

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

How strong is the evidence that people with clinical depression have lower-than-normal levels of Serotonin (or other neurotransmitters)?

Clarification of question using the *PRO* structure

Patients: People with clinical depression
Association: Lower-than-normal levels of Serotonin (or other neurotransmitters)
Outcome: Clinical depression

Clinical and research implications

A meta-analysis of molecular imaging studies demonstrated significant reductions in serotonin reuptake sites (5-HTT) in the midbrain and amygdala in depressed patients. However, due to the unknown reliability of the studies included in the meta-analysis, no definite clinical implications should be made from the current evidence. In terms of research implications, the authors stated that their results “may encourage imaging studies of the specific role of serotonergic pathology in the striatum in the context of geriatric depression.” They also stated that larger, more adequately powered studies are needed. The results from this meta-analysis also demonstrated that age matching in molecular imaging studies is critical, as even small differences in mean age between groups effect the validity of results.

What does the evidence say?

Number of included studies/reviews (number of participants)

One meta-analysis met the inclusion criteria for this BEST summary (Gryglewski et al. 2014).

Main findings

The aim of the meta-analysis was to evaluate serotonin transporter (5-HTT) changes reported in molecular imaging studies of people with major depressive disorder (MDD). Relevant studies were searched in November 2013. This paper included data from 18 studies comprising of 364 depressed patients (who were not taking antidepressant medication at the time of the study) and 372 healthy controls. Meta-analysis revealed significant reductions of 5-HTT in some parts of the brain in MDD patients compared to healthy controls, including the midbrain (Hedges’ $g = -0.49$, [95% CI -0.84 to -0.14]), the amygdala (Hedges’ $g = -0.50$, [95% CI -0.78 to -0.22]), and the putamen or its subparts (Hedges’ $g = -0.56$, [95% CI -1.05 to -0.08]). No significant differences in 5-HTT were observed in the brainstem, thalamus, striatum, or cortical regions, although 5-HTT reductions were observed in the brainstem, thalamus and striatum. Cumulative meta-analysis of studies conducted in the brainstem and amygdala demonstrated greater reductions in more severely depressed patients. The authors also found greater reductions in 5-HTT with increasing age ($p < 0.01$).

Authors’ conclusions

The authors concluded that “molecular imaging findings indeed reveal widespread reductions of ~ 10% in 5-HTT availability in MDD, which may predict altered spatial-temporal dynamics of serotonergic neurotransmission.”

Reliability of conclusions/Strength of evidence

While this study included meta-analyses and the methodology appears robust and appropriate, it is unclear if the authors followed a systematic review protocol. It is not stated how many reviewers were involved in the process of finding and extracting data from the papers, and if the included studies were quality assessed. Without knowing the quality of the studies included in the meta-analyses, the reliability of the results is uncertain.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on the strength of the evidence suggesting people with clinical depression have lower-than-normal levels of Serotonin.

Date question received: 06/07/2015

Date searches conducted: 10/07/2015

Date answer completed: 23/07/2015

References

Systematic reviews

Gryglewski, G., Lanzenberger, R., Kranz, G. S., & Cumming, P. (2014). Meta-analysis of molecular imaging of serotonin transporters in major depression. *Journal of Cerebral Blood Flow & Metabolism*, 34(7), 1096-1103.

