Effects of tranquilization therapy in elderly patients suffering from chronic non-communicable diseases: A meta-analysis

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ABSTRACT

The current meta-analysis searched the literature connected to different tranquilizers used to treat elderly people and assessed it in terms of dose, types of outcomes and adverse effects, to determine a safe and acceptable tranquilizer and its optimal dose. A systematic literature review was undertaken for randomized controlled trials, case-control, retrospective and prospective studies on the use of tranquilizers in elderly patients, using the PubMed, Ebsco, SCOPUS and Web of Science. PICOS

criteria were used to select studies, and pertinent event data was collected. This meta-analysis includes 16 randomized control trials spanning the years 2000 to 2022, using the data from 2224 patients. The trials that were included used various tranquilizers such as diazepam, alprazolam, temazepam and lorazepam, and indicated high treatment efficacy and low adverse effects. With a *p*-value of 0.853 for Egger's test and 0.13 for Begg's test, the current meta-analysis shows a minimal probability of publication bias. A recent meta-analysis supports the use of tranquilizers in older people to treat sleeplessness, epilepsy or anxiety, but only at modest doses, because large doses are harmful and produce numerous withdrawal symptoms.

Keywords: tranquilizers, benzodiazepines, insomnia, epilepsy, anxiety, seniors

INTRODUCTION

The term "healthy" refers to being free of all physical, mental and social maladies. However, stress is a major health risk in the elderly due to changing lifestyles and keeping up with growth (1). Many people worldwide suffer from non-communicable diseases such as diabetes, hypertension, hyperthyroidism or hypothyroidism, which can lead to organ problems such as kidney disease, liver damage and cardiac problems (2, 3). Most senior people develop anxiety, sadness and sleep disturbances, as a result of these non-communicable diseases, which negatively impact their mental and physical health as well as their family and social lives (4, 5). Patients' metabolic parameters vary as a result of insomnia and sleep disorders, including blood glucose and electrolyte levels, hormone imbalances, and stress, dyspepsia, and depression. Neurotransmitter levels can also be changed, resulting in seizures and epilepsy. As a result, sorting these linked effects of non-communicable illnesses is a medical problem because they affect not only the patient but also their family, caregivers, and social surrounds. Different medicines, such as sedatives, receptor-antagonists, hypnotics and tranquilizers, are utilized to treat the related insomnia, epilepsy and anxiety symptoms (6-8).

Due to their rapid action, shorter half-lives, and minimal side-effects, various antipsychotic agents or neuroleptics drugs such as sedatives, hypnotics, receptor antagonists, and benzodiazepines tranquilizers have been approved by the FDA for the treatment of chronic insomnia and major mental disturbances in elderly patients. In this meta-analysis, we systematically review the available literature (randomized controlled trials, prospective and retrospective studies) on the use of various tranquilizers in elderly patients with various non-communicable diseases and assess their potential benefits in comparison to control drugs (9).

Tranquilizers are a class of medications that have a calming effect and reduce anxiety, stress, fear, panic attacks and agitation, by depressing the central nervous system. They are used to treat mental diseases such as schizophrenia, bipolar disorder and depression (9-11). In their review study, Schroeck *et al*. (12) stated that tranquilizers are ideal for the treatment of insomnia with no worsening side-effects. Similarly, Buscemi *et al*. (13) found, in their review and meta-analysis of randomized controlled trials, that both benzodiazepines and non-benzodiazepine tranquilizers are safe and effective for the treatment of chronic insomnia in adults. The effectiveness and possible benefits of tranquilizers in the treatment of depression in adolescents and older individuals were documented by Di Vincenzo *et al*. (14). In their review study, Dalacorte *et al*. (15) discussed the use of tranquilizers in the treatment of pain in older individuals.

Benzodiazepines such as diazepam, alprazolam, lorazepam, temazepam, and others are commonly used tranquilizers, as documented and suggested in many researches. Alldredge *et al*. (16) and Cock *et al*. (17), both reported on the safety and efficacy of lorazepam in the treatment of epilepsy in the elderly. Temazepam was found to be a safe and effective tranquilizer for treating insomnia in adults by Morin *et al.* (18) and Voshaar *et al.* (19). Diazepam was used as a pain reliever in adults by Pramod *et al.* (20). Pokharel *et al* (21) reported on alprazolam's possible benefits for sleep problems in senior individuals, whereas Puustinen *et al*. (22) and Carberry *et al*. (23) reported on temazepam's potential benefits for sleep disorders.

