Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In adults with depression, what is the association between antidepressant use and suicidal behaviours?"

Clarification of question using *PRO* structure

Population: Adults with depression
Risk Factor: Antidepressant use
Outcome: Suicidal behaviours

Clinical and research implications

Evidence from one good quality systematic review and one large, well conducted, nested case-control study suggests that, whilst selective serotonin re-uptake inhibitor (SSRI)/antidepressant use was associated with reduced suicide risk in adults and older adults, it may be associated with increased risk in children and young adults. Data from the case-control analysis also indicated that, in people treated with antidepressants, periods of treatment initiation, discontinuation and dose change were all associated with increased suicide risk. Given the complexity of the issue of confounding when exploring the relationship between antidepressant use and suicide risk, further large scale studies, particularly looking at antidepressant groups other than SSRIs, may be useful to confirm and expand upon these findings.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two studies, one systematic review of observational studies,[1] and one additional large nested case-control study,[4] which reported data relevant to this evidence summary. Two further studies were identified and excluded;[2,3] one was a large registry study which examined the contribution of increased antidepressant use to an observed reduction in suicide rates at a national level and did not provide data on suicide risk associated with antidepressant use,[2] and the second study[3] was included in the systematic review.[1] The systematic review included observational studies of people with a diagnosis of major depression and assessed the risk of attempted or completed suicide in different age groups exposed to selective serotonin re-uptake inhibitors (SSRIs).[1] The retrospective nested case-control study included cases (suicide attempts) and controls derived from a population with a diagnosis of depression; the primary aim of this study was to assess suicide risk associated with discontinuation of antidepressant treatment, but data on risk associated with other factors (age group, previous depressive illness, co-morbidities, type of antidepressant, and other phases of antidepressant treatment) were also reported.[4]

Main Findings

The systematic review found that exposure to SSRIs was associated with increased risk of attempted or completed suicide in adolescents (odds ratio (OR) 1.92 (95% CI: 1.51 to 2.44)), based on data from five studies, and reduced risk of attempted or completed suicide in adults (OR 0.57 (95% CI: 0.47 to 0.70)), based on data from five studies, and older adults (≥65 years) (OR 0.46 (95% CI: 0.27 to 0.79)), based on data from five two studies.[1] Analyses from the nested case-control study indicated that, overall, after adjusting for confounding factors (depression severity, co-morbidities, and other medication use), antidepressant use was associated with a statistically significant reduction in suicide risk.[4] Amongst participants with any antidepressant use, both the paediatric population (5-18 years) and young adults (19-24 years) were at higher risk for suicide attempts than adults, after adjusting for other factors; ORs 1.75 (95% CI: 1.58 to 1.95) and 1.33 (95% CI: 1.19 to 1.50), respectively.[4] Analysis of suicide risk associated with different phases of antidepressant use, using prior but not current antidepressant use as the reference population, indicated that risk of suicide was increased during the discontinuation phase (OR 1.61 (95% CI: 1.34 to 1.92)), during titration up (OR 2.62 (95% CI: 2.13 to 3.22)) or down (OR 2.19 (95% CI: 1.67 to 2.87)), and during the initiation phase of antidepressant treatment (OR 3.42 (95% CI: 2.97 to 3.94)).[4]

Authors Conclusions

The systematic review concluded that the use of SSRIs may be associated with a reduced risk of suicide in adults with depression, but may increase suicidality in adolescents. The nested case-control study noted the difficulty, due to multiple confounding factors, in assessing links between antidepressant use and suicidality and concluded that discontinuation of antidepressants was associated with a significantly increased risk for suicide attempts, with the highest risk being associated with the treatment initiation period.

Reliability of conclusions/Strength of evidence

One good quality systematic review provided evidence to suggest that, whilst SSRI use was associated with reduced risk of attempted or completed suicide in adults and older adults, it may be associated with increased risk in adolescents.[1] It should be noted that, whilst the pooled estimates or OR for suicide risk cannot be considered reliable (primarily due to differences in the confounding factors adjusted for by individual studies), the direction of effect was consistent for all studies within population groups (towards increased risk for adolescents and towards decreased risk for adults and older adults).[1] The case-control analysis was based on a large study, which used robust analytical methods and considered the effects of potential confounders.[4] Data from this study also indicated that, in people treated with antidepressants, suicide risk was greater in younger age groups (≤24 years).[4] In people treated with antidepressants, periods of treatment initiation, discontinuation and dose change were all associated with increased suicide risk.[4] The conclusions of both studies reflect the data presented and are likely to be reliable.

