

Best Evidence Summaries of Topics in Mental Healthcare

BEST in MH *clinical question-answering service*

Question

What is the evidence for long-term lithium use as a cause of cognitive problems in older adults?

Clarification of question using the *PRO* structure

Patients: Older adults
Risk factor: Long-term lithium use
Outcome: Cognitive problems

Clinical and research implications

No definite clinical implications can be made based on the available evidence. More studies are needed to assess the impact of long-term lithium on cognitive outcomes/problems in older adults. Only one study met the inclusion criteria for this BEST summary, which found no relationship between duration of lithium use and cognitive function. The methodology employed by this study, however, reduces the reliability of these findings. The authors suggested that "...a possible next step in the evaluation of the benefits of lithium treatment on brain health, [is] a short-term (one-year) prospective randomised controlled trial of add-on lithium versus placebo in older adults with BD who have had minimal recent lithium exposure, evaluating both cognitive and brain imaging outcomes as well as measuring biomarkers..". The authors then suggested that this be followed-up with a long-term study, depending on the outcomes.

What does the evidence say?

Number of included studies/reviews (number of participants)

One case-control study met the inclusion criteria for this BEST summary (Gildengers et al. 2015).

Main findings

This study examined if long-term lithium exposure was related to brain health, including better cognitive function, in 58 older adults (mean age 64.5 years) with bipolar disorder (BD) and 21 healthy controls of a similar age. The authors found no significant association between cognitive performance and duration of lithium treatment among those participants with BD (correlation 0.165, $p=0.22$). The authors also examined grey matter volume, overall white matter integrity, and total white matter hyperintensity burden. As these results are not directly relevant to the research question, they have not been presented here.

Authors' conclusions

The authors concluded that lithium treatment appears to be related to better brain integrity in older individuals with BD, but that the findings need to be confirmed with a larger sample size. The authors did not make any explicit conclusions relating to cognitive performance.

Reliability of conclusions/Strength of evidence

As the authors of this study noted, their sample size was small, and the analysis was cross-sectional with lithium exposure assessed retrospectively. We also note that only 33 participants included in this study had long-term lithium exposure. Given the methodological limitations, this study was considered to have a high risk of bias. The authors, however, appropriately stated that their findings need to be confirmed with a larger study.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on long-term lithium use as a cause of cognitive problems in older adults.

Date question received: 09/07/2015

Date searches conducted: 15/07/2015

Date answer completed: 20/07/2015

References

Cohort / Case-control studies

Gildengers, A. G., Butters, M. A., Aizenstein, H. J., Marron, M. M., Emanuel, J., Anderson, S. J., ... & Reynolds, C. F. (2014). Longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder. *Bipolar Disorders*, 17, 248-256.

Results







Case-control studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Gildengers et al. (2015)	<p><i>Participants:</i></p> <p>Patient group: Individuals aged 50 years or older diagnosed with bipolar I or bipolar II disorder referred from community, outpatient clinics and inpatient units. To be included, patients had to present with clinical euthymia for four weeks preceding neurocognitive assessment, (euthymia measured on the Hamilton Rating Scale (HRSD) and the Young Mania Rating Scale (YMRS)). Patients were not included in the study if they had (i) a history of dementia or neurological disorder affecting the central nervous system; (ii) electroconvulsive therapy with the preceding six months; (iii) substance abuse within the preceding 12 months.</p> <p>Control group: Individuals with no history of psychiatric or neurological conditions, with the average group age, education level and cardiovascular health matching</p>	N=138 (100 participants with bipolar disorder (BD) and 38 controls) enrolled; cognitive and neuroimaging data was obtained from 58 participants with BD and 21 controls.	<p>Of the 58 participants with BD, 33 had taken lithium and 25 had <1 year, or no exposure.</p> <p>There was no significant association between duration of lithium treatment and global cognitive function (correlation 0.165, $p=0.22$).</p> <p>There was no significant association between duration of lithium treatment and total grey matter volume.</p> <p>There was a significant association between duration of lithium treatment and white matter integrity. Regression analysis demonstrated that longer duration of lithium treatment and younger age were significantly associated with higher white matter integrity.</p> <p>There was a significant association between duration of lithium treatment and white matter hyperintensity (WMH) burden, but this relationship was not observed in regression analysis.</p> <p>Exploratory analyses of antipsychotic exposure revealed no significant differences in cognitive function and brain integrity between those with antipsychotic exposure and those without it.</p>	High

