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Review Article

Antidepressants and Road Safety: A Systematic Review and Network Meta-Analysis of RCTs on Driving Impairment

Homayoun Sadeghi-Bazargani[1], Razieh Abdolrahmanzadeh[2*#], Mahshad Narimani[2], Melika Ahmadi Bonabi[2], Sepita Taghizadeh[2], Morteza Ghojazadeh[3*#]

[1]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Introduction: Antidepressants are useful for treating mood disorders, but because of their cognitive and psychomotor adverse effects, they may make driving less safe. This study is the first network meta-analysis (NMA) comparing driving impairment across antidepressant classes using standardized measures.

Methods: We systematically searched five databases, including PubMed, Scopus, Embase, Cochrane CENTRAL, and Google Scholar, through June 2025. From 5285 screened records, we included 27 RCTs comprising 736 participants in this systematic review, with 13 studies eligible for network meta-analysis. We assessed driving performance using standardized mean differences with 95% credible intervals and ranked treatments by P-scores for treatment ranking.

Results: NMA revealed differential impairment patterns across antidepressant classes, with substantial heterogeneity observed. Paroxetine demonstrated dose-dependent effects, showing potential impairment at 10 mg dosage but neutral effects at 20 mg. Mianserin 10 mg showed modest impairment, while most SSRIs, including fluoxetine and paroxetine 20mg, exhibited minimal driving effects. Sedating antidepressants such as amitriptyline and mirtazapine showed greater impairment, particularly during acute administration phases.

Conclusion: In conclusion, the effects of antidepressants on driving performance vary according to the type and dose of medication, with sedating antidepressants showing greater potential for driving impairment, particularly during acute administration. Clinicians should consider dose-dependent effects and individual responses when prescribing antidepressants to patients who drive. Further research using standardized driving assessments in real-world populations is needed to strengthen the evidence base.

Introduction

Depression is the most common cause of mental distress in later life, and it greatly reduces the quality of life in adults. It is one of the most common personal and public health problems in the world and affects around 300 million individuals worldwide, according to the World Health Organization (WHO).[1-3]

Antidepressants should be viewed as a component of a comprehensive treatment plan for depressed patients that typically includes psychological therapies and social interventions.[4] Antidepressants appear to function by resolving chemical imbalances, especially a deficiency in serotonin in the brain, to effectively treat depression.[5,6]

Drowsiness, low blood pressure, suicidal thoughts, dizziness, decreased seizure threshold, nausea, and anxiety are a few of the adverse effects of antidepressants. Psychomotor driving capacity may be affected by any of these alone or together.[7,8] There is a potential risk of using any substance while engaging in skilled activities like driving, since all such compounds have a mechanism of action in the central nervous system (CNS).[9] The possible effects of antidepressant usage on driving abilities in the senior population are becoming a major problem due to the rise in the number of older drivers taking antidepressants.[10,11]

Motor vehicle safety is a significant public health concern. Attentional and executive functioning issues might decrease one's degree of driving fitness.[12] Road safety is crucial for individuals receiving therapy for mental diseases, as ceasing driving can impact social and economic well-being, highlighting the importance of maintaining mobility. Improving this crucial matter demands a methodical, ongoing, and broad strategy.[13,14]

Drug-driving interactions are a complex topic with

***Corresponding Authors:** Razieh Abdolrahmanzadeh, Email: raziehabdolrahmanzadeh@gmail.com and Morteza Ghojazadeh, Email: ghojazadehm@hotmail.com
#These authors contributed equally to this work as the corresponding authors

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administrative and legal implications. Most drug information imposes driving restrictions. Patients suffering from mental illnesses and neurological disorders may face legal challenges. Evidence is required to evaluate their relationship and minimize such limitations.[15] Previous reviews of antidepressants' effects on driving have been limited by their narrow focus on specific drug classes (e.g., SSRIs/TCAs), lack of NMA for comparative evaluation, and incomplete assessment of both psychomotor and driving measures.[16] A recent systematic review and meta-analysis by Kamphuis et al. (2023)[17] investigated the influence of both depression and antidepressant use on driving performance. Their work provided valuable insights, particularly identifying a significant negative effect on vigilance. However, that synthesis had certain limitations that our current study aims to address. Specifically, Kamphuis et al. included studies with varied methodologies and outcome measures, which may have contributed to heterogeneity, and their analysis did not separately isolate the effect of antidepressant pharmacotherapy from the impact of the depression syndrome itself. Furthermore, they did not employ a network meta-analytic approach, which precludes a quantitative ranking of different antidepressant classes based on their comparative impact on driving.

Our study builds upon this earlier work by focusing exclusively on the pharmacological effects of antidepressants as assessed in RCTs, incorporating a larger and more recent set of RCTs, utilizing standardized driving outcome measures (e.g., SDLP), and, for the first time, applying a network meta-analysis to directly compare and rank the driving impairment profiles across a broad spectrum of antidepressant agents. This approach enables us to offer clinicians more nuanced, evidence-based guidance on antidepressant selection for patients who drive.

Methods

Protocol and registration

This systematic review and NMA were prospectively registered with PROSPERO (CRD42023461463) before data collection, in accordance with best practices for reducing reporting bias in evidence synthesis. The registered protocol specifies our pre-defined search strategy, inclusion criteria, and analytical methods.

We conducted this NMA following PRISMA 2020 guidelines and the PRISMA-NMA extension. The completed checklist confirms comprehensive reporting of both standard and NMA-specific items.[18,19]

Eligibility criteria

We employed the PICOS framework to establish our inclusion criteria for the systematic review.[20] The Population of interest comprised adults aged 18 years or older of both sexes. The intervention included all classes of antidepressant medications compared against a placebo control. Primary outcomes focused on driving performance measures, specifically Standard Deviation of Lateral Position (SDLP), Critical Fusion Frequency (CFF), Critical Tracking Test (CTT), Divided Attention Task (DAT), and Choice Reaction Time Task (CRT). We restricted our analysis to randomized controlled trials (RCTs) to ensure the highest quality evidence.

In addition to the primary inclusion criteria, studies eligible for the NMA were required to meet two additional conditions: they must report quantitative driving test outcomes such as Standard Deviation of Lateral Position (SDLP) or braking latency, and must provide comparable effect size data suitable for network modeling, including measures of variance for all treatment comparisons.

We included studies with both healthy volunteers and clinically depressed patients to comprehensively evaluate the pharmacological and therapeutic effects of ADs. For studies involving patients, we extracted data on depression severity scales (e.g., HDRS, MADRS) to account for potential confounding by disease state.

Non-RCT human laboratory studies (e.g., observational or single-arm designs), crossover trials that lacked proper washout periods or randomization Sequences were our exclusion criteria. Non-experimental designs (case reports, editorials) and studies with irrecoverable missing outcome data were not included.

Information sources and search strategy

We conducted a comprehensive, protocol-driven systematic search across five electronic databases (PubMed/MEDLINE, Scopus, Embase, Cochrane CENTRAL, and Google Scholar) from inception through June 2, 2025. The search targeted RCTs examining the effects of antidepressant medications on driving performance in adults (≥ 18 years, both sexes). The search strategy was developed using both controlled vocabulary specific to each database (MeSH terms for PubMed, Emtree for Embase) and relevant free-text terms. The detailed list of search terms used for developing the search strategy for this study is displayed in the Supplementary file 1. Our search approach combined three key conceptual domains: antidepressant medications, driving performance measures, and randomized controlled trial methodology. Additionally, we performed manual searches of reference lists from all included studies and relevant review articles, along with targeted searches of key journals in psychopharmacology and traffic medicine, to identify any potentially eligible studies not captured by our electronic database searches. We also screened clinical trial registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform to identify any unpublished or ongoing studies that might meet our inclusion criteria. The complete results of our search process, including the number of records identified from each source, are presented in the PRISMA flow diagram.

Study selection process

All identified records were imported into EndNote version 21 (Clarivate Analytics) for reference management.