What do guidelines say?

NICE Guidelines for depression (2010, CG90) make the following recommendations regarding suicide risk in adults with depression who are prescribed antidepressants;

"There is a small risk of inducing suicidal ideation in younger people starting antidepressants. Although the most recent data suggests the cut-off for this is around 25 years old, previous advice from the MHRA suggests the cut-off should be around 30. Practitioners should seek strategies to reduce risk as far as possible for people who are at increased risk of suicide, including prescribing drugs with relatively low toxicity and prescribing small amounts of drugs. They should refer people at high risk to specialist mental health services."

"A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important."

"Take into account toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. Be aware that:

- compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose
- tricyclic antidepressants (TCAs), except for lofepramine, are associated with the greatest risk in overdose." (Pp. 465)

"Always ask people with depression directly about suicidal ideation and intent. If there is a risk of self-harm or suicide:

- assess whether the person has adequate social support and is aware of sources of help
- arrange help appropriate to the level of risk
- advise the person to seek further help if the situation deteriorates."

"If a person with depression presents considerable immediate risk to themselves or others, refer them urgently to specialist mental health services."

"Advise people with depression of the potential for increased agitation, anxiety and suicidal ideation in the initial stages of treatment; actively seek out these symptoms and:

- ensure that the person knows how to seek help promptly
- review the person's treatment if they develop marked and/or prolonged agitation."

"Advise a person with depression and their family or carer to be vigilant for mood changes, negativity and hopelessness, and suicidal ideation, and to contact their practitioner if concerned. This is particularly important during high-risk periods, such as starting or changing treatment and at times of increased personal stress."

"If a person with depression is assessed to be at risk of suicide:

- take into account toxicity in overdose if an antidepressant is prescribed or the person is taking other medication; if necessary, limit the amount of drug(s) available,
- consider increasing the level of support, such as more frequent direct or telephone contacts,
- consider referral to specialist mental health services." (Pp. 120)

The evidence contained in this summary is consistent with current guidelines.

Date question received: 11/11/2103
Date searches conducted: 11/11/2013
Date answer completed: 25/11/2013

References

Systematic reviews

1) Babui, C., Esposito, E. and Cipriani, A. (2009) Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *Canadian Medical Association Journal 180* (**3**) pp. 291-297.

Randomised controlled trials

2) Valuck, R.J., Orton, H.D. and Libby, A.M. (2009) Antidepressant Discontinuation and Risk of Suicide Attempt: A Retrospective, Nested Case-Control Study. *Journal of Clinical Psychiatry 70* (**0**).

Guidelines

3) National Institute for Health and Care Excellence (2010) Depression. The NICE Guideline on The Treatment and Management of Depression in Adults. (Updated Edition) CG90. London: National Institute for Health and Care Excellence. http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Barbui et al. (2009)	Not reported (Search covered 01/1990 – 06/2008)	*Population:* People with a diagnosis of major depression, of either sex and any age. *Risk factor/Exposure:* Selective serotonin reuptake inhibitors (SSRIs). Outcome: Reported completed or attempted suicide (ICD 9 or 10 definition), did not include the following suicidal related events; preparatory acts toward imminent suicidal behaviours, suicidal ideation and self injurious behaviour. *Study design:* Observational cohort or case-control studies.	8 studies >200,000 participants	This review aimed to assess the risk of attempted or completed suicide associated with exposure to SSRIs, amongst people of different ages with depression. Three of the included studies used completed suicide as the outcome measure, three used attempted suicide and two used a combined measure of attempted or completed suicide. Five studies provided separate data on adolescents and two studies provided separate data on elderly participants (≥65 years). Two of the eight included studies did not included any adjustment for confounders or matching criteria; the remaining studies were described as including adjustment for >3 confounders, but no further details were reported. Exposure to SSRIs in adolescents was associated with increased risk of attempted or completed suicide OR 1.92 (95% CI: 1.51	The article reported a clear research objective and appropriate inclusion criteria were defined. Searches included two bibliographic databases and reference screening and no language restrictions were applied, minimising the likelihood of relevant articles being missed. Review processes (study selection, data extraction and quality assessment) were preformed