Various randomized controlled studies have reported the benefits of various benzodiazepine tranquilizers, such as diazepam, for anxiety, alprazolam for sleep disruption, and lorazepam for epilepsy, as described by Guo *et al.* (24), Wang *et al.* (25) and Nene *et al.* (26). For anxiety and sleep difficulties, Hackett *et al.* (27) recommended diazepam, while Asghar *et al.* (28) recommended alprazolam. Other researchers indicated lorazepam for epilepsy, alprazolam for sleep disorders, and diazepam for epilepsy, *e.g.*, in the reports of Kamdar *et al.* (29), Huo *et al.* (30) and Meanovi *et al.* (31).

All of these trials have clearly shown the benefits of various tranquilizers or tranquilization therapy in older patients with chronic non-communicable diseases, but only at an optimum low dose, as higher doses or long-term use are linked to harmful withdrawal symptoms. While some research, such as that of Prakash *et al.* (32) concluded that tranquilizers should not be prescribed to elderly people because of their negative side-effects and the impact they have on their family and social lives, in a separate study published in 2013, Rogers *et al.*

(33) indicated that opioid tranquilizers have negative side-effects, but also provided ways for managing them, such as dose optimization and drug schedule.

Because of the conflicting literature reports on the potential benefits and risks of tranquilization therapy in elderly patients, we conducted a thorough review and analysis of the available studies on tranquilizers and evaluated the effects of tranquilization therapy on elderly patients with chronic non-communicable diseases and their families, in the current meta-analysis.

EXPERIMENTAL

Search techniques

From the year 2000 to 2022, search was undertaken in the databases of Medline (through PubMed), Cinahl (*via* Ebsco), Scopus and Web of Science. Keywords like tranquilizer, diazepam, temazepam, alprazolam, lorazepam, placebo, insomnia, epilepsy, anxiety, randomized controlled trials, were employed to look for relevant studies. All included papers followed the PRISMA principles, and studies were chosen at random, regardless of language, publication status, or study type (prospective, retrospective, clinical trial). Patient demographics and event data from the included studies (16-31) were gathered and tallied.

Criteria for inclusion and exclusion

A total of 1654 studies on treatment of non-communicable diseases in older people were found from 2000 to 2022, out of which only those studies that used tranquilizers for the treatment of non-communicable diseases in older people with full text data and sufficient event data for 2x2 table were included. Studies with insufficient data, studies reporting on the use of other imaging modalities, and similar studies published before 2000 were excluded from the current analysis.

Analytical standard and source of heterogeneity evaluation

Review Manager (RevMan, Version 5, The Nordic Cochrane Center, Copenhagen; the Cochrane Collaboration, 2020) software was used to create the Cochran Q statistic and I2 index to examine heterogeneity. The use of different case-control, prospective and retrospective studies, different numbers of patients, assessment of different biochemical parameters and scores for analysis of improvement in health conditions, and the use of different tranquilizers and control drugs were all investigated as potential sources of heterogeneity.

Analytical statistics

The diagnostic odds ratio was determined using the DerSimonian and Laird approach (35) for statistical analysis. A 2x2 table was created using the event data, and RevMan software was used to do a meta-analysis. The Mantel Haenszel test with random bivariate mode (36) was used to calculate the pooled diagnostic odds ratio and risk ratio with 95 % confidence intervals, as well as their respective forest plots, and heterogeneity of included studies (chi^2 value, Q value, df value, I2 value and *p*-value) was assessed using RevMan software. RevMan software was also used to create the risk of bias summary, and MedCalc software was used to create Deek's funnel plot in order to estimate the risk of publication bias of the included studies (37). A bar histogram was created to compare the negative effects of tranquilizers and control medications.

RESULTS AND DISCUSSION

Outcomes of literature search for meta-analysis

Through electronic searches of several databases, *viz*., MEDLINE, PubMed, Ebsco, Scopus, Web of Science we discovered a total of 1654 studies related to treatment of elderly patients suffering from chronic non-communicable diseases. By reviewing the titles and abstracts of these investigations, we were able to exclude 296 of them, leaving 1358 records to be reviewed. We also eliminated 870 studies due to faulty references and duplication, leaving only 488 studies for final screening. Three-hundred-ninety (390) studies out of 488 were rejected due to inclusion criteria as mentioned above, and the remaining 98 studies' eligibility was further investigated. Inadequate evidence and improper comparison criteria for creating 2x2 tables for review were the main reasons for omission. Finally, 16 researches within the years 2000 to 2022 met the inclusion requirements, namely, the use of tranquilizers for the treatment of non-communicable diseases in senior patients, as shown in Fig. 1.

A total of 2224 senior individuals are there in the selected studies (16-31). Age of the patients included in the research spans from 45 to 75 years, with 64 % of males and 36 % females. Patients were chosen at random and treated with various tranquilizers such as alprazolam, lorazepam, temazepam, and diazepam, as well as various control medications. Table I shows the demographic characteristics of the patients included in this meta-analysis.

Meta-analysis findings

RevMan software was used to conduct the meta-analysis. As shown in Table II, the risk of bias for included studies was examined, and publication bias was analyzed using the MedCalc software. Fig. 2 summarizes the risk of bias, whereas Fig. 3 depicts the risk of bias graph.

The funnel plot (Fig. 4) and findings of the Egger and Begg and Mazumdar tests show that the current meta-analysis has a low probability of publication bias. The significance level (*p*-value) for both statistical tests was greater than 0.05, *i.e.*, 0.853 for Egger's test and 0.13 for Begg's test, indicating a low likelihood of publication bias (38).

The odds ratio of the included studies was estimated using RevMan software to compare the outcomes of tranquilization therapy in older individuals with health conditions such as epilepsy, sleep disorders, or anxiety to the outcomes of control medications such as receptor antagonists or placebo. Fig. 5 illustrates the Forest plot of odds ratios and data heterogeneity. With a chi2 value of 8.33, df value 3, I2 value 64 %, Z value 2.25, and *p*-value of 0.02 for diazepam, we derived a pooled odds ratio (OR) of 0.41 (95 %, CI 0.19–0.89). Alprazolam had OR of 0.34 (95 %, CI 0.20–0.58), a chi2 value of 0.9, a df value of 3, a Z value of 3.94, and a *p*-value of 0.0001. Temazepam had OR of 0.51 (95 %, CI 0.30–0.87), with a chi2 value of 1.48, df value 3, Z value 2.45, and *p*-value of 0.01, while lorazepam showed OR of 1.22, df value 3, Z value 3.46, and *p*-value of 0.0005. All of these findings are statistically significant ($p < 0.05$), and the forest plot (39) shows that they encourage the usage of tranquilizers.

Based on the above mentioned results, the tranquilizers have a better likelihood of treating health conditions like epilepsy, sleep disorders, and anxiety in senior individuals than control medications, or placebo, but only at the prescribed low dose, as large doses and long-term usage are dangerous and induce unpleasant withdrawal symptoms.

The risk ratio of the studies that were included was also calculated using RevMan software, and the resulting forest plot is displayed in Fig. 6**.** Diazepam had a pooled risk ratio (RR) of 0.77 (95 % CI: 0.70–0.85), chi2 value of 1.91, df value of 3, Z value of 5.36, and *p*-value of 0.00001, alprazolam had RR of 0.83 (95 % CI 0.75–0.91), chi2 value of 0.35, df value of 3, Z value of 3.94, and *p*-value of 0.0001. The RR value for temazepam was 0.84 (95 % CI 0.73–0.96), with a chi2 value of 0.94, df value 3, Z value 2.60, and *p*-value of 0.009, while RR value for lorazepam was 0.84 (95 % CI 0.76–0.93), with chi2 value of 1.15, df value 3, Z value 3.37, and *p* value 0.0005. With *p* lower than 0.05, all of these findings are statistically significant. The risk ratio value is less than one, indicating that the use of prescribed low-dose

tranquilizers in older patients is safe (40). These findings are statistically significant (p <0.05), demonstrating that tranquilization therapy for older patients is both effective and safe. An I2 score more than 50 % implies that tranquilization therapy is beneficial.

With a p <0.05, all of these values are statistically significant and illustrate the potential benefits of an appropriate low dose of tranquilization therapy for insomnia and anxiety in older people.

Tranquilization therapy has been linked to negative side-effects such as shallow breathing, paranoia and aggressive conduct (41-43). As a result, the adverse effects of both tranquilizers and control medications were compared in this meta-analysis, as indicated in the histogram **(**Fig. 7**)**. The graph shows that tranquilizers had less side-effects and withdrawal symptoms in elderly patients than the control group, indicating that they might be regarded safe and effective (44, 45).

Limitations of the study

The heterogeneity of tranquilizers used and tests done by various pathologists, which impact the probability of false-negative results, is a limitation of this study. Many trials that showed comparable benefits with other medications like hypnotics, did not mention receptor antagonists, therefore, judging the comparative accuracy has an impact on the findings. Data from other relevant research that compare the effects of tranquilizers to other sedatives or hypnotics can also be added to emphasize their value. Similarly, the effects of these drugs on patients of different age groups and gender can also add up the reliability of the results. To see the variability, complete information on the patient's case history, physical examination, and pathological tests should be used to improve the effectiveness of tranquilization therapy in older patients with health conditions such as epilepsy, sleep difficulties, or anxiety.