Duplicate citations were removed using both automated tools and manual verification. The eligibility assessment of the first screening was performed independently by two reviewers (RA and MA) based on the title and abstract. The second screening was done on full text with the inclusion and exclusion criteria by the same reviewers independently. Disagreements were resolved through double-checking of the article with a third reviewer (MG) when consensus could not be reached. During the second screening, the selection was narrowed to RCTs. Cohen's Kappa statistic was used to measure the degree of agreement between two researchers.

Data collection and extraction process

Two independent reviewers (ST, MN) performed data extraction using a piloted, standardized form in Microsoft Excel 2019 (Microsoft Corporation). The correctness of the extracted data was examined by two reviewers. Again, we resolved all discrepancies through consensus.

We abstracted the following variables from each study:

- Population characteristics: Sample size, demographic data (mean age, sex distribution), status, diagnostic criteria for depression (e.g., DSM-5, ICD-11), driving experience
- Intervention: Type, dose, duration, Treatment duration, and washout period (if applicable)
- Compression: Type, dose, duration of placebo or active comparator details
- Outcome Measures: Primary driving performance measures (SDLP, CFF, etc.), Effect sizes with measures of variance
- Study Characteristics: First author, Year of publication, Country, Trial design (parallel, crossover)

For studies reporting only graphical data, numerical values were extracted using WebPlotDigitizer (v4.7), a validated tool widely used in systematic reviews to extract data from figures.[21]

We extracted data on dosing schedules (e.g., nocturnal vs. daytime administration) where reported. However, significant variability in dosing protocols across studies precluded systematic analysis of temporal drug effects. For sedative ADs, we noted whether driving tests were conducted during peak plasma concentrations or after washout periods.

Statistical Analyses

We conducted a Bayesian NMA using a random-effects model in R v3.6.2 with the netmeta package, which accounts for both direct and indirect treatment comparisons within a unified framework. Treatments were ranked by surface under the cumulative ranking curve (SUCRA) values, derived from P-scores (range: 0–1), where higher values indicate greater probability of superiority versus competing interventions.[22] The network-level inconsistency (global inconsistency) was presented by I^2.[23] I^2 heterogeneity of 25% was deemed low, 50% moderate, and 75% as substantial heterogeneity. Furthermore, the direct and indirect assessments were compared in order to investigate node-split inconsistencies. In case of a noteworthy difference ($P < 0.05$) between the direct and indirect assessments, the direct assessment was presented as the combined estimate within the league tables. Comparison-adjusted funnel plots were made for each potential comparison, with every paper acting as the control group, in order to detect any publishing bias or small study effect.

Risk of bias assessment

The risk of bias (RoB) assessment for RCTs was conducted using the Cochrane RoB 2 tool, in accordance with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[24] This tool evaluates five distinct domains to determine the overall RoB. The judgment for the second domain, which pertains to RoB due to deviations from the intended interventions, was utilized to quantify the impact of the assignment to intervention. Each domain was classified as either "Low RoB," "Some Concerns," or "High RoB." Following the evaluation of individual domains, studies with only one domain rated as "Some Concerns" out of five were categorized as having "Low RoB." Studies with two or more domains rated as "Some Concerns" were classified under "Some Concerns," while studies with any domain rated as "High RoB" were deemed to have a "High RoB." The RoB for each study was assessed independently by two authors (MG and RA), with discrepancies resolved through discussion. Disagreements between assessors (<15% of cases) were resolved through consensus meetings with a third reviewer (MN).

Results

Study selection and characteristics

A total of 5285 records were identified. After removing duplicates and screening articles based on title and abstract, 60 articles remained. Nine studies were excluded because their full texts could not be retrieved despite our requests to the authors and libraries. [25-33]

We sent an email to the authors of the unavailable full-text papers to request their papers, but we didn't get an answer. The remained studies were reviewed in full-text, and 27 reports were included (PRISMA flow diagram, Figure 1). The Kappa agreement in study selection between RA and MA was estimated to be 95 percent (excellent agreement). Of the 27 included studies, only 13 (48%) met the additional criteria for NMA by reporting standardized driving test outcomes with extractable effect sizes. The Netherlands had the highest number of articles, with 13, followed by the United Kingdom, with five articles. All studies were RCTs, and 21(77.8%) studies had a crossover design. Ten of the listed studies used a three-way design, seven a four-way design, and one a five-period design. There were 22 (92.6%) double-blinded studies and only two single-blinded articles. In the collection of articles, twenty-six treatments were examined. Mirtazapine, the medication that was studied

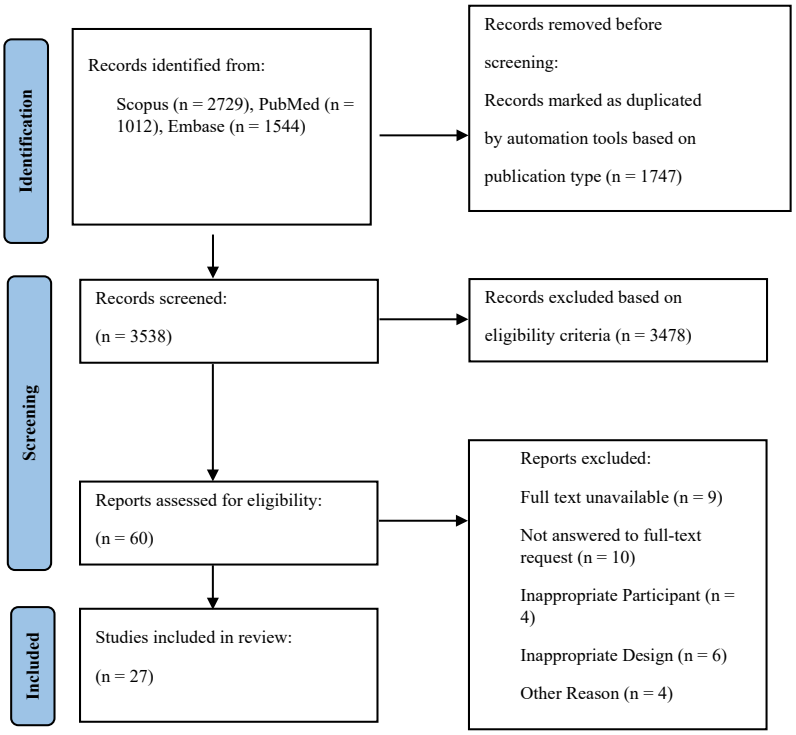


Figure 1. PRISMA 2020 flow diagram of study selection process for the network meta-analysis of antidepressant effects on driving performance

more than any other, was examined in 8 studies.[34-41] The next one is Mianserin in 5 studies.[34,42-45]Amitriptyline was examined in 4 studies.[46-49] Moclobemide was examined in 3 studies.[42,43,50] Fluoxetine was examined in 3 studies.[50-52]Paroxetine was studied in 3 studies.[35,47,49] Thirteen studies (48%) were included in the NMA.[34,38-42,44,47-49,51,53,54] The Remaining studies were excluded due to insufficient data and various measurement indices. The publishing date of the included papers spanned from 1992 to 2025. The sample sizes varied between 7 [48] to 25 [54] in each study. Most of the studies were crossover, placebo-controlled, and double-blinded. All the data were analyzed with pre-protocol analysis. The washout period ranged between 3 and 35 days (median: 7 days). Earlier research (e.g., from 1977) tended to emphasize broad, general investigations into antidepressants, whereas more recent studies (e.g., from 2024) offer more nuanced and detailed analyses. Table 1 shows an overview of the first author and publication year, Study design and country, Sample size and participant demographics (age, sex), Key inclusion criteria related to driving experience, Intervention details (medication, dose, dosing regimen), Washout period, Primary outcome measures assessed, and a summary of the key findings related to driving performance

Risk of bias assessment

The risk of bias assessment results for the 27 included studies were provided using RoB2. The overall risk of bias for 15 studies (56%) was high, while 9 studies (33%) had some concerns and 3 studies (11%) were low-risk. Figure 2a displays the traffic light plot for assessing the risk of bias of each included clinical study, whereas Figure 2b displays the weighted plot for assessing the total risk of bias by each domain.