	<p>to the patient group.</p> <p><i>Outcomes:</i></p> <p>Clinical measures: General medical health was measured with the Cumulative Illness Rating Scale–Geriatric (CIRS-G) and vascular disease burden was measured with the Framingham Stroke Risk Profile (FSRP). Duration of lithium use was provided.</p> <p>Neurocognitive assessment: 21 validated individual tests were administered across multiple cognitive domains (information processing; memory, language, visuospatial ability).</p> <p>Neuroimaging: Magnetic Resonance Imaging (MRI) was used to measure regional grey and white matter brain volumes and cerebral spinal fluid.</p>			
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Risk of bias:

Case-control studies

	RISK OF BIAS (ASSESSED USING SIGN GUIDANCE FOR CASE-CONTROL STUDIES)					
	Question (clearly focussed)	Subject selection (taken from comparable populations, loss to follow-up)	Outcome assessment (reliable, blinded to exposure)	Confounding (accounted for in design and analysis)	Statistical analysis (reporting of confidence intervals)	Overall assessment
Gildengers et al. 2015						



Low risk



High risk



Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>Guidelines</i>			
NICE	Lithium cognitive	16	0
<i>Systematic Reviews</i>			
Medline	<ol style="list-style-type: none"> 1. Medline; (older adj6 adults).ti,ab; 45116 results. 2. Medline; exp AGED/; 2424114 results. 3. Medline; 1 OR 2; 2436262 results. 4. Medline; exp LITHIUM/; 20274 results. 5. Medline; (long adj1 term).ti,ab; 558391 results. 6. Medline; 4 AND 5; 976 results. 7. Medline; exp MILD COGNITIVE IMPAIRMENT/; 2838 results. 8. Medline; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 67810 results. 9. Medline; 7 OR 8; 68251 results. 10. Medline; 3 AND 6 AND 9; 1 results. 11. Medline; (((("systematic* review*") OR meta-analytic* OR metanalysis OR metaanalysis OR ("meta analysis") OR meta-synthesis OR metasynthesis OR ("meta synthesis") OR meta-regression OR metaregression OR ("meta regression") OR (synthes* adj3 literature) OR (synthes* adj3 evidence) OR ("integrative review") OR ("data synthesis") OR ("research synthesis") OR ("narrative synthesis") OR ("systematic study") OR ("systematic studies")))).ti,ab; 129358 results. 12. Medline; META-ANALYSIS AS TOPIC/; 14051 results. 13. Medline; meta-analysis.ti,ab,pt; 81760 results. 14. Medline; (((("systematic comparison*") OR ("systematic overview*") OR ("evidence based review") OR ("comprehensive review") OR ("critical review") OR ("quantitative review") OR ("structured review") OR ("realist review") OR ("realist synthesis")))).ti,ab; 23775 results. 	0	0

	<p>15. Medline; 11 OR 12 OR 13 OR 14; 170324 results.</p> <p>16. Medline; ((medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR ("included studies") OR ("inclusion studies") OR ("inclusion criteria") OR ("selection criteria") OR ("selection criteria") OR ("predetermined criteria"))).ti,ab; 183990 results.</p> <p>17. Medline; ((medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR ("included studies") OR ("inclusion studies") OR ("inclusion criteria") OR ("selection criteria") OR ("selection criteria") OR ("predetermined criteria"))).ab; 181179 results.</p> <p>18. Medline; (((("predefined criteria") OR (assess* adj3 (quality OR validity)) OR (select* adj3 (study OR studies)) OR (data adj3 extract*) OR ("extracted data") OR (data adj2 abstracted) OR (data adj3 abstraction) OR ("published intervention") OR ((study OR studies) adj2 evaluat*) OR (intervention* adj2 evaluat*) OR ("confidence interval") OR heterogeneity OR pooled OR pooling OR ("odds ratio*")) OR Jadad OR coding))).ti,ab; 955213 results.</p> <p>19. Medline; 16 OR 17 OR 18; 1077128 results.</p> <p>20. Medline; 15 AND 19; 92414 results.</p> <p>21. Medline; review.ti; 285876 results.</p> <p>22. Medline; 19 AND 21; 58277 results.</p> <p>23. Medline; ((review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*))).ti,ab; 135096 results.</p> <p>24. Medline; 15 OR 20 OR 22 OR 23; 277665 results.</p> <p>25. Medline; (letter OR editorial OR comment).pt; 1404529 results.</p> <p>26. Medline; exp ANIMALS/; 17911109 results.</p> <p>27. Medline; exp HUMANS/; 13889624 results.</p> <p>28. Medline; 26 NOT 27; 4021485 results.</p> <p>29. Medline; 25 OR 28; 5371628 results.</p>		
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	30. Medline; 24 NOT 29; 260568 results. 31. Medline; 30 [Limit to: Publication Year 2010-2015]; 131022 results. 32. Medline; 10 AND 31; 0 results.		
Embase	1. EMBASE; (older adj6 adults).ti,ab; 57613 results. 2. EMBASE; exp AGED/; 2293716 results. 3. EMBASE; 1 OR 2; 2315444 results. 4. EMBASE; exp LITHIUM/; 41803 results. 5. EMBASE; (long adj1 term).ti,ab; 725253 results. 6. EMBASE; 4 AND 5; 2653 results. 7. EMBASE; exp MILD COGNITIVE IMPAIRMENT/; 12395 results. 8. EMBASE; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 98954 results. 9. EMBASE; 7 OR 8; 100999 results. 10. EMBASE; 3 AND 6 AND 9; 13 results. 11. EMBASE; 10 [Limit to: (EBM-Evidence Based Medicine Systematic Review)]; 0 results.	0	0
PsychINFO	1. PsycInfo; (older adj6 adults).ti,ab; 33078 results. 2. PsycInfo; exp AGED/; 342 results. 3. PsycInfo; 1 OR 2; 33352 results. 4. PsycInfo; exp LITHIUM/; 5106 results. 5. PsycInfo; (long adj1 term).ti,ab; 97545 results. 6. PsycInfo; 4 AND 5; 643 results. 7. PsycInfo; exp MILD COGNITIVE IMPAIRMENT/; 3261 results. 8. PsycInfo; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 57768 results. 9. PsycInfo; 7 OR 8; 57871 results. 10. PsycInfo; 3 AND 6 AND 9; 1 results. 11. PsycInfo; ((systematic* adj1 review*) OR meta-analytic* OR metanalysis OR metaanalysis OR (meta adj1 analysis) OR meta-synthesis OR metasynthesis OR (meta adj1 synthesis) OR meta-regression OR . AND metaregression OR (meta adj1 regression) OR (synthes* adj3 literature) OR (synthes* adj3 evidence) OR (integrative adj1 review) OR (data adj1 synthesis) OR (research adj1 synthesis) OR (narrative adj1 synthesis) OR (systematic adj1 study) OR (systematic adj1 studies)).ti,ab; 37561 results.	0	0