CONCLUSIONS

The present meta-analysis focuses on the four benzodiazepine tranquilizer medicines temazepam, lorazepam, alprazolam, and diazepam, and finds that all of them are safe and effective for the treatment of insomnia, anxiety, pain, and epilepsy when taken at the recommended low dose. However, the term "low dose" is critical because long-term or excessive usage of these medications at an incorrect dosage is extremely harmful and dangerous. Based on statistically significant results and fewer adverse effects, this meta-analysis favours the use of tranquilization therapy in elderly patients with chronic non-

communicable diseases when taken for a prescribed duration at an optimum low dose. Furthermore, the tranquilizers at an optimal and prescribed low dose have fewer adverse effects and withdrawal symptoms in elderly patients than controls, making them safe and effective.

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The PRISMA (preferred reporting items for systematic reviews and meta-analyses) normative requirements was used in the current investigation, with the registration number HMU/IRB/2021/789.

Conflict of interest. - The authors declare no competing interests.

Author's contributions. - JL and LJ: concept and design of the study, YC and HL: data analysis; XH, HL, and FZ: collecting the data and helping in data analysis; QZ and JZ: proofreading and drafting of the manuscript; PL: writing of the article, critical revision, and final guarantor of the manuscript, *i.e*., corresponding author.

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Table I. Demographic summary of the included studies

Type of study	Sample size[a]	Duration of study	Health condition	Tranqui-lizer used	Dosage (mg)	Number of patients[b]	Positive outcome	Adverse effects	Control drug	Dosage (mg)	Number of patiens[c]	Positive outcome	Adverse effects	Reference
Randomized controlled trial	205	5 months	Epilepsy	Lorazepam	2	66	30	26	Diazepam	10	68	40	38	Alldredge *et al.* (16)
Randomized controlled trial	90	18 months	Epilepsy	Lorazepam	4	17	11	6	Diazepam	10	46	38	13	Cock *et al.* (17)
Randomized controlled trial	60	8 weeks	Insomnia	Temazepam	20	20	15	1	Placebo	20	20	19	4	Morin *et al.* (18)
Randomized controlled trial	163	4 weeks	Insomnia	Temazepam	20	79	50	19	Zolpidem	10	84	65	21	Voshaar *et al.* (19)
Randomized controlled trial	35	1 week	Pain	Diazepam	5	10	7	2	Placebo	10	25	18	9	Pramod *et al.* (20)
Randomized controlled trial	84	4 days	Sleep disorder	Alprazolam	0.5	20	15	2	Melatonin	3	20	18	5	Pokharel *et al.* (21)
Randomized controlled trial	92	3 years	Insomnia	Temazepam	20	34	25	5	Placebo	20	44	35	12	Puustinen *et al.* (22)
Randomized controlled trial	28	4 days	Sleep apnoea	Temazepam	10	9	5	2	Placebo	10	8	6	4	Carberry *et al.* (23)
Randomized controlled trial	111	10 days	Anxiety	Diazepam	5	55	32	11	Lofexidine	0.72	56	38	19	Guo *et al.* (24)
Retrospecti-ve study	231	3 weeks	Sleep disturbances	Alprazolam	0.4	77	61	8	Bailemian capsule	4 caps.	87	82	18	Wang *et al.* (25)
Prospective study	118	3 days	Epilepsy	Lorazepam	0.1	60	35	10	Sodium valproate	20	58	43	19	Nene *et al.* (26)
Randomized controlled trial	540	8 weeks	Anxiety &sleep disorders	Diazepam	5	160	111	12	Placebo	10	170	158	39	Hackett *et al.* (27)

Comparative observation-nal study	117	2 months	Sleep disturbances	Alprazolam	0.5	38	25	11	Melatonin	3	79	64	13	Asghar *et al.* (28)
retrospective study	165	6 days	Epilepsy	Lorazepam	2	74	60	7	Placebo	10	91	85	12	Kamdar *et al.* (29)
Randomized controlled trial	96	2 weeks	Sleep disorder	Alprazolam	0.4	48	32	7	Eszopiclone	3	48	41	17	Huo *et al.* (30)
Randomized controlled trial	89	7 days	Sleep disturbances	Diazepam	5	43	28	8	Placebo	10	43	35	12	Mešanović *et al.* (31)

[a] Total number of patients enrolled for the study.

[b] Total number of patients selected for tranquilizer arm.

[c] Total number of patients selected for control arm.