Most of the studies had a low risk of bias in the measurement of outcome (25 [92.6%]) and selection of reported results (22 [81.5%]). Out of the 27 included studies, 18 (66.6%) had a low risk of bias due to the randomization process and deviations from the intended interventions. In 12 studies (44.4%), bias due to missing outcome data caused some concerns or a high risk of bias.

Participants

In total, 736 subjects participated in studies, 56% of whom were male and 43% of whom were female (4 participants were unknown). In eight studies, participants were assigned to two or more groups. The participants' ages ranged from 18 to 72 years.

In 20 of the studies, participants were healthy volunteers. In some studies, healthy participants were examined through a medical examination, including an ECG, urine analysis, hematology, blood biochemistry, drugs of abuse screen, psychiatric interview, biochemical and hematological profile, health interviews, and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM) before being accepted for the experiment.

In seven studies, participants had certain conditions. Major depressive disorder (MDD), persistent depressive disorder (PDD), chronic neuropathic pain, attention deficit hyperactivity disorder (ADHD), and primary insomnia were among them. Different versions of the DSM were the most prominent diagnostic tests for diagnosing psychiatric conditions, including MDD, PDD, and ADHD. In addition, the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MADRS), and Mini International Neuropsychiatric

Table 1. Overview of participant demographics, study designs, dosing protocols, and driving-related performance outcomes across all included studies

No	First Author	Year	Country	Study Design	Participants, N (Male/ Female)	Comparator Group	Age Range or Mean ± SD (years)	Driving Experience Requirements	Type of Usage	Washout Period	Primary Outcome Measures	Summary of Key Effects on Driving
1	J. G. Ramaekers[34]	1998	Netherlands	DB, Crossover	18 (9/9)	–	21–35	–	Fixed evening dosing	–	CFF; CTT; CRT; sustained attention; highway driving	Mirtazapine/ mianserin impaired early; tolerance incomplete.
2	F. Ridout[35]	2003	UK	DB, Crossover	12 (2/10)	–	21–42 (median 26)	License ≥ 3 yrs	BID dosing at 09:30 & 21:30 (Days 1-4)	7 days	BRT; CFF; CRT	Paroxetine → no BRT impairment, improved CFF/ CRT; mirtazapine impaired.
3	A. Brunnauer[36]	2008	Germany	Parallel	40 (22/18)	10 (5/5)	47.4 ± 8.5 / 44.0 ± 4.4	License	–	–	Driving simulation	Mirtazapine & reboxetine improved driving over 14 days.
4	J. Shen[37]	2009	Canada	Parallel	14 (2/12)	14 (4/10)	45.9 ± 11.9 / 45.4 ± 11.8	License	30 min prior to bedtime	–	Real on-road driving	Active treatment (mirtazapine) improved road position & reduced crashes.
5	K. Iwamoto[38]	2013	Japan	DB, Crossover	13 (13/0)	–	32–49	License ≥ 10 yrs; ≥ 5000 km/yr	Continuous bedtime dosing	≥7 days	Road-tracking; car-following; harsh-braking	Mirtazapine 7.5 mg → minimal effects; 15 mg impaired.
6	K. Sasada[39]	2013	Japan	DB, Crossover	19 (19/0)	–	26–49	License ≥ 5 yrs; ≥ 5000 km/yr	Continuous bedtime dosing	≥7 days	Road-tracking; car-following; harsh-braking	Mirtazapine ↑ SDLP & sleepiness.
7	E. L. Theunissen[40]	2013	Netherlands	DB, Crossover	24 (11/13)	–	31 ± 8.3	License > 3 yrs; ≥ 5000 km/yr	Self-administered	≥14 days	Highway driving; cognitive tests; sleep scale	Vortioxetine non-inferior; mirtazapine impaired (Day 2 only).
8	A. Van de Loo[41]	2017	Netherlands	DB, Crossover	24 (12/12)	–	21–60 (mean 27.1 ± 8.49)	License > 3 yrs; ≥ 5000 km/yr	Study medications were self-administered.	6 days	On-road driving test	Esketamine non-inferior; mirtazapine ↑ SDLP.
9	J. G. Ramaekers[42]	1992	Netherlands	DB, Crossover	18 (9/9)	–	26–54	License; ≥ 8000 km/yr (past 5 yrs)	Complex TID dosing schedule*	≥13 days	CFF; CTT; DAT; RCT; CRT	Mianserin impaired; moclobemide → no impairment.
10	J. G. Ramaekers[43]	1994	Netherlands	DB, Crossover	18 (9/9)	16 (8/8)	23–54	License; ≥ 8000 km/yr (past 5 yrs)	Oral TID dosing	13 days	CFF; CTT; DAT; RCT; CRT	MAO-Is → no impairment; brofaromine improved; mianserin/doxepin impaired early.
11	J. F. O'Hanlon[44]	1998	Netherlands	DB, Crossover	22	–	22–40	License; > 8000 km/yr (past 3 yrs)	Oral dosing	≥27 days	Driving; psychomotor; vigilance	Venlafaxine → no impairment; mianserin impaired multiple domains.
12	F. Ridout[45]	2001	UK	DB, Crossover	16 (10/6)	–	21–44 (median 29)	License ≥ 3 yrs	Oral dosing with identical capsules	≥7 days	BRT; CRT; CFF; LARS	Tianeptine → no impairment; mianserin ↓ CFF & slowed responses.
13	I. Hindmarch[46]	1988	UK	Crossover	10 (0/10)	–	28–55	–	Morning dosing on test days	7 days	CFF; CRT; Stroop; Simulated Car Tracking; VAS; Leeds Sleep Evaluation	Amitriptyline impaired; lofepramine & nomifensine → no impairment.
14	H. W. Robbe[47]	1995	Netherlands	DB, Crossover	16 (16/0)	–	21–28	License; ≥ 5000 km/yr (past 3 yrs)	–	≥13 days	CFF; CTT; recall; divided attention; Sternberg; tapping; visual discrimination	Amitriptyline impaired (strong, early); paroxetine 20 mg → no effect; 40 mg → mild impairment.
15	D. S. Veldhuijzen[48]	2006	Netherlands	DB, Crossover	7	–	–	License; ≥ 5000 km/yr (past 3 yrs)	–	6 days	Standard driving test; tracking; divided attention	Amitriptyline impaired SDLP acutely; no difference after 2 weeks.
16	K. Iwamoto[49]	2008	Japan	DB, Crossover	17 (17/0)	–	30–42(mean 35.8 ± 3.3)	License ≥ 10 yrs; ≥ 5000 km/yr	Oral dosing with identical capsules	≥7 days	Road-tracking; car-following; harsh-braking	Amitriptyline impaired; paroxetine → no impairment.

Table 1. Continued.