Results



Systematic reviews


Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Gryglewski et al. (2015)	11/2013	<p><i>Participants:</i> Patient group: Patients with major depressive disorder, not currently taking antidepressant medication. Control group: Healthy controls. Controls were age-matched in 11 of 18 studies, and gender-matched in 13 studies.</p> <p><i>Measurement:</i> Single-photon emission computed tomography (SPECT; 9 studies) or positron emission tomography (PET; 9 studies).</p> <p><i>Outcome:</i> Primary outcome: Levels of the Serotonin transporter, 5-HTT, in seven brain regions: (i) Brainstem; (ii) Midbrain; (iii) Thalamus; (iv) Striatum/Putamen; (v) Amygdala; (vi) Frontal Cortex; (vii) Cingulate Cortex. Secondary outcomes: (i) Demographic data including age and gender; (ii) depression severity scores; (iii) types of tracer (i.e. PET or</p>	18 (736 participants - 364 depressed participants & 372 controls)	The authors stated that there was no significant findings regarding 5-HTT in the brainstem and MDD (summary effect: -0.22 [95%CI: -0.58 to 0.13, with low heterogeneity [$I^2=10\%$]) (4 studies with 91 patients and 63 controls). There was also no significant overall effect in the thalamus (summary effect: -0.24 [95%CI: -0.72 to 0.23, with high heterogeneity [$I^2=82\%$]) (13 studies with 275 patients and 310 controls), the striatum (summary effect: -0.32 [95%CI: -0.79 to 0.15, with considerable heterogeneity [$I^2=72\%$]) (10 studies with 204 patients and 214 controls), the frontal cortex (summary effect: -0.09 [95%CI: -0.82 to 0.65, with considerable heterogeneity [$I^2=65\%$]) (4 studies with 47 patients and 58 controls), or the cingulate cortex (summary effect: -0.03 [95%CI: -0.65 to 0.60, with considerable heterogeneity [$I^2=68\%$]) (7 studies with 127 patients and 166 controls).	Unclear


		<p>SPECT; (iv) psychiatric medication history.</p> <p><i>Study design:</i> Meta-analysis of case-control studies.</p>		<p>In the midbrain, the results showed lower 5-HTT binding in MDD patients (summary effect: -0.49 [95%CI: -0.84 to -0.14]), although there was considerable heterogeneity between the studies ($I^2=68.7\%$) (15 studies with 313 patients and 321 controls). When only studies investigating the putamen or its subparts were included in the analysis, a reduction of 5-HTT was observed with MDD (summary effect: -0.56 [95%CI: -1.05 to -0.08], $I^2=57\%$). There was also significant reduction of 5-HTT in the amygdala with MDD (summary effect: -0.50 [95%CI: -0.78 to -0.22], with no heterogeneity [$I^2=0\%$]) (5 studies with 96 patients and 128 controls).</p>	
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
Risk of bias:

Systematic reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Study 1					

 Low risk

 High risk

 Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>Guidelines</i>			
NICE	serotonin depression	46	0
<i>Systematic Reviews</i>			
MEDLINE	13. Medline; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 0 results. 14. Medline; "clinical depression".ti,ab; 1680 results. 15. Medline; "clinically depress*".ti,ab; 607 results. 16. Medline; depress*.ti,ab; 332242 results. 17. Medline; (clinical* adj2 depress*).ti,ab; 7600 results. 18. Medline; 13 OR 14 OR 15 OR 16 OR 17; 332242 results. 19. Medline; exp SEROTONIN/; 63250 results. 20. Medline; NEUROTRANSMITTER/; 0 results. 21. Medline; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 264833 results. 22. Medline; (lower adj3 level* AND serotonin).ti,ab; 731 results. 23. Medline; 19 OR 20 OR 21 OR 22; 323810 results. 24. Medline; 18 AND 23; 11148 results. 25. Medline; DEPRESSION/; 80545 results. 26. Medline; DEPRESSIVE DISORDER, MAJOR/; 20165 results. 27. Medline; 18 OR 25 OR 26; 355507 results. 28. Medline; DOPAMINE/; 62627 results. 29. Medline; NOREPINEPHRINE/; 81148 results. 30. Medline; HISTAMINE/; 33915 results. 31. Medline; EPINEPHRINE/; 50188 results. 32. Medline; ACETYLCHOLINE/; 46118 results. 33. Medline; 23 OR 28 OR 29 OR 30 OR 31 OR 32; 524444 results.	102	1

