Increased Risk of Dementia in Patients with Anti-depressants: A Meta-analysis of Observational Studies

Supplementary Appendix

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Yao-Chin Wang[1, 2, 4] ; Po-An Tai[3]; Tahmina Nasrin Poly[1, 4]; Md. Mohaimenul Islam[1, 4]; Hsuan-Chia Yang[1, 4]; Chieh-Chen Wu[1 ,4]; Yu-Chuan (Jack) Li[1, 4, 5*]

Table S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	**1**	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	**2**	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	**3**	Describe the rationale for the review in the context of what is already known.	3
Objectives	**4**	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	**5**	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	**6**	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	**7**	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	**8**	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	**9**	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	**10**	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	**11**	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	4
Risk of bias in individual studies	**12**	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	**13**	State the principal summary measures (e.g., risk ratio, difference in means).	4

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Supplementary Table S2: Search strategy

Key word	MeSH term
Anti-depressants SSRIs Tricyclics Monoamine oxidase inhibitors (MAOIs")	Anti-depressant [All Fields] AND ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "drugs"[All Fields]) AND ("serotonin uptake inhibitors"[Pharmacological Action] OR "serotonin uptake inhibitors"[MeSH Terms] OR ("serotonin"[All Fields] AND "uptake"[All Fields] AND "inhibitors"[All Fields]) OR "serotonin uptake inhibitors"[All Fields] OR "ssris"[All Fields]) ("antidepressive agents, tricyclic"[Pharmacological Action] OR "antidepressive agents, tricyclic"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields] AND "tricyclic"[All Fields]) OR "tricyclic antidepressive agents"[All Fields] OR "tricyclics"[All Fields])
Dementia	("dementia"[MeSH Terms] OR "dementia"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])

Table S3. Modified Newcastle-Ottawa Scale for Risk of Bias Assessment

Case Control Studies	Cohort Studies

Selection:
 1. <u>Is the case definition adequate?</u>
    a) yes, with independent validation
    b) yes, e.g., record linkage or based on self-reports
    c) no description
 2) <u>Representativeness of the cases</u>
    a) consecutive or obviously representative series of cases
    b) potential for selection biases or not stated
 3) <u>Selection of Controls</u>
    a) community controls
    b) hospital controls
    c) no description
 4) <u>Definition of Controls</u>
    a) no history of disease (endpoint)
    b) no description of source
	Selection
	 1) <u>Representativeness of the exposed cohort</u>
	    a) truly representative of the average adult in the community
	    b) somewhat representative of the average adult in the community
	    c) selected group of users e.g. ,nurses, volunteers
	    d) no description of the derivation of the cohort
	 2) <u>Selection of the non-exposed cohort</u>
	    a) drawn from the same community as the exposed cohort
	    b) drawn from a different source
	    c) no description of the derivation of the non-exposed cohort
	 3) <u>Ascertainment of exposure</u>
	    a) secure record (e.g., surgical records)
	    b) structured interview
	    c) written self-report
	    d) no description
	 4) <u>Demonstration that outcome of interest was not present at study start</u>
	    a) yes
	    b) no

Comparability:
 1) <u>Comparability of cases and controls on the basis of the design or analysis</u>
    a) study controls for age
    b) study controls for any additional factor
	Comparability
	 1) <u>Comparability of cohorts on the basis of the design or analysis</u>
	    a) study controls for age
	    b) study controls for any additional factor

Exposure	Outcome

Exposure
1) <u>Ascertainment of exposure</u>
    a) secure record (e.g., pharmacy records)
    b) structured interview where blind to case/control status
    c) interview not blinded to case/control status
    d) written self-report or medical record only
    e) no description
2) <u>Same method of ascertainment for cases and controls</u>
    a) yes
    b) no
3) <u>Non-Response rate</u>
    a) same rate for both groups
    b) non respondents described
    c) rate different and no designation
	Outcome
	1) <u>Assessment of outcome</u>
	    a) independent blind assessment
	    b) record linkage
	    c) self-report
	    d) no description
	2) <u>Adequacy of follow up of cohorts</u>
	    a) complete follow up - all subjects accounted for
	    b) subjects lost to follow up unlikely to introduce bias: i.e.,<10% small number, lost, or description provided of those lost
	    c) follow-up rate < 90% and no description of those lost
	    d) no statement