**S1 Protocol**

**Extract from Specific Aims (NIH grant submission, grant funded, National Heart, Lung, and Blood Institute [HL081707])**

Hypnotic prescriptions for U.S. adults increased from 5.3 million in 1999 to 20.8 million in 2010, with the most frequent use by persons 65 years of age or older.1,2 The 3 most commonly prescribed hypnotics are the benzodiazepines, selective benzodiazepine receptor agonists (sBzRAs), and trazodone.3 Observational studies of hypnotics and mortalityconsistently have found that benzodiazepines and sBzRAs are associated with a 60 to 73% increased risk of all-cause mortality.4,5 Controversial biological plausibility and study limitations have led most to conclude that the association is not causal.6,7

One mechanism by which benzodiazepines and sBzRAs could increase mortality is nocturnal respiratory impairment, which causes apnea, hypoxemia and hypercapnia. These are associated with sympathetic activation and increased risk of cardiac arrhythmias and cardiovascular death,8-12 the most common cause of death in the U.S.13 Benzodiazepines impair respiration: they decrease respiratory muscle strength and endurance,14 decrease oxyhemoglobin saturation (SpO2) in anesthetized patients,15 produce obstructive apnea and hypopnea in overdose,16 impair minute ventilation, decrease SpO2 and cause hypercapnia in patients with chronic obstructive pulmonary disease,17,18 have synergistic respiratory depressant effects in combination with opioids19,20 that increase the risk of fatal overdoses,21 and reduce minimum nocturnal SpO2 in patients with sleep apnea.22 The hypothesis that these adverse respiratory effects increase cardiovascular risk is supported by our preliminary data showing a dose-related increase in the incidence of out-of-hospital cardiovascular deaths (most commonly sudden cardiac death) for benzodiazepines (§a.2.d). The sBzRAs impair respiration to a lesser degree22-27 and the available data indicate trazodone causes minimal, if any, respiratory impairment.27-32 Thus, trazodone could have better cardiovascular safety than the benzodiazepines and possibly the sBzRAs.

Opioid analgesics could potentiate the adverse cardiovascular effects of benzodiazepines and sBzRAs. Concurrent opioid-hypnotic use is frequent; in 2014, an estimated 26% of patients with a benzodiazepine prescription also had an opioid prescription.33 Opioid analgesics cause a dose-related impairment in all phases of respiratory activity34,35 and cause or exacerbate sleep-disordered breathing.34,36,37 We recently found38 that long-acting opioid users had a 65% increase in the risk of out-of-hospital cardiovascular death (hazard ratio = 1.65 [1.10-2.46]), evidence that medications that impair nocturnal respiration have adverse cardiovascular effects.Combined respiratory effects of benzodiazepines and opioids also could increase cardiovascular risk, a hypothesis supported by our preliminary data indicating a synergistic increase in cardiovascular death risk with concurrent benzodiazepine-long-acting opioid use. Thus, the adverse cardiovascular effects of some hypnotics might only be present in combination with opioids.

Despite the use of prescribed hypnotics by millions of patients, the potential association with increased mortality has not materially affected clinical practice or public health policy because it is nearly universally considered as due to bias. However, an important harm of benzodiazepines and sBzRAs may have been overlooked. The nocturnal respiratory impairment-cardiovascular death mechanism provides a biologically plausible basis for this association and suggests clinically meaningful between-drug differences. Some limitations of extant studies could have underestimated the true risk. Thus, rigorous study of the relative cardiovascular safety of frequently prescribed hypnotics, without and with concurrent opioids, is needed to guide clinical practice.

We plan to study the cardiovascular effects of hypnotics in Medicare enrollees—who have the most frequent hypnotic use and greatest susceptibility to increased mortality—to test the hypotheses that:

**Aim 1. In the absence of opioid use, the risk of out-of-hospital cardiovascular and total mortality for benzodiazepine and sBzRA users is greater than that for trazodone users.**

**Aim 2. Concurrent use of opioid analgesics potentiates the risk of cardiovascular mortality for patients with benzodiazepine or sBzRA use.**

**Extract from Analysis Plan (HL081707)**

1. Sources of Data

We will obtain study data from computerized files of medical encounters for Medicare beneficiaries maintained by the CMS Research Data Assistance Center (ResDAC). We will restrict our request to beneficiaries with medication coverage (enrolled part D) in a fee-for-service plan (not enrolled part C, Medicare Advantage) and not enrolled because of disability.

2. Study Hypnotics

All prescriptions for drugs with an FDA-approved hypnotic indication are considered hypnotics because off-label use is minimal, given the rapid onset of drowsiness. Other drugs frequently prescribed for insomnia that guidelines describe as hypnotics6,39 are considered hypnotics if the dosing schedule is once/day and there is no evidence of a different indication.

3. Cohort Inclusion/Exclusion

Cohort eligibility criteria are designed to identify patients beginning a course of hypnotic therapy, with no past use of any benzodiazepine or trazodone, with adequate information in the Medicare files to determine study covariates and who are unlikely to have a short-term elevated risk of death from a known condition. As in our previous studies,38 we exclude patients with serious illness that poses short-term increased risk of death to reduce confounding by hypnotic use in terminally ill patients and to decrease the likelihood that cardiovascular deaths are related to prior illness. We do not require a sleep disorder diagnosis because this diagnosis often is not recorded in clinical practice.

4. Covariates

A key design element is controlling for potential confounders that vary according to the three types of hypnotics. Thus, as in our long-acting opioid study (§a.3.b), we will tightly match the groups according to covariates with a plausible direct or indirect relation to both hypnotic initiation and cardiovascular or total mortality; as in our previous studies38 there will be more than 100 covariates.

5. Endpoints

Out-of-hospital cardiovascular death is an appropriate clinical endpoint to study medication-related respiratory impairment in large populations because 1) it can be efficiently ascertained from death certificates and,2) for patients with no life-threatening illness, most such deaths are sudden cardiac deaths. Out-of-hospital cardiovascular deaths will be identified from the death certificate underlying cause of death based on the ACC/AHA criteria.40

Total mortality is a coprimary endpoint for two reasons. First, some hypnotics plausibly could increase the risk of death from non-cardiovascular causes; for example, both benzodiazepines and sBzRAs are linked to increased risk of injuries.41-44 Second, this endpoint guards against differential misclassification of cause of death; for example, a nocturnal death might be more frequently classified as an overdose for benzodiazepine patients than for trazodone patients.

6. Analysis

The analysis will include three *a priori* comparisons: benzodiazepine vs trazodone, sBzRA vs trazodone, and benzodiazepine vs sBzRA for each of the two coprimary endpoints. We will not adjust for multiple comparisons, given that each comparison is planned, *a priori* and hypothesis-based; however, p-values will be calculated permitting Bonferroni corrections. Relative risk will be estimated with HRs calculated from Cox regression models.

**Material changes from Original Analysis Plan**

1. As more accurate sample size estimation became possible, we realized that the propensity-score matching originally envisioned would materially reduce sample size and power. Thus, the primary analysis used propensity-score stratification. A sensitivity analysis was performed with propensity-score matching.

2. We changed the primary endpoint to include all out-of-hospital deaths, the primary endpoint for our previous investigation of opioids in chronic non-cancer pain.45 We made this change for two reasons. First, we became concerned that out-of-hospital cardiovascular deaths would be under-ascertained. Second, the broader endpoint captures the respiratory-related deaths that occasionally are a consequence of some study hypnotics and opioids.

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