	<p>34. Medline; 27 AND 33; 18703 results.</p> <p>35. Medline; 34 [Limit to: Publication Year 2010-2015]; 2804 results.</p> <p>36. Medline; (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 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; 128143 results.</p> <p>37. Medline; META-ANALYSIS AS TOPIC/; 14045 results.</p> <p>38. Medline; meta-analysis.ti,ab,pt; 81638 results.</p> <p>39. Medline; (systematic adj1 comparison* OR systematic adj1 overview* OR "evidence based 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; 28219 results.</p> <p>40. Medline; 36 OR 37 OR 38 OR 39; 173157 results.</p> <p>41. Medline; review.ti,ab,pt; 2386384 results.</p> <p>42. Medline; (medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo 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 "predetermined criteria").ti,ab; 185453 results.</p> <p>43. Medline; (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).ti,ab; 950822 results.</p> <p>44. Medline; 41 OR 42 OR 43; 3273838 results.</p> <p>45. Medline; 40 AND 44; 139483 results.</p> <p>46. Medline; review.ti; 285620 results.</p> <p>47. Medline; 44 AND 46; 285620 results.</p> <p>48. Medline; (review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*)).ti,ab; 134956 results.</p> <p>49. Medline; 40 OR 45 OR 47 OR 48; 477658 results.</p> <p>50. Medline; (letter OR editorial OR comment).pt; 1404081 results.</p>		
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	<p>51. Medline; exp ANIMALS/; 17905365 results.</p> <p>52. Medline; exp HUMANS/; 13884983 results.</p> <p>53. Medline; 51 not 52; 4020382 results.</p> <p>54. Medline; 50 OR 53; 5370109 results.</p> <p>55. Medline; 49 not 54; 446600 results.</p> <p>56. Medline; 35 AND 55 [Limit to: Publication Year 2010-2015]; 102 results.</p>		
EMBASE	<p>1. EMBASE; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 41416 results.</p> <p>2. EMBASE; "clinical depression".ti,ab; 2269 results.</p> <p>3. EMBASE; "clinically depress*".ti,ab; 777 results.</p> <p>4. EMBASE; depress*.ti,ab; 416623 results.</p> <p>5. EMBASE; (clinical* adj3 depress*).ti,ab; 10249 results.</p> <p>6. EMBASE; 1 OR 2 OR 3 OR 4 OR 5; 424771 results.</p> <p>7. EMBASE; exp SEROTONIN/; 80913 results.</p> <p>8. EMBASE; NEUROTRANSMITTER/; 29266 results.</p> <p>9. EMBASE; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 307783 results.</p> <p>10. EMBASE; (lower adj3 level* AND serotonin).ti,ab; 857 results.</p> <p>11. EMBASE; 7 OR 8 OR 9 OR 10; 408120 results.</p> <p>12. EMBASE; 6 AND 11; 17686 results.</p> <p>13. EMBASE; 12 [Limit to: Publication Year 2010-2015]; 6272 results.</p> <p>14. EMBASE; 13 [Limit to: (EBM-Evidence Based Medicine Meta Analysis or Systematic Review) and Publication Year 2010-2015]; 96 results.</p> <p>15. EMBASE; exp META ANALYSIS/; 95961 results.</p> <p>16. EMBASE; (meta ADJ analy* OR metaanalys*).tw; 102832 results.</p> <p>17. EMBASE; (systematic ADJ review*1 OR overview*1).tw; 210370 results.</p> <p>18. EMBASE; 15 OR 16 OR 17; 311409 results.</p> <p>18. EMBASE; 15 OR 16 OR 17; 311409 results.</p> <p>19. EMBASE; cancerlit.ab; 665 results.</p> <p>20. EMBASE; cochrane.ab; 45712 results.</p>	214	0

