooled