Texas Medical Association
Physicians Caring for Texans

# *TexMed 2016 Clinical Abstract*

Please complete all of the following sections:

**Procedure and Selection Criteria**

- Submissions not directly related to quality improvement or research may be accepted and should follow the standardized format outlined below. Content should enhance knowledge in the field of clinical care and be relevant to a given patient population.

**PROJECT NAME:** Does Anxiolytic and Hypnotic Kills?

**Institution or Practice Name:** UT Health, Houston

**Setting of Care:** Educational Institute

**Primary Author:** Ajay K Parsaik

**Is the Primary Author a TMA member?** ☒ Yes ☐ No

**Secondary Author:** Singh B.

**Other Members of Project Team:** Mascarenhas SS, Darrow KhoshChashm, Hashmi A, John V, Okusaga O

## Clinical

**Background (15 points max):** *Describe the purpose for sharing the content. What caused this subject matter to be approached? Why is this content important to share? What is the potential impact if this content is not shared?*

1) Benzodiazepines and hypnotics use is common in the general population and is estimated to range between 3.5% and 11.7%. As per latest evidence, its use is highest among the elderly, ranging from 7% to 43%.

2) Most of the prescriptions for long term benzodiazepines are written by non-psychiatrists.

3) Benzodiazepines/ hypnotics use may increase daytime sleepiness, depressive symptoms, suicidality, road accidents, falls, and may raises the concern for abuse and dependency. In addition, benzodiazepines may have acute deleterious effects on memory and cognition and may increase the risk of Alzheimer type dementia. Limited evidence suggests that it may increase the risk of cancer and infections.

4) Because of above risks and deleterious effects, it is possible that hypnotics and anxiolytics use may increase the premature mortality. To answer this question, numerous studies have evaluated the mortality risk associated with anxiolytics and hypnotics use. However, inconsistent results have been reported.

5) Therefore, we performed a systematic review and meta-analysis of all available studies evaluating the mortality risk associated with anxiolytics and hypnotics use, to quantify the magnitude of this association and appraise the quality of the supporting evidence for this association.

6) Potential impact of not sharing this information would keep most providers unware of this deleterious effect of anxiolytics and hypnotics. Therefore, it is important that all providers should know about the latest evidence regarding associated mortality risk and should be careful while prescribing anxiolytic or hypnotic drugs. Also, it is their moral duty to inform the patients about potential mortality risk and evidence supporting it.

**Intended Stakeholders (15 points max):** *Identify those individuals, organizations, or interest groups that could be potentially impacted by this information or benefit by obtaining this information.*

1) All hospitals, primary care settings, nursing homes, home health systems, and mental health institutes would be benefited given that benzodiazepines and other anxiolytics/hypnotics use is very common in all settings. Primary care physicians (PCP) would be benefited more given that most people with mild depression and anxiety goes to PCP for treatment due to associated stigma with psychiatric services. As per evidence, most of the long term benzodiazepines are prescribed by PCPs, possibly due to less expertise with other psychiatry medications. Therefore, non-psychiatrists have low threshold for prescribing benzodiazepines.

2) People sufferings from anxiety, depression, chronic insomnia and other mental health issues would get benefited from this information given that they have low threshold for benzodiazepines use due to quick action. However, most patients taking benzodiazepines are resistant to discontinue it later, even though benzodiazepines are indicated for short term use only. Therefore, educating them about serious deleterious effects including premature mortality associated with benzodiazepines use may motivate them to switch to alternate safer treatment. In addition, general population abusing benzodiazepines or using benzodiazepines chronically for different indications would also get benefitted from this knowledge.

**Description of Accomplished Work (25 points max):** *Provide an overview of the work that was accomplished, including any specific methods, tools or techniques. Also, include any milestones or key accomplishments. Note charts, graphs and tables here and send as addendum with abstract form.*

**Methods**:

1) Major data bases including Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, references cited in the potentially eligible articles and conference proceedings of major psychiatry, internal medicine and pharmacology organizations were searched through April 10, 2014. All titles and abstracts were screened by two reviewers, followed by full text review of selected articles and data extraction.

2) We used the Newcastle – Ottawa Quality Assessment Scale to assess the methodological quality of included studies.

3) The pooled hazard ratio (HR) for mortality associated with anxiolytics and hypnotics use was calculated using DerSimonian and Laird random effects model. $I^2$ statistic and Cochran's Q test was used to assess the heterogeneity across the included studies.

**Results:**

4) After screening 2,188 articles (Figure 1), 25 studies (24 cohort, 1 case-control) enrolling 2,350,093 patients with 59% females (age 18-102 years) were included in the meta-analysis.
5) HA users had 43% higher risk of mortality than non-users (HR, 1.43; 95% CI, 1.12-1.84) (Figure 2) but significant heterogeneity was observed in the analyses.

6) To find the cause of heterogeneity we did several subgroups analysis (Table 1). Subgroup analysis as per study location, study population, duration of anxiolytics and hypnotics use, duration of follow up and quality of included studies did not define heterogeneity, however population characteristics – age was able to explain the study heterogeneity (p=0.01, Table 1). Studies with mixed age subjects had highest risk of mortality (OR 1.74, 95% 1.25-2.44). To assess whether any individual study or group of studies had a dominant effect on the meta-analytic HR, each study was excluded and its effect on the main summary estimate and Cochran's Q test P value for heterogeneity was evaluated. No individual study markedly affected the summary estimate or P value for heterogeneity but after removing 6 studies from the pool, risk estimate decreased to 21% but heterogeneity in the pooled HR was resolved.

7) Eight studies reported risk estimates for each gender category and pooled results from these studies showed increased risk of mortality among men (HR=1.60, 95% CI=1.29-1.99) and women (HR=1.68, 95% CI=1.38-2.04

8) Pooled results from 10 studies showed higher mortality among benzodiazepines users compared to non-users (HR = 1.60, 95% CI = 1.03, 2.49), while pooled results from 5 studies showed an increased risk of mortality with Z-drugs use although the effect could not reach statistical significance (HR = 1.73, 95% CI = 0.95, 3.16).

9) All studies scored reasonably highly on the quality assessment tool.

10) Publication bias: Quantitatively, there was no evidence of publication bias (Egger's regression test: t value =0.66, df =23, p value= 0.51).

11) Most studies reported all-cause mortality, but 12 studies reported cause-specific mortality with suicides, cardiovascular and cancer related deaths among the common causes among HA users. However, no temporal association was reported.

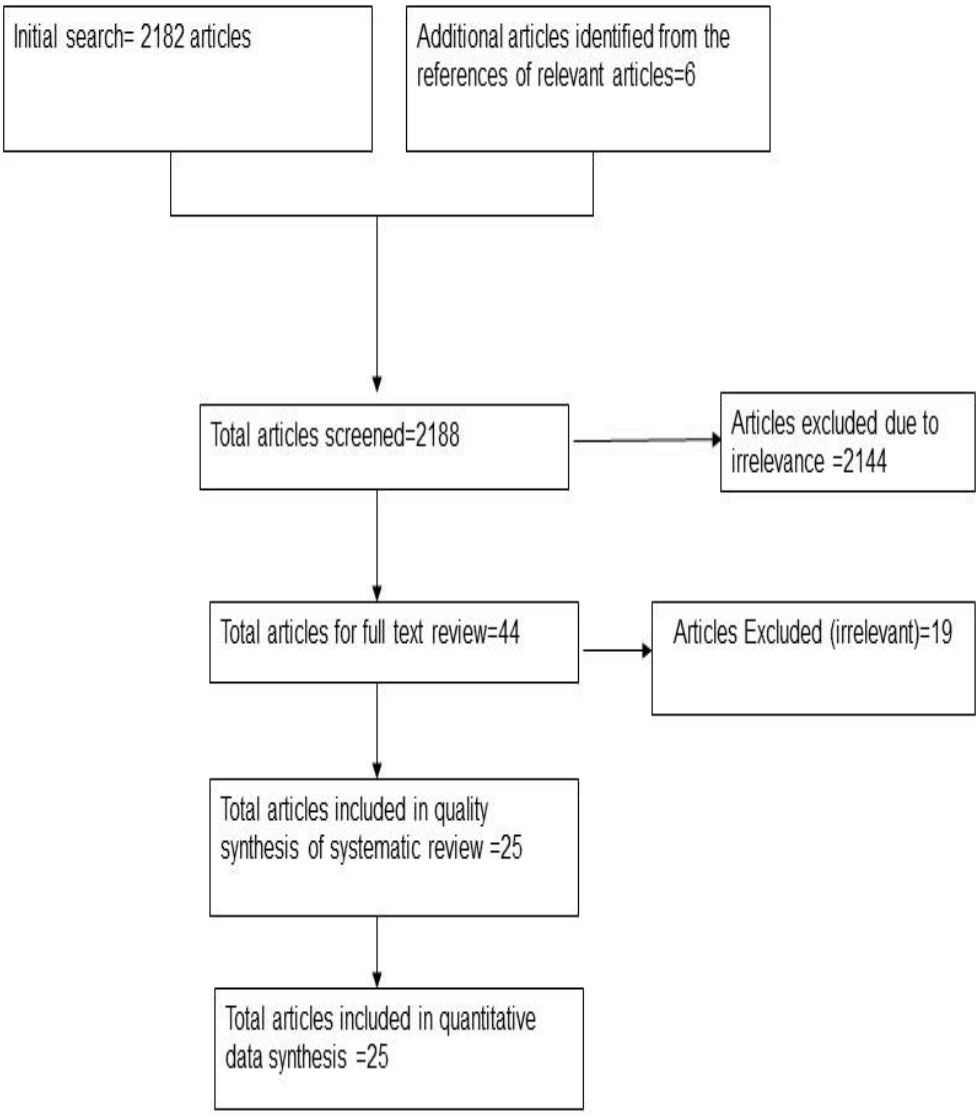


Fig. 1. Flow diagram for the selection of references

Figure 2. Mortality risk associated with hypnotics and anxiolytic use

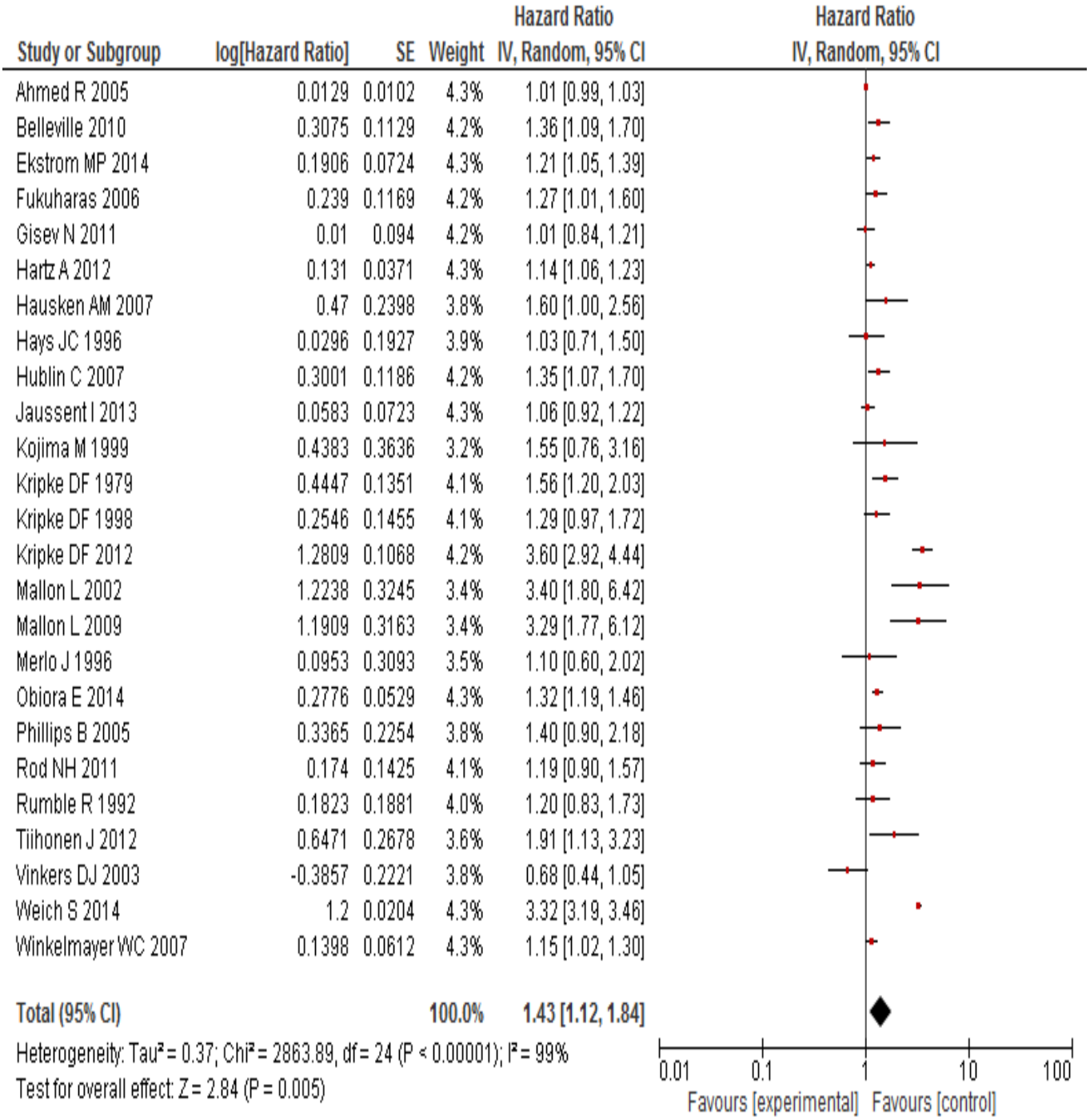

Table 1. Subgroup Analysis

| **Subgroups** | **Number of studies** | **Risk Ratio** | **95% confidence interval** | **p-value for difference between the sub-groups** |
|---|---|---|---|---|
| a) Study location | | | | |
| US | 7 | 1.46 | 1.08, 1.97 | 0.93 |
| Non-US | 18 | 1.43 | 1.03, 1.98 | |
| b) Duration of anxiolytics//hypnotics | | | | |
| = One month | 5 | 1.30 | 1.05, 1.60 | 0.53 |
| > 1 month | 7 | 1.54 | 0.95, 2.51 | |
| c) Follow-up duration | | | | |
| ≤ 10 years | 16 | 1.38 | 1.01, 1.90 | 0.97 |
| > 10 Years | 9 | 1.37 | 1.15, 1.64 | |
| d) Quality of studies using Newcastle – Ottawa Quality Assessment Scale | | | | |
| NOS score ≤7 | 5 | 1.86 | 1.36, 2.55 | 0.11 |
| Score > 7 | 20 | 1.33 | 1.00, 1.75 | |
| e) Study Population | | | | |
| Population based | 11 | 1.18 | 1.02, 1.36 | 0.15 |
| Specific cohort | 14 | 1.54 | 1.11, 2.15 | |
| f) Covariates adjustment | | | | |
| Adjusted for minimal covariates | 14 | 1.50 | 1.06, 2.13 | 0.34 |
| Not adjusted for minimal covariates | 11 | 1.26 | 1.14, 1.40 | |
| g) Population characteristics age, overall p=0.01* | | | | |
| 1. Age < 50 years | 2 | 1.30 | 1.00, 1.69 | 0.17 (1 vs 2) |
| 2. Age > 50 years | 8 | 1.07 | 0.98, 1.16 | 0.006* (3vs2) |
| 3. Mixed age | 14 | 1.74 | 1.25, 2.44 | 0.18 (3 vs 1) |