				to 2.44), based on data from five studies (2 reported attempted suicide as the outcome measure, 1 reported completed suicide and 2 used a combined outcome measure). Exposure to SSRIs in adults was associated with decreased risk of attempted or completed suicide OR 0.57 (95% CI: 0.47 to 0.70), based on data from five studies (3 reported attempted suicide as the outcome measure, 1 reported completed suicide and one used a combined outcome measure). Exposure to SSRIs in older adults (≥65 years) was associated with decreased risk of attempted or completed suicide OR 0.46 (95% CI: 0.27 to 0.79), based on data from five two studies (1 reported attempted suicide as the outcome measure and 1 reported completed suicide).	independently by two reviewers, reducing the potential for error and/or bias. The methodological quality of included studies was assessed using a published tool, suitable for observational studies. A simple random effects model was used to derive an overall pooled OR for suicide. Given the clear clinical and statistical heterogeneity between studies, pooled effect measures are highly questionable. The individual; included studies either

					reported un-adjusted ORs, or reported the results of risk modelling which attempted to account for potential confounders (number and specific confounders varied between studies), i.e. the ORs were derived by different methods in different populations. Combining studies reporting different outcomes (attempted versus completed suicide) may also be problematic.

Randomised controlled trials

Author	Inclusion criteria	Number of	Summary of results	Risk of bias

(year)		**participants**		
Valuck et al. (2009)	*Population*: Patients of any age, with new episodes of depression (defined using the specification of the National Committee for Quality Assurance's Healthcare Effectiveness Data Information Set and ICD-9 criteria); a period of 120 days before diagnosis during which no other depression related diagnoses appeared in the claims history; and a period of 90 days before diagnosis during which no other antidepressant medication claims appeared in the history. *Risk factor/exposure:* Antidepressant use. *Outcome:* Suicide attempt; identified from insurance claims.	n= 52,271	This study aimed to assess the effects of antidepressant discontinuation on the risk of suicide attempts. The study used a retrospective nested case control design, derived from a cohort of 2.4 million patients with depression, in which observation periods were taken backwards from the suicide attempt, or for matched controls, were taken from the case's suicide attempt date. Cases and controls were matched by age (±1 year), gender and geographic region. The final sample included 41,815 controls with no missing drug exposure data and 10,456 cases with no missing drug exposure data. Study participants were aged between 5 and 89 years. A case-control analysis was performed; the dependent (outcome) variable was case (suicide attempt) versus control, and the independent (predictor) variables were the following: any (versus no) antidepressant drug exposure; among antidepressant users, current and past short- and long-term use; and separately (conditional logistic regression), the phase of antidepressant treatment (discontinuation, titration up or down, initiation, early or late maintenance, or prior therapy). After adjustment for confounding factors (depression severity, co-morbidities, and other medication use), the risk of a suicide attempt was 0.62 for those receiving any antidepressant(s) compared to those receiving none ($P < .001$).	This study was not an RCT and its methodological quality cannot be assessed using the Cochrane risk of bias tool.

			Cases were significantly more likely than controls to have had a prior depressive episode (OR 1.18 (95% CI: 1.12 to 1.24)), an inpatient stay associated with depression (OR 2.13 (95% CI: 1.91 to 2.38)) and psychotherapy (OR 1.29 (95% CI: 1.17 to 1.42)). Cases were also significantly more likely to have diagnoses of bipolar disorder (OR 1.62 (95% CI: 1.40 to 1.88)), schizophrenia (OR 1.40 (95% CI: 1.05 to 1.87)), anxiety (OR 1.20 (95% CI: 1.10 to 1.31)), and substance use disorder (OR 2.56 (95% CI: 2.33 to 2.81)), and to have been prescribed antiepileptic medications, atypical antipsychotics, or anxiolytics. Cases were more likely than controls to have had any antidepressant use during the observation period (71% versus 59%, $P < .001$). For those 32,070 cases and controls who had any antidepressant use during the observation period, cases were more likely to have had multiple antidepressants (54% versus 33%, $P < .001$). For those with any antidepressant use, cases were also more likely than controls to have received SNRI (OR 1.54 (95% CI: 1.17 to 2.03)). Amongst participants with any antidepressant use, both the paediatric population (5-18 years) and young adults (19-24 years) were at higher risk than adults, after adjusting for other factors; ORs 1.75 (95% CI: 1.58 to 1.95) and 1.33 (95% CI: 1.19 to 1.50), respectively. Analysis of the risk associated with different phases of	