No	First Author	Year	Country	Study Design	Participants, N (Male/ Female)	Comparator Group	Age Range or Mean ± SD (years)	Driving Experience Requirements	Type of Usage	Washout Period	Primary Outcome Measures	Summary of Key Effects on Driving
17	J. G. Ramaekers[50]	1997	Netherlands	Double-blind	22 (13/9)	19 (12/7)	18–65	License; ≥ 5000 km/yr (past 3 yrs)	Post-meal dosing	–	On-road driving test	Driving differences linked to benzodiazepine-enzyme interactions.
18	J. G. Ramaekers[51]	1995	Netherlands	DB, Crossover	18 (10/8)	–	21–45	License; ≥ 5000 km/yr (past 3 yrs)	Evening dosing for 22 days	35 days	CFF; sustained attention; highway driving; car-following	Dothiepin & fluoxetine → minor psychomotor impairment; no driving impairment.
19	S. J. Wilson[52]	2002	UK	DB, Crossover	12 (12/0)	–	Mean 27.5 (SD 3.84)	License ≥ 2 yrs	22:00 h nightly dosing	≥35 days	Visual attention; tracking simulator	Fluoxetine improved some performance; no driving impairment.
20	M. W. Van Laar[53]	1995	Netherlands	DB, Crossover	12 (6/6)	12 (6/6)	Adults 24–38; Elderly 60–72	License; ≥ 8000 km/yr (past 5 yrs)	Oral BID dosing	7 days	SDLP highway driving; psychomotor tests; sleep latency	SDLP changes linked to metabolic interactions.
21	F. M. Dijkstra[54]	2022	Netherlands	Single-blind, crossover	27 (9/18)	–	22–60(mean 37.3 ± 10.6)	License > 5 yrs; regular driving	Self-administered at 16:00	5–14 days	On-road driving test	Esketamine → no impairment; alcohol impaired.
22	A. J. Roth[55]	2012	USA	Double-blind	16 (4/12)	–	18–65 (mean 44 ± 11)	–	Trazodone capsules	Week 2 washout	MSLT; VAS; posturography; memory; simulated driving	Trazodone → mild cognitive impairment but improved sleep.
23	A. B. Clayton[56]	1977	UK	Double-blind	40 (40/0)	40 (40/0)	18–29	–	Single dose on test day	–	Weaving task; auditory logic task; gap acceptance task	Imipramine ↑ risk-taking; viloxazine → no impairment.
24	F. Hashemian[57]	2011	Iran	Double-blind	18 (7/11)	12 (5/7)	31.3 / 32.1	–	–	–	Reaction time (visual & auditory)	Reboxetine improved visual tasks; auditory tasks unchanged.
25	F. Richet[58]	2004	France	DB, Crossover	12	–	18–30	Experienced drivers	Milnacipran 50 mg (+/- alcohol)	10.5 days	Vigilance; postural stability; on-road; VAS	Milnacipran → no impairment; no interaction with alcohol.
26	J. G. Ramaekers[59]	2011	Netherlands	DB, Crossover	32 (16/16)	–	33 ± 9	License > 3 yrs; > 5000 km/yr	Dosing on Days 1-7	≥7 days	Highway test; cognitive & psychomotor	Esmirtazapine 1.5 mg → no effect; 4.5 mg impaired acutely (tolerance with dosing).
27	S. Su[60]	2022	USA	DB, Crossover	97	–	21–65	License	oral administration	6–14 days	Vigilance-divided attention; driving simulation	Rapastinel → no impairment.

Abbreviations: BID: twice daily; BRT: Brake Reaction Time; CFF: Critical Fusion Frequency; CRT: Choice Reaction Time; CTT: Critical Tracking Test; DAT: Divided Attention Task; DB: Double-blind; LARS: Linear Analog Rating Scale; MAO-Is: Monoamine Oxidase Inhibitors; MSLT: Multiple Sleep Latency Test; NR: Not Reported; RCT: Response Competition Task; SDLP: Standard Deviation of Lateral Position; SSS: Stanford Sleepiness Scale; TID: three times daily; VAS: Visual Analog Scale.
Symbols: →: resulted in/ showed; ↑: increased; ↓: decreased.

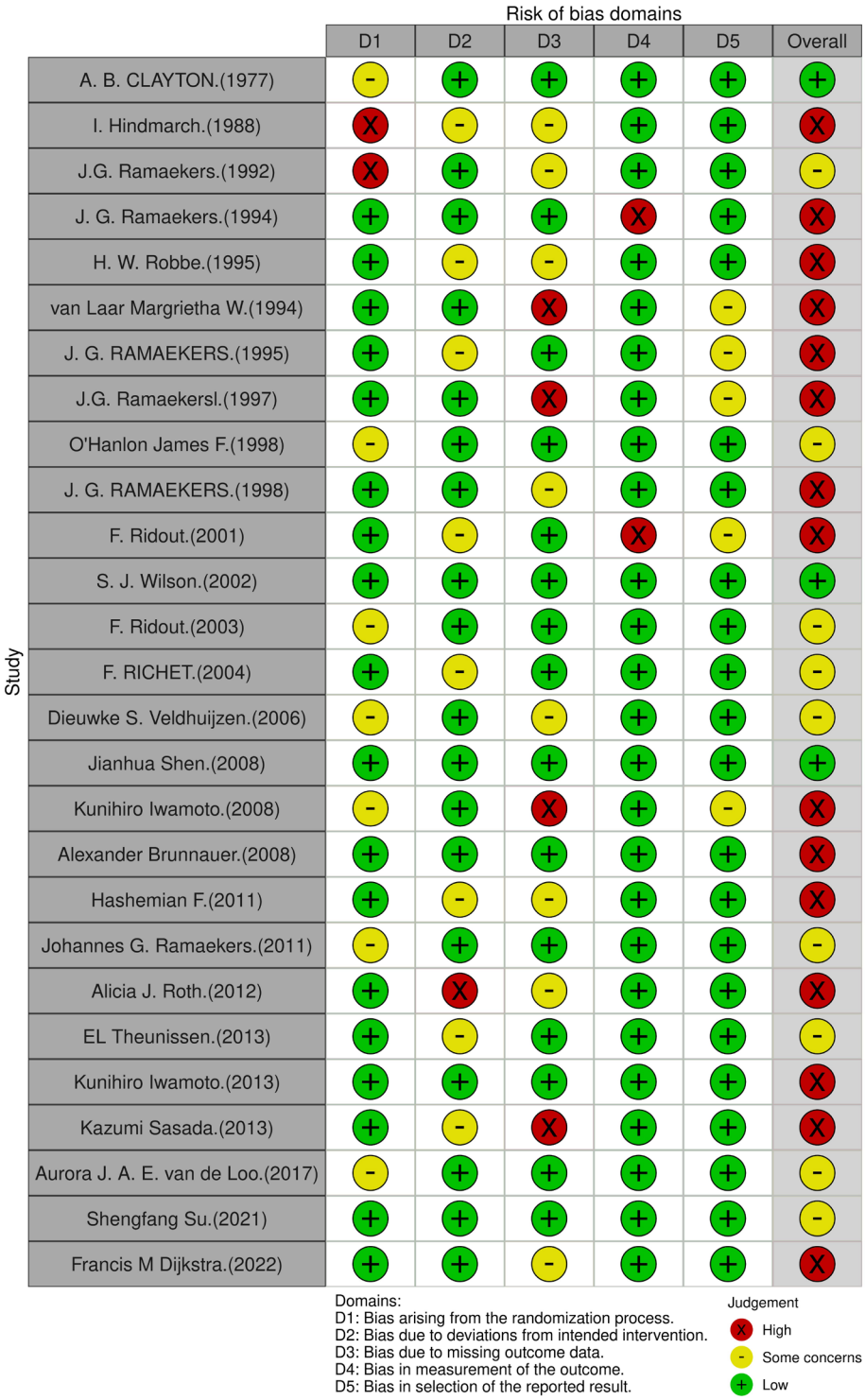
*Detailed schedule: First dose at 07:30, 08:45, or 10:00; subsequent doses 5h and 10h later. Moclobemide in 1st/3rd doses; mianserin in all three

Interview (MINI) were used for the diagnosis of depression. The Visual Analogue Scale (VAS), which measures pain intensity, has been used to diagnose and identify the severity of chronic benign neuropathic pain. Self-reported Conner's global index questionnaire and Hamilton anxiety and depression questionnaires were used to include ADHD patients. Primary insomnia was determined by an unstructured interview with a board-certified sleep physician who followed the appropriate DSM-IV.

In 22 studies were mentioned possessing a valid driving license and having driving experience were mentioned as inclusion criteria. The most frequent inclusive driving experiences were at least 8000 km/year during the previous 5 years and at least 5000 km/year during the previous 3 years. Seven studies mentioned the inclusive body mass index (BMI), which was mostly between 18 and 32 kg/m2.

Normal binocular visual acuity, corrected or uncorrected, using public transportation or not operating their own vehicles during treatment periods, and dietary restrictions or limitations for alcohol or caffeine were factors mostly considered for participant inclusion and study conduct. In some studies, participants had to refrain from any form of medication during the period of participation, but oral contraceptives were allowed in some studies. Among the studies mentioned, the allowed blood alcohol concentration (BAC) was $\leqslant 0.05\%$.

a)



b)

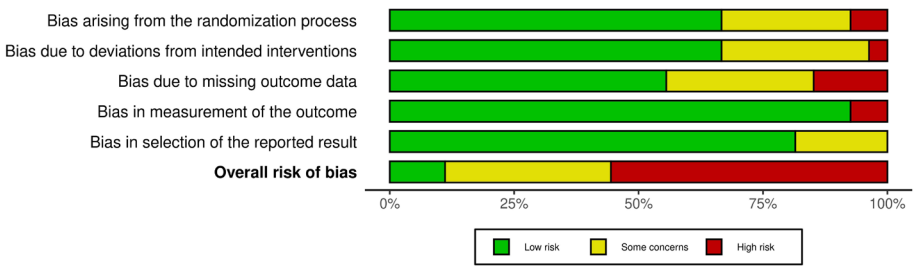


Figure 2. Risk of bias assessment using the Cochrane RoB 2 tool: a) traffic light plot and b) weighted plot. The colors indicate the risk level for each domain: Green and red colors represent low and high risk of bias, respectively. Yellow represents some concerns. D1: randomization process; D2: deviations from the intended interventions; D3: missing outcome data; D4: measurement of the outcome; and D5: selection of the reported result

Medicine

The time of taking each medicine was based on the study design, but it varied between just once on test days and 43 consecutive days. The washout period for treatment periods ranged from 5 days to 35 days. Except for Esketamine intranasal administration in two studies, almost all medications were administered encapsulated and orally.

Measurements

Psychometric Measurements

The most frequently used tests in the studies were the critical fusion frequency (CFF), the critical tracking test (CTT), Moskowitz's (1973) divided attention task (DAT), and the choice reaction time task (CRT). The other tests that were less commonly recruited in the studies were Erikson and Erikson's (1974) response competition task (RCT), the Stroop color/word test (Stroop, 1935), and a gap acceptance task. Sustained Attention to Response Test (SART) and Continuous Recall (CONT, Hunter, 1975), Sternberg Test (ST, Sternberg, 1969), Constant Tapping (TAP, Michon, 1966) Visual Discrimination (DIS, Nuechterlein et al, 1983) Vigilance test (VIG), selective attention test, postural stability testing, the CogScreen Symbol Digit Coding (SDC) test, and training or practice on the Country Vigilance-Divided Attention (CVDA).

Driving

Real on-road driving and simulated driving were the two types of driving tests implemented in the studies that were included, with real driving being more common. The most frequent test was road tracking. The participants were instructed to maintain a consistent speed (usually 95 km/h) while maintaining a steady lateral position inside the right lane in an instrumented car in real-world driving situations. In certain studies, the possibility of passing a car moving more slowly in the same lane was suggested. A qualified driving instructor was present and intervened when necessary. The route they took was around 100 kilometers long in most of the studies. Along with the aforementioned test, other, less frequent evaluations in real driving included car-following and harsh braking.

The car-following test determines the coefficient of variation of the distance between the preceding car and the subject's own car.[61] The subject has to keep a set distance between the automobiles in this test. The harsh-braking test assesses the mean brake reaction time in seven braking attempts to avoid colliding with humanoid models that dashed into the road at random.

The primary goal of the virtual driving settings was to provide the closest representation of real-world driving situations. Some studies aimed to imitate dangerous conditions in accordance with the goals they pursued. In the experiments, visual and auditory feedback were also supplied in order to deliver an instruction or a task. The simulators also had wheels and pedals. In certain studies, speed limitations were mandated.

In simulated driving, the number of lane exceedances, lane exceedance maximums (maximum lateral deviation from the lane center), duration of exceedance, total number of collisions, reaction times (such as choice and brake reaction times), standard deviation of road position, and deviation from posted speed were measured. There was also a designated period for practice before the actual testing.

In a study [55] the task at hand was interactive, with participants receiving bonuses and penalties based on their performance quality.

Subjective Measurements

Sleep and personal feelings measures were among the subjective metrics included in the investigations. In the majority of the studies, sleepiness questionnaires were the method of choice. Leeds and Mulders were the most often used. The studies also included the Karolinska Sleepiness Scale (KSS), the Stanford Sleep Scale (SSS), the Milford Epworth Sleepiness Scale, and the Groningen Sleep Quality Scale. In order to identify potential adverse effects, the visual analog scale was the most frequently applied assessment. This scale shows the prevalence and severity of potential side effects such as sleepiness, weakness, headache, tiredness, anxiety, nausea, dizziness, and memory loss. Additionally, it is used to evaluate the subjective driving performance as well as any mood changes the participants may have encountered throughout the test.[34,42,53]

Effects

According to the extraction table, the use of the drugs Viloxazine, Lofepramine, Nomifensine, Moclobemide, Brofaromine, Dothiepin, Fluoxetine, Venlafaxine, Tianeptine, Milnacipran, Vortioxetine, and Esketamine had no apparent effect on the participants' performance, although one study using dothiepin and Fluoxetine found that sustained attention was reduced. Nearly all facets of performance were impacted by the drugs Mianserin and amitriptyline. Imipramine increased the individuals' willingness to take risks. Participants' driving abilities were reduced by the drugs doxepin and ketamine. Mirtazapine and imipramine showed little effect on psychomotor performance. Amitriptyline had a positive control (sedative) on psychomotor performance.

Mirtazapine, Reboxetine, and Rapastinel were found to improve driving performance. The meta-analysis results demonstrated that paroxetine 10 mg showed the highest potential for improving driving performance (MD = -7.85; 95% CI: -19.95 to 4.25). Mianserin 10 mg exhibited a notable effect (MD = -4.19; 95% CI: -12.13 to 3.74), while trazodone 25 mg showed modest improvement in driving performance (MD = -2.47; 95% CI: -14.43 to 9.49). However, these differences were not statistically significant ($P > 0.05$). Some impacts on cognitive and memory skills were dose-related, Nefazodone 200mg, for instance, slightly decreased performance at high dosages while improving it at low levels. The effects of mirtazapine on performance and sleep were dose-related

as well. Furthermore, single dosages of Esmirtazapine and zopiclone increased SDLP. Paroxetine 20 mg showed no effect on performance; however, paroxetine 40 mg had a modest effect on the road-tracking task as well as other psychomotor assessments. Vigilance was influenced by Venlafaxine, Mianserin, and amitriptyline. Imipramine, Nefazodone, Mianserin, Dothiepin, and Amitriptyline all had an impact on reaction time, with Dothiepin having a reducing effect and Amitriptyline and Mianserin raising it.

Reboxetine did not alter performance when an auditory stimulus was present, but it did when a visual stimulus was the only stimulus. The extra dose of the medicine Venlafaxine didn't produce any noticeably different outcomes. Dothiepin enhanced REM, and fluoxetine decreased it during daytime naps. It was also said that Nefazodone and Imipramine did not produce daytime drowsiness and that trazodone even reduced it.

Most studies with sedative ADs (e.g., mirtazapine, trazodone) administered doses at bedtime and assessed driving performance the following morning (e.g., 10–12 hours post-dose). For esketamine, all included trials evaluated driving ≥ 6 hours post-administration, aligning with clinical guidelines that prohibit driving during acute intoxication.

Network Meta-analysis

Thirteen studies were included in the network meta-analysis. An NMA was conducted based on a multi-treatment random-effects model NMA for the studies with SDLP measurement and adequate data. The network geometry of antidepressant treatment comparisons for driving impairment is shown in Figure 3. Global network heterogeneity was high for the antidepressant treatment network ($I^2 = 90.3\%$).