Table II. Risk assessment for included studies

	Alldredge *et al.* (16)	Cock *et al.* (17)	Morin *et al.* (18)	Voshaar *et al.* (19)	Pramod *et al.* (20)	Pokharel *et al.* (21)	Puustinen *et al.* (22)	Carberry *et al.* (23)	Guo *et al.* (24)	Wang *et al.* (25)	Nene *et al.* (26)	Hackett *et al.* (27)	Asghar *et al.* (28)	Kamdar *et al.* (29)	Huo *et al.* (30)	Mešanović *et al.* (31)
Was a consecutive or random sample of patients enrolled?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive the same reference standard	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Was the sample frame appropriate to address the target population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were study participants sampled in an appropriate way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were valid methods used for the identification of the condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there appropriate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

statistical analysis?

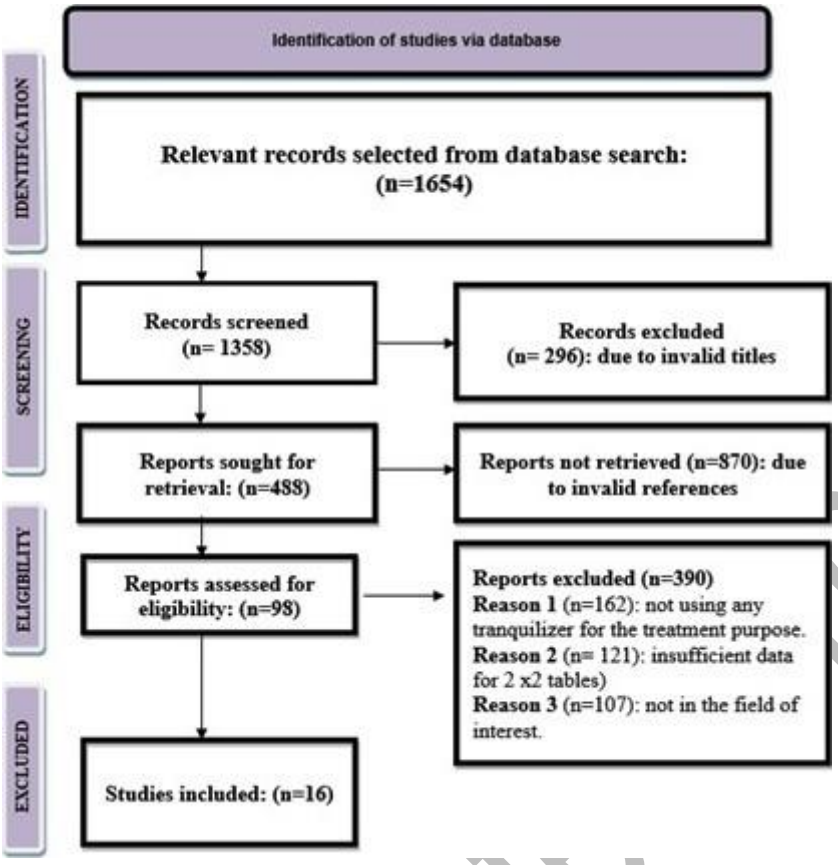

Fig. 1. PRISMA flow diagram of the study group.

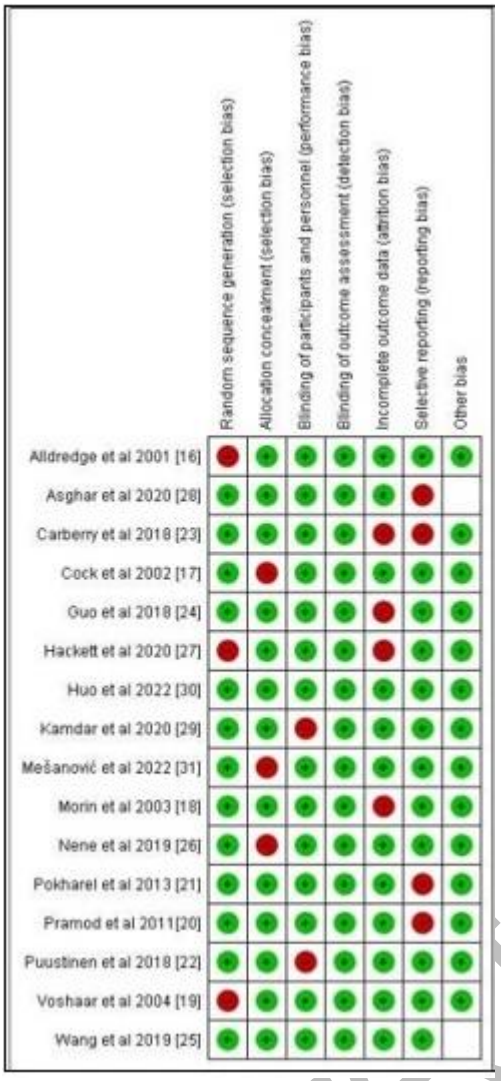

Fig. 2. Risk of bias graph.