	<ol style="list-style-type: none">21. EMBASE; embase.ab; 45005 results.22. EMBASE; (psychlit OR psychlit).ab; 955 results.23. EMBASE; (psychinfo OR psycinfo).ab; 10776 results.24. EMBASE; (cinahl OR cinhal).ab; 14004 results.25. EMBASE; "science citation index".ab; 2437 results.26. EMBASE; bids.ab; 476 results.27. EMBASE; 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26; 72526 results.28. EMBASE; "reference lists".ab; 11329 results.29. EMBASE; bibliograph*.ab; 15394 results.30. EMBASE; hand-search*.ab; 5264 results.31. EMBASE; "manual search*".ab; 3166 results.32. EMBASE; "relevant journals".ab; 927 results.33. EMBASE; 28 OR 29 OR 30 OR 31 OR 32; 32413 results.34. EMBASE; "data extraction".ab; 13630 results.35. EMBASE; "selection criteria".ab; 21981 results.36. EMBASE; 34 OR 35; 34302 results.37. EMBASE; review.pt; 2058112 results.38. EMBASE; 36 AND 37; 17185 results.39. EMBASE; letter.pt; 890765 results.40. EMBASE; editorial.pt; 480078 results.41. EMBASE; ANIMAL/; 1669028 results.42. EMBASE; HUMAN/; 15957438 results.43. EMBASE; 41 AND 42; 415033 results.44. EMBASE; 41 NOT 43; 1253995 results.45. EMBASE; 39 OR 40 OR 44; 2609825 results.46. EMBASE; 18 OR 27 OR 33 OR 38; 347956 results.47. EMBASE; 46 NOT 45; 336300 results.48. EMBASE; 13 AND 47 [Limit to: Publication Year 2010-2015]; 214 results.		
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<p>PsycINFO</p>	<p>13. PsycInfo; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 94652 results.</p> <p>14. PsycInfo; "clinical depression".ti,ab; 1747 results.</p> <p>15. PsycInfo; "clinically depress*".ti,ab; 799 results.</p> <p>16. PsycInfo; depress*.ti,ab; 229504 results.</p> <p>17. PsycInfo; (clinical* adj2 depress*).ti,ab; 7263 results.</p> <p>18. PsycInfo; 13 OR 14 OR 15 OR 16 OR 17; 233087 results.</p> <p>19. PsycInfo; exp SEROTONIN/; 14297 results.</p> <p>20. PsycInfo; NEUROTRANSMITTER/; 299 results.</p> <p>21. PsycInfo; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 27955 results.</p> <p>22. PsycInfo; (lower adj3 level* AND serotonin).ti,ab; 351 results.</p> <p>23. PsycInfo; 19 OR 20 OR 21 OR 22; 41275 results.</p> <p>24. PsycInfo; 18 AND 23; 6533 results.</p> <p>25. PsycInfo; 24; 6533 results.</p> <p>26. PsycInfo; 25 [Limit to: Publication Year 2010-2015]; 2118 results.</p> <p>27. PsycInfo; (systematic adj1 review OR meta-analytic* OR metaanalysis OR metaanalysis OR meta adj1 analysis OR meta-synthesis OR metasynthesis OR meta adj1 synthesis OR meta-regression OR 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; 35283 results.</p> <p>28. PsycInfo; meta-analysis.ti,ab,pt; 16118 results.</p> <p>29. PsycInfo; (systematic adj1 comparison* OR systematic adj1 overview* OR "evidence based 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; 12294 results.</p> <p>30. PsycInfo; 27 OR 2 OR 28 OR 29; 46419 results.</p> <p>31. PsycInfo; review.ti,ab,pt; 310557 results.</p> <p>32. PsycInfo; (medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo 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</p>	<p>85</p>	<p>0</p>
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	<p>internet adj3 search* OR included adj1 studies OR inclusion adj3 studies OR inclusion adj1 criteria OR selection adj1 criteria OR "predetermined criteria").ti,ab; 3653190 results.</p> <p>33. 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).ti,ab; 135102 results.</p> <p>34. PsycInfo; 31 OR 32 OR 33; 3654628 results.</p> <p>35. PsycInfo; 30 AND 34; 46190 results.</p> <p>36. PsycInfo; review.ti; 122999 results.</p> <p>37. PsycInfo; 34 AND 36; 122999 results.</p> <p>38. PsycInfo; (review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*)).ti,ab; 52677 results.</p> <p>39. PsycInfo; 30 OR 35 OR 37 OR 38; 186943 results.</p> <p>40. PsycInfo; (letter OR editorial OR comment).pt; 156316 results.</p> <p>41. PsycInfo; exp ANIMALS/; 6773 results.</p> <p>42. PsycInfo; exp HUMANS/; 1795 results.</p> <p>43. PsycInfo; 41 not 42; 6460 results.</p> <p>44. PsycInfo; 40 OR 43; 162445 results.</p> <p>45. PsycInfo; 39 not 44; 180392 results.</p> <p>46. PsycInfo; META ANALYSIS/; 14573 results.</p> <p>47. PsycInfo; 45 OR 46; 182232 results.</p> <p>48. PsycInfo; 26 AND 47 [Limit to: Publication Year 2010-2015]; 85 results.</p>		
<i>Primary Studies</i>			
MEDLINE	<p>13. Medline; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 0 results.</p> <p>14. Medline; "clinical depression".ti,ab; 1680 results.</p> <p>15. Medline; "clinically depress*".ti,ab; 607 results.</p> <p>16. Medline; depress*.ti,ab; 332242 results.</p>	378	0