			antidepressant use was conducted in participants with any antidepressant use during the observation period, excluding those on multiple antidepressants; the reference group in the logistic regression analysis comprised participants previously, but not currently on antidepressants. The risk of suicide was increased during the discontinuation phase, compared to prior use (OR 1.61 (95% CI: 1.34 to 1.92)). Increased risk was also apparent during titration up (OR 2.62 (95% CI: 2.13 to 3.22)) or down (OR 2.19 (95% CI: 1.67 to 2.87)) and during the initiation phase of antidepressant treatment (OR 3.42 (95% CI: 2.97 to 3.94)).	

Risk of Bias

Systematic reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Barbui et al. (2009)	☺	☺	☺	☺	☹

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Valuck et al. (2009)	This study was not an RCT and its methodological quality cannot be assessed using the Cochrane risk of bias tool.					

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Antidepressants AND suicide	64	1
DARE	(suicid*) IN DARE 182 Delete 2 MeSH DESCRIPTOR Suicide, Attempted EXPLODE ALL TREES 38 Delete 3 MeSH DESCRIPTOR Suicide EXPLODE ALL TREES 99 Delete 4 MeSH DESCRIPTOR Self-Injurious Behavior EXPLODE ALL TREES 119 Delete 5 #1 OR #2 OR #3 OR #4 240 Delete 6 (antidepress* OR anti-depress*) IN DARE 746 Delete 7 MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES 621 Delete 8 #6 OR #7 944 Delete 9 #5 AND #8	61	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Depressive Disorder] explode all trees 6913 #2 Enter terms for search depressiondepression 29978 #3 Enter terms for search #1 and #2#1 and #2 5665 #4 MeSH descriptor: [Suicide] explode all trees 532 #5 Enter terms for search "suicide ideation""suicide ideation" 62 #6 Enter terms for search #4 or #5#4 or #5 563 #7 Enter terms for search #3 and #6#3 and #6 141 #8 MeSH descriptor: [Antidepressive Agents] explode all trees 4591 #9Enter terms for searcanti-drepressants or antidepressants7264	68	

	#10Enter terms for searc#8 or #99347 #11Enter terms for searc#7 and #10 71 Central only 68		
PsycINFO	1. PsycINFO; exp MAJOR DEPRESSION/; 88755 results. 2. PsycINFO; depression.ti,ab; 162783 results. 3. PsycINFO; "depressive disorder*".ti,ab; 19020 results. 4. PsycINFO; 1 OR 2 OR 3; 179895 results. 5. PsycINFO; SUICIDAL IDEATION/ OR ATTEMPTED SUICIDE/ OR SUICIDE [+NT]/; 26652 results. 6. PsycINFO; "suicide ideation".ti,ab; 1055 results. 7. PsycINFO; 5 OR 6; 26835 results. 8. PsycINFO; (suicide adj3 ideation).ti,ab; 1669 results. 9. PsycINFO; 7 OR 8; 26922 results. 10. PsycINFO; 4 AND 9; 7153 results. 11. PsycINFO; exp ANTIDEPRESSANT DRUGS/; 31132 results. 12. PsycINFO; antidepressant*.ti,ab; 28256 results. 13. PsycINFO; 11 OR 12; 43284 results. 14. PsycINFO; 10 AND 13; 762 results. 15. PsycINFO; CLINICAL TRIALS/; 7121 results. 16. PsycINFO; random*.ti,ab; 124078 results. 17. PsycINFO; groups.ti,ab; 354765 results. 18. PsycINFO; (double adj3 blind).ti,ab; 17387 results. 19. PsycINFO; (single adj3 blind).ti,ab; 1342 results. 20. PsycINFO; EXPERIMENTAL DESIGN/; 8846 results. 21. PsycINFO; controlled.ti,ab; 77265 results. 22. PsycINFO; (clinical adj3 study).ti,ab; 7605 results. 23. PsycINFO; trial.ti,ab; 65318 results. 24. PsycINFO; "treatment outcome clinical trial".md; 25260 results. 25. PsycINFO; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 548085 results. 26. PsycINFO; 14 AND 25; 247 results.	247	
Embase	15. EMBASE; exp MAJOR DEPRESSION/; 34620 results.	56	