Based on the forest plot in Figure 4, the mean difference in driving performance between the medication and the placebo is computed with 95% credible intervals. This mean difference is a direct comparison of the two tested medications to the placebo group. Although the mean difference between the two groups was not statistically significant (considering that the credible intervals include zero), the mean difference in driving performance in people who took Paroxetine 10 mg, Paroxetine 20 mg, and Mianserin 10 mg may be of interest. Table in the Supplementary file 2 displays the findings of the indirect

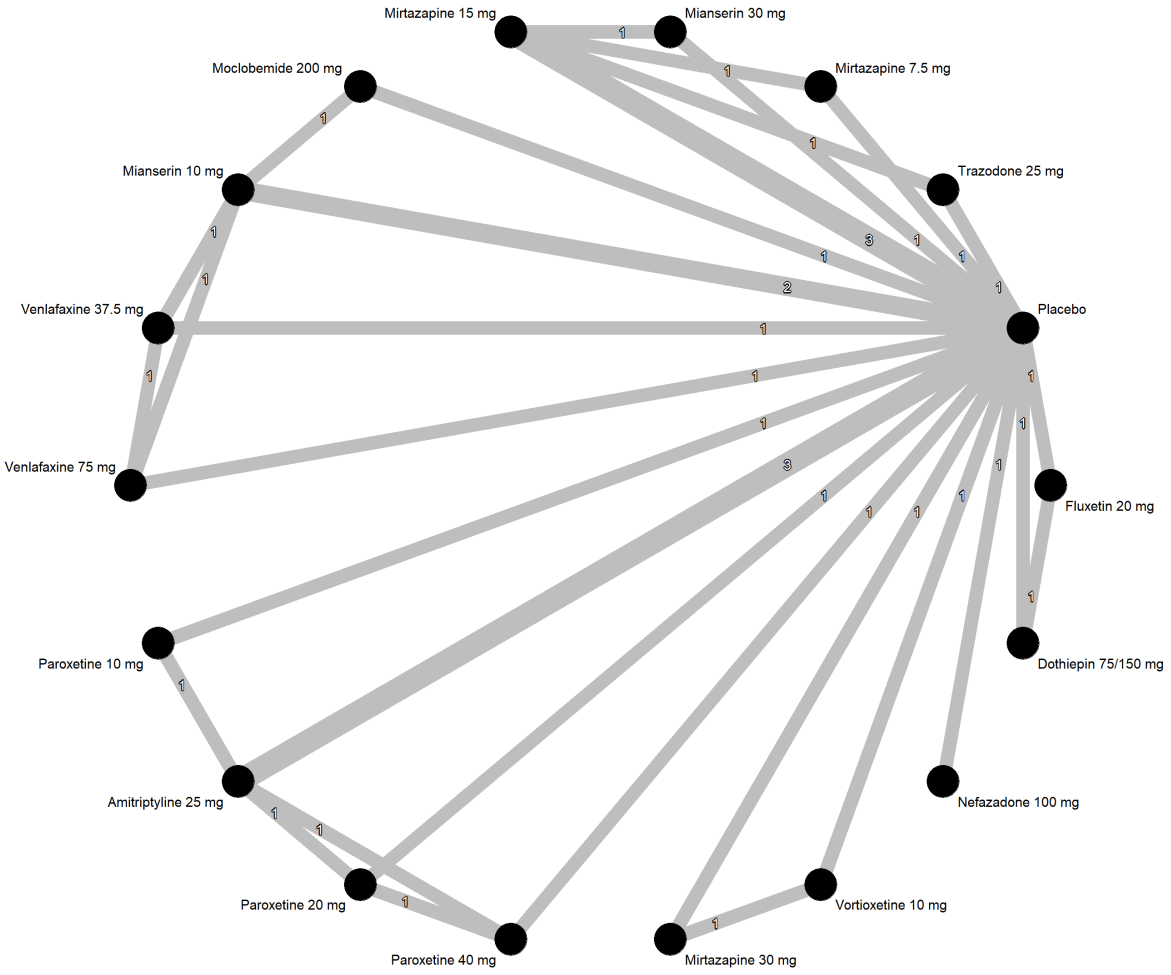


Figure 3. Network Geometry of Antidepressant Treatment Comparisons for Driving Impairment

comparison, which were used to compare all of the requested treatments received from the network meta-analysis.

In Table 2, the value of the p-score is shown in order to rank the studied treatments in terms of effectiveness in driving performance. The P-score analysis from the NMA revealed that paroxetine 10 mg demonstrated the highest P-scores in both fixed (0.96) and random (0.83) effects models, establishing it as the most effective medication for improving driving performance. Mianserin 10 mg (fixed P-score: 0.80; random: 0.72) and dothiepin 75/150 mg (fixed P-score: 0.81; random: 0.60) ranked next in effectiveness. Comparison between fixed and random effects models showed significant ranking differences. While paroxetine 10 mg showed clear superiority in the fixed effects model, this advantage was less pronounced in the random effects model, indicating potential heterogeneity across studies. Venlafaxine 37.5 mg (random P-score: 0.39) and paroxetine 20 mg (random P-score: 0.27) received the lowest rankings.

Dose-response analysis indicated that paroxetine at 10 mg was more effective than higher doses (20 mg and 40 mg). Mianserin showed better performance at the lower dose (10 mg) compared to the higher dose (30 mg). Mirtazapine demonstrated an inverse dose relationship, with 7.5 mg being more effective than 15 mg and 30 mg doses.

P-scores ranged from 0.01 for venlafaxine 37.5 mg to 0.96 for paroxetine 10 mg. For most medications, fixed effects model P-scores were higher than random effects model scores, suggesting between-study heterogeneity.

The top five medications based on P-scores were paroxetine 10 mg, mianserin 10 mg, dothiepin 75/150 mg, amitriptyline 25 mg, and trazodone 25 mg. These results may help select medications with minimal driving impairment, though clinical interpretation should also consider mean differences and credible intervals.

Table 2. Ranking of antidepressants by driving impairment risk based on P-Scores from network meta-analysis (higher values indicate less impairment)

Antidepressant (Generic name, Dose/Mg)	P-score (Fixed-effects)	P-score (Random-effects)
Paroxetine 10	0.9613	0.8255
Mianserin 10	0.8004	0.7191
Dothiepin 75/150	0.8117	0.6037
Trazodone 25	0.6958	0.5949
Moclobemide 200	0.5985	0.5847
Mirtazapine 30	0.6522	0.5344
Venlafaxine 75	0.1825	0.5091
Mianserin 30	0.5331	0.4827
Mirtazapine 7.5	0.4953	0.4787
Mirtazapine 15	0.5277	0.4595
Placebo	0.4173	0.4562
Fluoxetine 20	0.3142	0.4382
Amitriptyline 25	0.8882	0.4294
Vortioxetine 10	0.2576	0.4274
Nefazodone 100	0.2341	0.4226
Venlafaxine 37.5	0.0161	0.3876
Paroxetine 40	0.4721	0.3731
Paroxetine 20	0.1423	0.2739

Publication Bias Assessment

The funnel plot analysis (Supplementary file 3) demonstrated symmetrical distribution of study effect sizes around the pooled estimate, with most data points falling within the 95% credible interval boundaries. This assessment strengthens confidence in the validity of our meta-analytic conclusions regarding antidepressant effects on driving performance.

Discussion

To our knowledge, this study is a comprehensive systematic review, meta-analysis, and NMA of the effects of antidepressant agents on driving performance. While most of the antidepressants have a similar effect, their safety and adverse effects vary in different classes. The impact of antidepressants on numerous neurotransmitter systems is linked to a significant number of their adverse effects.[62] Epidemiologic studies have shown mixed results on the association between depression and traffic accidents, as some suggest a link, while others show no association. Recent studies show minor increases in traffic accident risks associated with antidepressant use, especially after treatment changes.[63] This synthesis provides a crucial evidence base for clinicians managing depressed patients who drive, while highlighting important gaps requiring further investigation to optimize both mental health outcomes and traffic safety

This systematic review synthesized evidence from 27 original studies to assess the effects of antidepressants on adult driving performance and to evaluate the methodologies employed in this research field.