	<p>17. Medline; (clinical* adj2 depress*).ti,ab; 7600 results.</p> <p>18. Medline; 13 OR 14 OR 15 OR 16 OR 17; 332242 results.</p> <p>19. Medline; exp SEROTONIN/; 63250 results.</p> <p>20. Medline; NEUROTRANSMITTER/; 0 results.</p> <p>21. Medline; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 264833 results.</p> <p>22. Medline; (lower adj3 level* AND serotonin).ti,ab; 731 results.</p> <p>23. Medline; 19 OR 20 OR 21 OR 22; 323810 results.</p> <p>24. Medline; 18 AND 23; 11148 results.</p> <p>25. Medline; DEPRESSION/; 80545 results.</p> <p>26. Medline; DEPRESSIVE DISORDER, MAJOR/; 20165 results.</p> <p>27. Medline; 18 OR 25 OR 26; 355507 results.</p> <p>28. Medline; DOPAMINE/; 62627 results.</p> <p>29. Medline; NOREPINEPHRINE/; 81148 results.</p> <p>30. Medline; HISTAMINE/; 33915 results.</p> <p>31. Medline; EPINEPHRINE/; 50188 results.</p> <p>32. Medline; ACETYLCHOLINE/; 46118 results.</p> <p>33. Medline; 23 OR 28 OR 29 OR 30 OR 31 OR 32; 524444 results.</p> <p>34. Medline; 27 AND 33; 18703 results.</p> <p>35. Medline; 34 [Limit to: Publication Year 2010-2015]; 2804 results.</p> <p>36. Medline; exp COHORT STUDIES/; 1427309 results.</p> <p>37. Medline; cohort*.af; 381998 results.</p> <p>38. Medline; "controlled clinical trial".pt; 89085 results.</p> <p>39. Medline; EPIDEMIOLOGIC METHODS/; 29676 results.</p> <p>40. Medline; exp CASE-CONTROL STUDIES/; 714196 results.</p> <p>41. Medline; (case* AND control*).af; 638028 results.</p> <p>42. Medline; 36 OR 37 OR 38 OR 39 OR 40 OR 41; 2158030 results.</p> <p>43. Medline; 35 AND 42 [Limit to: Publication Year 2010-2015]; 378 results.</p>		
EMBASE	<p>1. EMBASE; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 41416 results.</p> <p>2. EMBASE; "clinical depression".ti,ab; 2269 results.</p> <p>3. EMBASE; "clinically depress*".ti,ab; 777 results.</p>	763	0