	16. EMBASE; depression.ti,ab; 267598 results. 17. EMBASE; "depressive disorder*".ti,ab; 26939 results. 18. EMBASE; 15 OR 16 OR 17; 284785 results. 19. EMBASE; SUICIDAL IDEATION/ OR ATTEMPTED SUICIDE/ OR SUICIDE [+NT]/; 60173 results. 20. EMBASE; "suicide ideation".ti,ab; 982 results. 21. EMBASE; 19 OR 20; 60304 results. 22. EMBASE; (suicide adj3 ideation).ti,ab; 1648 results. 23. EMBASE; 21 OR 22; 60358 results. 24. EMBASE; 18 AND 23; 12808 results. 25. EMBASE; exp ANTIDEPRESSANT DRUGS/; 0 results. 26. EMBASE; antidepressant*.ti,ab; 60795 results. 27. EMBASE; 25 OR 26; 60795 results. 28. EMBASE; 24 AND 27; 1937 results. 29. EMBASE; exp ANTIDEPRESSANT AGENT/; 298313 results. 30. EMBASE; 26 OR 29; 306181 results. 31. EMBASE; 24 AND 30; 4090 results. 32. EMBASE; random*.ti,ab; 857491 results. 33. EMBASE; factorial*.ti,ab; 22008 results. 34. EMBASE; (crossover* OR cross-over*).ti,ab; 68527 results. 35. EMBASE; placebo*.ti,ab; 197231 results. 36. EMBASE; (doubl* ADJ blind*).ti,ab; 141708 results. 37. EMBASE; (singl* ADJ blind*).ti,ab; 14079 results. 38. EMBASE; assign*.ti,ab; 234352 results. 39. EMBASE; allocat*.ti,ab; 80659 results. 40. EMBASE; volunteer*.ti,ab; 174833 results. 41. EMBASE; CROSSOVER PROCEDURE/; 38971 results. 42. EMBASE; DOUBLE BLIND PROCEDURE/; 118651 results. 43. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 360008 results. 44. EMBASE; SINGLE BLIND PROCEDURE/; 18506 results. 45. EMBASE; 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44; 1385889		

	results. 46. EMBASE; 31 AND 45; 760 results. 47. EMBASE; 46 [Limit to: Exclude MEDLINE Journals]; 56 results.		
Medline	15. MEDLINE; exp MAJOR DEPRESSION/; 0 results. 16. MEDLINE; depression.ti,ab; 220452 results. 17. MEDLINE; "depressive disorder*".ti,ab; 21320 results. 18. MEDLINE; 15 OR 16 OR 17; 227834 results. 19. MEDLINE; SUICIDAL IDEATION/ OR ATTEMPTED SUICIDE/ OR SUICIDE [+NT]/; 43718 results. 20. MEDLINE; "suicide ideation".ti,ab; 862 results. 21. MEDLINE; 19 OR 20; 43892 results. 22. MEDLINE; (suicide adj3 ideation).ti,ab; 1473 results. 23. MEDLINE; 21 OR 22; 43987 results. 24. MEDLINE; 18 AND 23; 7357 results. 25. MEDLINE; exp ANTIDEPRESSANT DRUGS/; 122927 results. 26. MEDLINE; antidepressant*.ti,ab; 46631 results. 27. MEDLINE; 25 OR 26; 138701 results. 28. MEDLINE; 24 AND 27; 1282 results. 29. MEDLINE; exp DEPRESSIVE DISORDER/; 82539 results. 30. MEDLINE; 18 OR 29; 251266 results. 31. MEDLINE; 23 AND 30; 9284 results. 32. MEDLINE; 27 AND 31; 1691 results. 33. MEDLINE; "randomized controlled trial".pt; 390285 results. 34. MEDLINE; "controlled clinical trial".pt; 89931 results. 35. MEDLINE; randomized.ab; 305789 results. 36. MEDLINE; placebo.ab; 163900 results. 37. MEDLINE; "drug therapy".fs; 1767235 results. 38. MEDLINE; randomly.ab; 216386 results. 39. MEDLINE; trial.ab; 321828 results. 40. MEDLINE; groups.ab; 1374482 results. 41. MEDLINE; 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40; 3428799 results. 42. MEDLINE; 32 AND 41; 1216 results.	1216	
Summary	**NA**	**NA**	

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