**Timeframe and Budget (20 points max):** *Provide the start and end dates for the work along with any financial implications that were incurred due to the work accomplished. Note charts, graphs and tables here and send as addendum with abstract form.*

Work was started in April 2014 and Finished in May 2015. We have no financial disclosure.

INTENDED USE:

1) Based on pooled results from 25 observational studies conducted across the world, there is moderate quality evidence (based on GRADE working group guidelines) suggesting that anxiolytics and hypnotics use is associated with increased mortality although the evidence supporting cause specific mortality was limited. Therefore, physicians should carefully consider the increased mortality risk while prescribing anxiolytic or hypnotic drugs in addition to other risk factors and contraindications.
2) Patients should be informed about the increased association of mortality with anxiolytics and hypnotics use. This further reiterates the importance of involving patients in decision making and explaining the merits of alternatives including non-pharmacological management for sleep and anxiety disorder so that patients can make well-informed decisions.
3) Further well designed studies adjusted for potential confounders are warranted to evaluate the temporal relationship between mortality risk and anxiolytics-hypnotics. Future studies should also focus on evaluating the underlying mechanism for increased mortality associated with anxiolytics and hypnotics use.

NOTE: I was not able to insert text under Intended use below. Therefore, I have inserted it here. Thanks, Ajay

**Intended Use (25 points max):** *Describe how this information could be used moving forward to impact patient care.*