Participants

Major depressive disorder (MDD) affects approximately

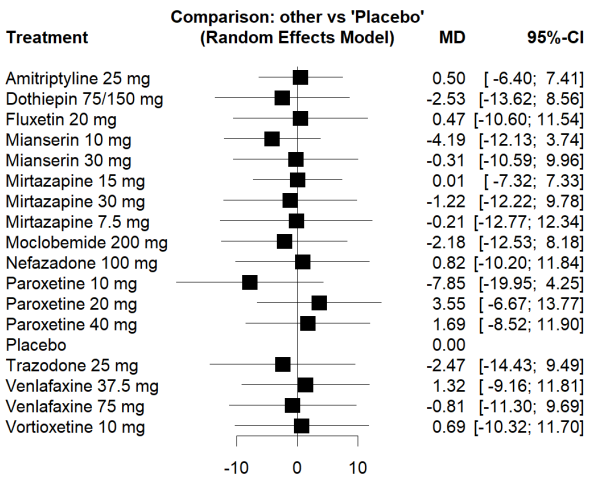


Figure 4. Forest plot of standardized mean differences (SMDs) for driving impairment across antidepressant classes versus placebo

7.1% of US adults, with the highest prevalence among individuals aged 35-55 years.[64,65] This demographic overlap with the driving population underscores the importance of understanding antidepressant effects on driving performance. Our findings demonstrate significant variability in driving impairment across different antidepressant classes, consistent with known differences in their pharmacological profiles.

The observed impairment patterns align with established cognitive deficits in depression, particularly in hazard perception and reaction time, key factors in road safety. Notably, sedating antidepressants showed greater impairment, suggesting that medication selection should consider patients' driving requirements. These effects may be compounded in novice drivers, who already exhibit reduced hazard perception skills.[66]

Several methodological considerations emerge from our study. First, the use of different depression assessment tools (HDRS, MADRS, MINI) across studies may influence outcome interpretation.[67-70] Second, the frequent off-label use of antidepressants for conditions like ADHD and chronic pain introduces potential confounding variables.[71-73] Third, polypharmacy [74] and alcohol [75] use represents important covariates that were inconsistently reported in included studies.

Our NMA revealed that driving impairment varies substantially by antidepressant class and dosage. These findings have direct clinical implications for medication selection in working-age adults who drive regularly. Future research should employ standardized driving assessments while controlling for depression severity, comorbid conditions, and concomitant medication use to better isolate drug effects.

Washout period

The placebo washout design in antidepressant trials may impact driving performance assessments. Our analysis found washout periods varied significantly (3-35 days), potentially affecting results, particularly for drugs with longer half-lives. Shorter washout periods correlated with greater outcome variability. The exclusion of "placebo responders" (10-15% of participants) may explain modest effect sizes in our findings. Additionally, single-dose testing protocols may not reflect real-world conditions where tolerance develops. These methodological considerations highlight the need for standardized, pharmacokinetic-adjusted washout periods and more ecologically valid testing schedules in future research.[76,77]

Measurements

Our analysis of psychometric tests (CFF, CTT, DAT, CRT) revealed differential sensitivity to antidepressant effects, with DAT showing the strongest correlation with driving impairment. Notably, studies using SDLP measurements demonstrated more consistent drug effects compared to simulator-based assessments, supporting its status as the gold standard. However, methodological variations across countries, particularly the use of real-road testing versus simulators, contributed to significant heterogeneity in our meta-analysis.

Effects

Antidepressants may reduce the signs and symptoms of depression, but they could also have side effects that make it unsafe to drive. Both antidepressants and depression itself could pose risks to driving safety.[7] Antidepressant subclasses may have various motor vehicle crash risks since adverse effects differ across subclasses.[78]

TCAs

Dothiepin, Amitriptyline, Imipramine, and Doxepin are classified as TCAs, a class of medications primarily used to treat MDD. These drugs are often considered second-line treatments alongside SSRIs.[79]

Imipramine, as demonstrated in a study by Clayton et al. (1977),[56] which had a low RoB, was found to increase risk-taking behavior. In contrast, a study by van Laar et al. (1995) [53] with a high RoB reported an initial adverse effect on driving behavior was reported, which diminished after repeated doses. Given the known side effects of Imipramine, such as dizziness, confusion, and impaired vision, concerns about its potential negative impact on driving performance are well justified.[80]

In the case of Dothiepin, the study by Ramaekers et al. (1995),[51] which had a high RoB, indicated a minimal adverse effect on driving ability. A subsequent study by Wilson et al. (2002),[52] with a low RoB, found no significant impact on driving performance. Dothiepin has also been associated with a greater decrease in rapid eye movement (REM) sleep latency and a milder reduction in REM duration, while heightening drowsiness and extending sleep duration.[51]

Several studies investigating the effects of Amitriptyline on driving performance (Hindmarch et al, 1988; Robbe and O'Hanlon, 1995; Veldhuijzen et al, 2006; Iwamoto et al, 2008) [46-49] largely confirmed its impairing effects. However, two studies (Robbe and O'Hanlon, 1995; Veldhuijzen et al, 2006) [47,48] noted that these negative effects were reduced with repeated dosing. The study by Iwamoto et al. (2008),[49] which focused on acute dosing, found pronounced impairments in driving ability. Notably, all studies had a high RoB, except for Veldhuijzen et al. (2006),[48] which had some concerns regarding RoB. Side effects of Amitriptyline are generally comparable to those of Dothiepin.[77] Veldhuijzen et al. (2006) [48] found that acute doses of Amitriptyline led to increased reaction times, indicating that taking this medication shortly before driving could compromise cognitive functions essential for safe driving. Thus, avoiding driving immediately after taking Amitriptyline is recommended for road safety.

Comparative studies have shown that Dothiepin tends to have fewer side effects compared to Amitriptyline. Furthermore, when it comes to overall therapeutic effectiveness, Dothiepin and Amitriptyline exhibit fairly similar outcomes.[82]

SSRIs

SSRIs are among the most commonly prescribed

antidepressants and are often recommended as a first-line treatment for MDD.[83]

Among these, Fluoxetine has been extensively studied for its impact on driving performance. While a study by Ramaekers et al. (1995) [51] with a high RoB, found minimal adverse effects on driving, subsequent studies (Ramaekers, Ansseau et al, 1997; Wilson, Bailey et al, 2002) [50,52] concluded that Fluoxetine had no significant impact on driving ability. The more robust study by Wilson and Bailey (2002) [52] had a low RoB, providing stronger evidence for the neutral effects of Fluoxetine on driving performance. This suggests that, despite some concerns in earlier studies, Fluoxetine may not pose a significant risk to driving safety when prescribed responsibly.

Fluoxetine's pharmacological profile is notable for its potent inhibition of serotonin reuptake and its long half-life (1–3 days), along with the presence of an active metabolite, norfluoxetine, which extends the half-life to 7–15 days. This necessitates a prolonged washout period in crossover studies.[52] Despite its efficacy, Fluoxetine is associated with side effects such as insomnia, nausea, diarrhea, and fatigue, which may influence daily functioning, including driving.[84]

Paroxetine, another SSRI, has also been assessed for its impact on driving. Initial findings by Robbe and O'Hanlon (1995) [47] indicated no effect on driving performance, although the study had a high RoB. A later study by Ridout et al. (2003) [35] suggested potential positive effects on driving skills but reported concerns about RoB. A third study by Iwamoto et al. (2008) [49] concluded that Paroxetine had no significant impact on driving, though the RoB remained high.