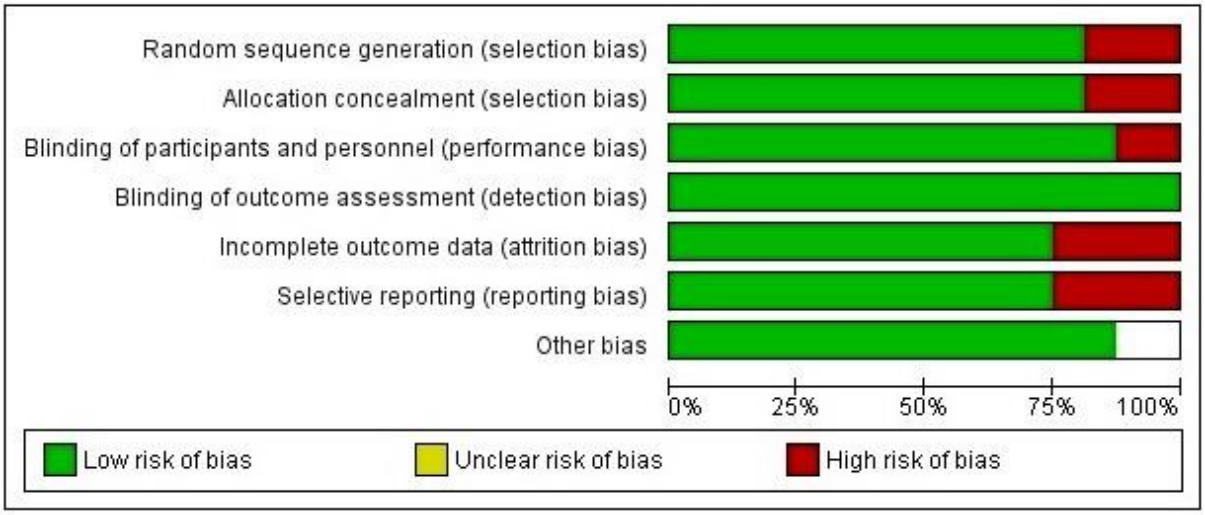

Fig. 3. Risk of bias summary.

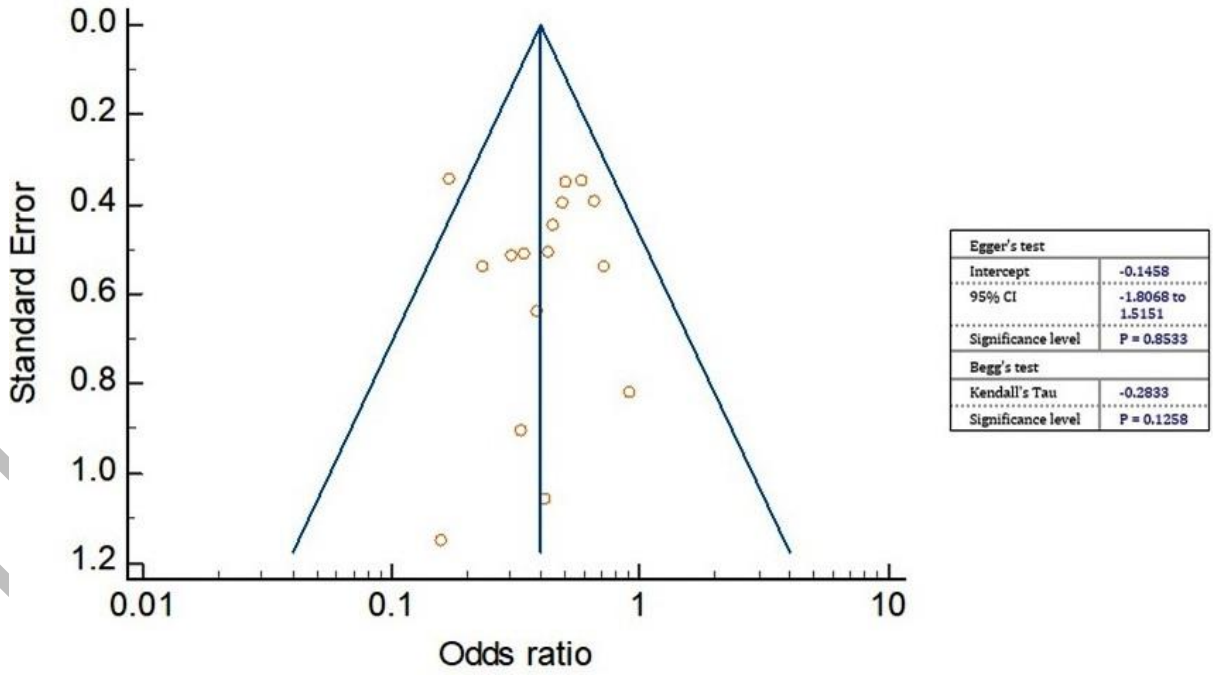

Fig. 4. Funnel plot for publication bias.