	<p>12. PsycInfo; meta-analysis.ti,ab,pt; 16165 results.</p> <p>13. PsycInfo; ((systematic adj1 comparison*) OR (systematic adj1 overview*) OR (evidence AND based AND review) OR (comprehensive adj1 review) OR (critical adj1 review) OR (quantitative adj1 review) OR (structured adj1 review) OR (realist adj1 review) OR (realist adj1 synthesis)).ti,ab; 22506 results.</p> <p>14. PsycInfo; 11 OR 12 OR 12 OR 13; 56415 results.</p> <p>15. PsycInfo; review.pt; 115184 results.</p> <p>16. PsycInfo; (medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR (included adj1 studies) OR (inclusion adj3 studies) OR (inclusion adj1 criteria) OR (selection adj1 criteria) OR (selection adj1 criteria) OR (predetermined AND criteria)).ab; 3657118 results.</p> <p>17. PsycInfo; ((predefined adj1 criteria) OR (assess* adj3 (quality OR validity)) OR (select* adj3 (study OR studies)) OR (data adj3 extract*) OR (extracted adj1 data) OR (data adj2 abstracted) OR (data adj3 abstraction) OR (published adj1 intervention) OR ((study OR studies) adj2 evaluat*) OR (intervention* adj2 evaluat*) OR (confidence adj1 interval) OR heterogeneity OR pooled OR pooling OR (odds adj1 ratio*) OR Jadad OR coding).ab; 131648 results.</p> <p>18. PsycInfo; 15 OR 16 OR 17; 3657118 results.</p> <p>19. PsycInfo; 14 AND 18; 56087 results.</p> <p>20. PsycInfo; review.ti; 123181 results.</p> <p>21. PsycInfo; 18 AND 20; 122650 results.</p> <p>22. PsycInfo; ((review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*))).ti,ab; 52761 results.</p> <p>23. PsycInfo; 14 OR 19 OR 21 OR 22; 192440 results.</p> <p>24. PsycInfo; (letter OR editorial OR comment).pt; 156584 results.</p> <p>25. PsycInfo; exp ANIMALS/; 6782 results.</p> <p>26. PsycInfo; exp HUMANS/; 1796 results.</p> <p>27. PsycInfo; 25 NOT 26; 6469 results.</p> <p>28. PsycInfo; 24 OR 27; 162722 results.</p>		
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	29. PsycInfo; 23 NOT 28; 185404 results. 30. PsycInfo; META ANALYSIS/; 14618 results. 31. PsycInfo; 29 OR 30; 186910 results. 32. PsycInfo; 31 [Limit to: Publication Year 2010-2015]; 63092 results. 33. PsycInfo; 10 AND 32; 0 results.		
Primary Studies			
MEDLINE	1. Medline; (older adj6 adults).ti,ab; 45116 results. 2. Medline; exp AGED/; 2424114 results. 3. Medline; 1 OR 2; 2436262 results. 4. Medline; exp LITHIUM/; 20274 results. 5. Medline; (long adj1 term).ti,ab; 558391 results. 6. Medline; 4 AND 5; 976 results. 7. Medline; exp MILD COGNITIVE IMPAIRMENT/; 2838 results. 8. Medline; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 67810 results. 9. Medline; 7 OR 8; 68251 results. 10. Medline; 3 AND 6 AND 9; 1 results.	1	0
EMBASE	1. EMBASE; (older adj6 adults).ti,ab; 57613 results. 2. EMBASE; exp AGED/; 2293716 results. 3. EMBASE; 1 OR 2; 2315444 results. 4. EMBASE; exp LITHIUM/; 41803 results. 5. EMBASE; (long adj1 term).ti,ab; 725253 results. 6. EMBASE; 4 AND 5; 2653 results. 7. EMBASE; exp MILD COGNITIVE IMPAIRMENT/; 12395 results. 8. EMBASE; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 98954 results. 9. EMBASE; 7 OR 8; 100999 results. 10. EMBASE; 3 AND 6 AND 9; 13 results.	13	1
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	4. PsycInfo; exp LITHIUM/; 5106 results. 5. PsycInfo; (long adj1 term).ti,ab; 97545 results. 6. PsycInfo; 4 AND 5; 643 results. 7. PsycInfo; exp MILD COGNITIVE IMPAIRMENT/; 3261 results. 8. PsycInfo; (cognit* adj6 (impair* OR disorder* OR problem* OR dysfunction*)).ti,ab; 57768 results. 9. PsycInfo; 7 OR 8; 57871 results. 10. PsycInfo; 3 AND 6 AND 9; 1 results.																																			
CENTRAL	<table><tr><td>ID</td><td>Search</td><td>Hits</td></tr><tr><td>#1</td><td>Old* adj6 adult*</td><td>213</td></tr><tr><td>#2</td><td>MeSH descriptor: [Frail Elderly] explode all trees</td><td>534</td></tr><tr><td>#3</td><td>#1 or #2</td><td>747</td></tr><tr><td>#4</td><td>MeSH descriptor: [Lithium] explode all trees</td><td>657</td></tr><tr><td>#5</td><td>long adj1 term</td><td>274</td></tr><tr><td>#6</td><td>#4 and #5</td><td>0</td></tr><tr><td>#7</td><td>cogniti* adj6 (impair* or disorder* or problem* or dysfunction*)</td><td>128</td></tr><tr><td>#8</td><td>MeSH descriptor: [Mild Cognitive Impairment] explode all trees</td><td>154</td></tr><tr><td>#9</td><td>#7 or #8</td><td>282</td></tr><tr><td>#10</td><td>#3 and #4 and #9</td><td>0</td></tr></table>	ID	Search	Hits	#1	Old* adj6 adult*	213	#2	MeSH descriptor: [Frail Elderly] explode all trees	534	#3	#1 or #2	747	#4	MeSH descriptor: [Lithium] explode all trees	657	#5	long adj1 term	274	#6	#4 and #5	0	#7	cogniti* adj6 (impair* or disorder* or problem* or dysfunction*)	128	#8	MeSH descriptor: [Mild Cognitive Impairment] explode all trees	154	#9	#7 or #8	282	#10	#3 and #4 and #9	0	0	0
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