The study by Robbe and O'Hanlon [47] provided evidence that adverse reactions to paroxetine are associated with the dosage, potentially affecting psychomotor performance when the dose reaches 40 mg per day or higher. Moreover, higher doses of this medication can result in reduced sleep quality, leading to fatigue and drowsiness. These effects can subsequently cause a loss of concentration, although to a lesser extent compared to amitriptyline. Paroxetine is as effective as older antidepressants like amitriptyline but tends to produce fewer and milder side effects.

SNRIs

SNRIs are substances that inhibit the reuptake of both serotonin (5-HT) and norepinephrine (NE) without causing the nonspecific and side-effect-inducing interactions associated with TCAs. SNRIs are quickly absorbed into the bloodstream after oral administration. Unlike many SSRIs, SNRIs tend to have relatively short half-lives, with some examples, like venlafaxine, having a half-life as short as 4 hours.[85]

Reboxetine, a norepinephrine reuptake inhibitor (NRI), has shown positive effects on driving performance in studies by Brunnauer et al. (2008) and Hashemian et al. (2011),[36,57] although both studies had a high RoB. This suggests that while NRIs like Reboxetine may benefit driving performance, further research with higher methodological rigor is needed to confirm these effects.

Other antidepressants

Mianserin, a tetracyclic antidepressant, has been shown to affect driving performance. In one study by Ramaekers, Swijgman et al, 1992,[42] no effect on driving was found, though the RoB was of concern. A subsequent study by Ramaekers, van Veggel et al, 1994 [43] indicated initial impairing effects that decreased with repeated doses, but this study also had a high RoB. Additional studies by O'Hanlon, Robbe et al, 1998; Ramaekers, Muntjewerff et al, 1998; Ridout and Hindmarch, 2001 [34,44,45] found negative effects of Mianserin on driving skills, with varying levels of RoB.

These findings suggest that Mianserin can compromise vigilance and attention, particularly in the early stages of treatment, posing risks for driving safety.[86] In conclusion, Mianserin's impact on driving is complex, and caution is warranted, particularly during the initial phase of treatment.

Mirtazapine, an atypical antidepressant, has been widely studied for its effects on driving. Five studies by Ramaekers, Muntjewerff et al, 1998; Ridout, Meadows et al, 2003; Sasada, Iwamoto et al, 2013; Theunissen, Street et al, 2013; van de Loo, Bervoets et al, 2017 [34,35,39-41] reported impairments in driving performance, with most studies having a high RoB. However, more recent research (Theunissen, Street et al, 2013; van de Loo, Bervoets et al, 2017) with lower RoB suggested some concerns. Interestingly, studies by Brunnauer et al. (2008) and Iwamoto et al. (2013) [36,38] concluded that Mirtazapine did not affect driving, though both had high RoB. Contrary to these findings, Shen et al. (2009) [37] reported that Mirtazapine actually improved driving performance, with a low RoB. These conflicting results highlight the variability in Mirtazapine's impact on driving, emphasizing the need for further well-designed studies.

Our findings from experimental studies demonstrate that certain antidepressants (particularly sedating medications) impair driving performance. These results align with epidemiological studies reporting increased crash risk for these drugs.[87] However, it should be noted that Experimental studies typically evaluate acute drug effects, whereas epidemiological studies examine chronic exposure outcomes. In real-world conditions, drivers may employ compensatory strategies not measurable in laboratory settings.

Clinicians should consider sedation profiles when prescribing antidepressants to drivers. For instance, mirtazapine (sedating) may require caution in the first week of use, while fluoxetine (non-sedating) appears safer.

Limitation

While comprehensive, this study has several important limitations. First, we restricted our analysis to English-language publications, potentially missing relevant non-English studies. The included studies spanned many years, introducing variability in methodologies and assessment

criteria. Furthermore, the inability to retrieve full texts for nine studies (as detailed in the Results section) introduces a potential for selection bias.

Methodological challenges included inconsistent measurement tools across studies, making direct comparisons difficult. When numerical data were unavailable, we had to extract information from graphs, which may introduce minor inaccuracies. Studies also varied significantly in their follow-up periods; we addressed this by focusing on initial and final assessment points.

These limitations primarily affect the generalizability of our findings rather than the internal validity of the analysis. They highlight important considerations for interpreting the results and designing future research in this area.

The high level of heterogeneity observed in the network meta-analysis ($I^2 = 90.3\%$) represents a significant limitation of this study. This substantial heterogeneity is likely attributable to several factors, including: variability in study populations (combining healthy volunteers and patients with diverse conditions such as major depressive disorder, neuropathic pain, ADHD, and insomnia), differences in study designs (e.g., short-term vs. long-term dosing, varied washout periods), the use of disparate driving performance measures (on-road vs. simulator driving, varied psychometric tests), and different medication dosages. Furthermore, the variable methodological quality of the included studies (with approximately 56% having a high risk of bias) may have contributed to this heterogeneity. This degree of heterogeneity challenges the generalizability of the pooled estimates and underscores the need for cautious interpretation of the treatment rankings derived from the model. Nevertheless, the identification of impairment patterns, particularly for strongly sedating medications, remains noteworthy even amidst this heterogeneity.

Conclusion and Future Studies

In conclusion, this study attempted to systematically review RCTs to assess the effect of antidepressant medications on driving performance and conduct an NMA of eligible studies to derive a clear and comparable conclusion on the influence of antidepressants on driving ability. Based on the NMA, treatments with fewer connections, such as Dothiepin, Nefazodone, and Moclobemide, warrant further investigation. Additionally, more extensive examination is needed for newly introduced antidepressants, including Esketamine, Scopolamine, and Psilocybin, and their comparative effects with other antidepressants. The comparative efficacy of many antidepressants remains insufficiently explored, highlighting the need for more rigorous and comprehensive studies in this domain. Notably, over the past decade, there has been a scarcity of research specifically addressing the impact of antidepressants on driving performance. To assess potential driving impairment, clinicians could monitor braking frequency patterns following antidepressant initiation as an objective measure of driving behavior changes. Like the study by Chen et al,[88] machine learning techniques can be used to analyze real-world naturalistic driving data to identify depression status and utilize Antidepressants in patients and examine whether specific demographics and medications improve or impair driving behavior.

There is a limited number of studies investigating the long-term effects of these drugs on driving performance. These findings underscore the critical need for studies rich in methodology to inform clinical decision-making and public health policy regarding antidepressant use in driving populations. While some antidepressants impair driving performance, the effect varies by drug and dose. Future studies should standardize driving assessments, include long-term follow-ups, and compare newer agents (e.g., Vortioxetine, Esketamine) against traditional options.

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Authors' Contribution

Conceptualization: Homayoun Sadeghi-Bazargani
Formal analysis: Morteza Ghojazadeh
Investigation: Razieh Abdolrahmanzadeh, Melika Ahmadi Bonabi, Mahshad Narimani, Sepita Taghizadeh
Methodology: Homayoun Sadeghi-Bazargani, Morteza Ghojazadeh,
Project administration: Morteza Ghojazadeh, Razieh Abdolrahmanzadeh
Supervision: Morteza Ghojazadeh, Razieh Abdolrahmanzadeh
Validation: Morteza Ghojazadeh
Visualization: Razieh Abdolrahmanzadeh, Melika Ahmadi Bonabi, Mahshad Narimani, Sepita Taghizadeh
Writing–original draft: Razieh Abdolrahmanzadeh, Melika Ahmadi Bonabi, Mahshad Narimani, Sepita Taghizadeh
Writing–review & editing: Homayoun Sadeghi-Bazargani, Razieh Abdolrahmanzadeh, Melika Ahmadi Bonabi, Mahshad Narimani, Sepita Taghizadeh

Competing Interests

All the authors declare that there is no conflict of interest regarding the publication of this paper

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary information files.

Ethical Approval

Not applicable.

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Supplementary Files

Supplementary file 1. Search Strategies
Supplementary file 2. Indirect Comparison Results of the Network Meta-Analysis

Supplementary file 3. Publication Bias Assessment

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