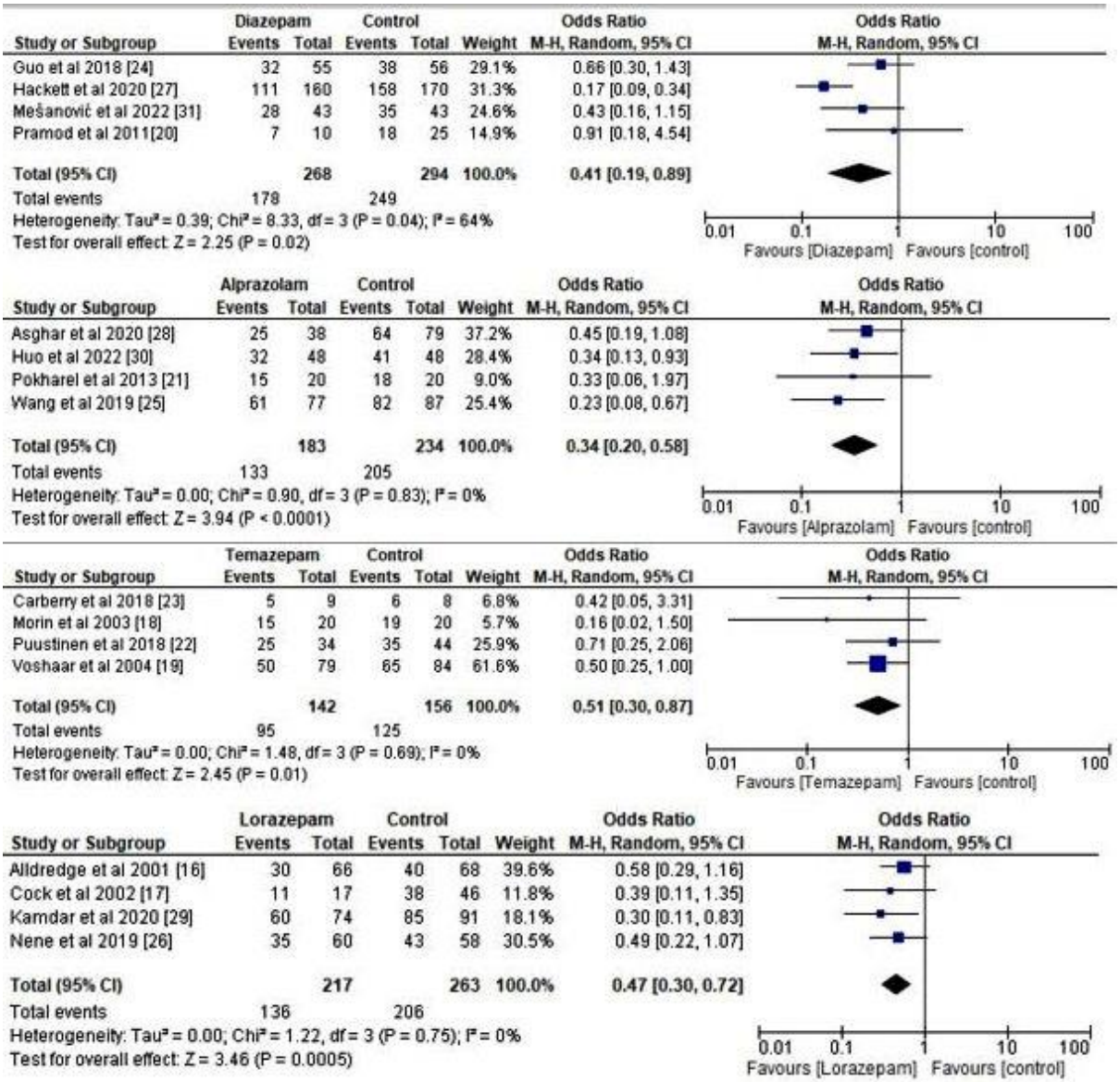

Fig. 5. Forest plot odds ratio of different tranquilizers versus control.

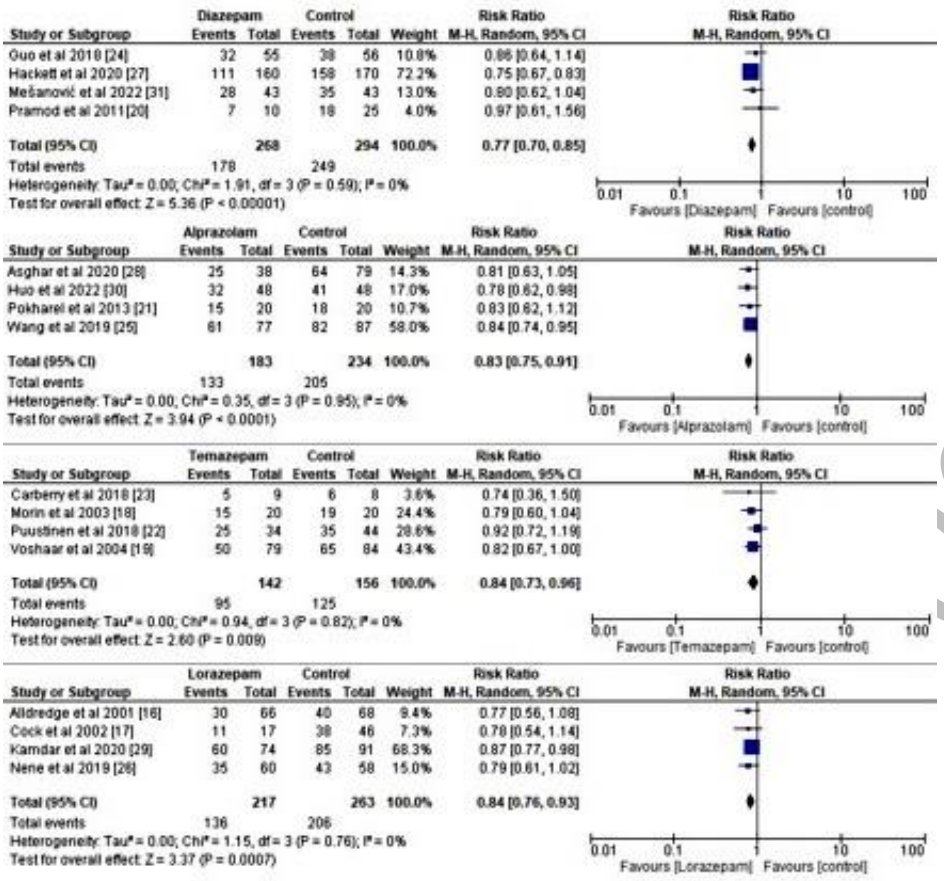

Fig. 6. Forest plot risk ratio of different tranquilizers versus control.

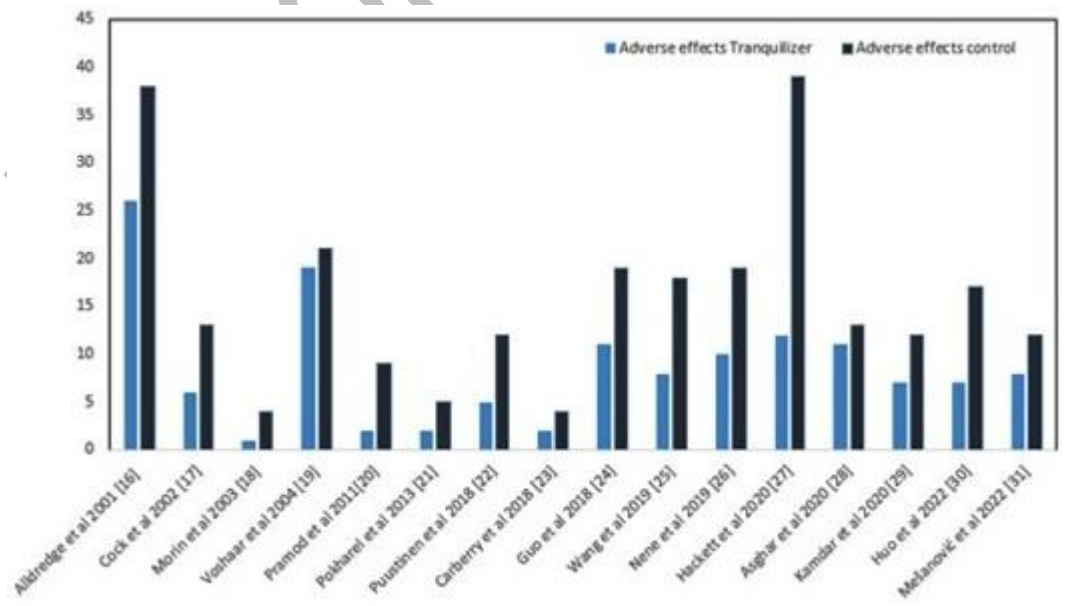

Fig. 7. Adverse effects of tranquilizer *versus* control.