	<p>4. EMBASE; depress*.ti,ab; 416623 results.</p> <p>5. EMBASE; (clinical* adj3 depress*).ti,ab; 10249 results.</p> <p>6. EMBASE; 1 OR 2 OR 3 OR 4 OR 5; 424771 results.</p> <p>7. EMBASE; exp SEROTONIN/; 80913 results.</p> <p>8. EMBASE; NEUROTRANSMITTER/; 29266 results.</p> <p>9. EMBASE; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 307783 results.</p> <p>10. EMBASE; (lower adj3 level* AND serotonin).ti,ab; 857 results.</p> <p>11. EMBASE; 7 OR 8 OR 9 OR 10; 408120 results.</p> <p>12. EMBASE; 6 AND 11; 17686 results.</p> <p>13. EMBASE; 12 [Limit to: Publication Year 2010-2015]; 6272 results.</p> <p>14. EMBASE; exp COHORT ANALYSIS/; 208022 results.</p> <p>15. EMBASE; exp LONGITUDINAL STUDY/; 79345 results.</p> <p>16. EMBASE; exp PROSPECTIVE STUDY/; 298060 results.</p> <p>17. EMBASE; exp FOLLOW UP/; 933140 results.</p> <p>18. EMBASE; cohort*.tw; 485577 results.</p> <p>19. EMBASE; exp CASE CONTROL STUDY/; 103149 results.</p> <p>20. EMBASE; (case* AND control*).tw; 468553 results.</p> <p>21. EMBASE; 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 2007072 results.</p> <p>22. EMBASE; 13 AND 21 [Limit to: Publication Year 2010-2015]; 763 results.</p>		
PsycINFO	<p>24. PsycInfo; MAJOR DEPRESSION/ OR MAJOR DEPRESSIVE DISORDER/ OR MAJOR DEPRESSIVE EPISODE/; 94652 results.</p> <p>25. PsycInfo; "clinical depression".ti,ab; 1747 results.</p> <p>26. PsycInfo; "clinically depress*".ti,ab; 799 results.</p> <p>27. PsycInfo; depress*.ti,ab; 229504 results.</p> <p>28. PsycInfo; (clinical* adj2 depress*).ti,ab; 7263 results.</p> <p>29. PsycInfo; 24 OR 25 OR 26 OR 27 OR 28; 233087 results.</p> <p>30. PsycInfo; exp SEROTONIN/; 14297 results.</p> <p>31. PsycInfo; NEUROTRANSMITTER/; 299 results.</p> <p>32. PsycInfo; (serotonin adj3 decrease* OR deplet* OR "low level*").ti,ab; 27955 results.</p> <p>33. PsycInfo; (lower adj3 level* AND serotonin).ti,ab; 351 results.</p>	470	0

	<p>34. PsycInfo; 30 OR 31 OR 32 OR 33; 41275 results.</p> <p>35. PsycInfo; 29 AND 34; 6533 results.</p> <p>36. PsycInfo; 35; 6533 results.</p> <p>37. PsycInfo; 36 [Limit to: Publication Year 2010-2015]; 2118 results.</p> <p>38. PsycInfo; (case* adj5 control* OR case adj3 comparison* OR case-comparison OR control AND group* NOT "literature review").ti,ab; 130913 results.</p> <p>39. PsycInfo; (cohort OR longitudinal OR prospective OR retrospective).ti,ab; 158674 results.</p> <p>40. PsycInfo; COHORT ANALYSIS/; 1163 results.</p> <p>41. PsycInfo; epidemiologic.ti,ab; 7530 results.</p> <p>42. PsycInfo; ("cross section*" OR "prevalence study").ti,ab; 49702 results.</p> <p>43. PsycInfo; 38 OR 39 OR 40 OR 41 OR 42; 322845 results.</p> <p>44. PsycInfo; 37 AND 43 [Limit to: Publication Year 2010-2015]; 470 results.</p>		
CENTRAL	<p>#1 MeSH descriptor: [Depressive Disorder, Major] explode all trees 2508</p> <p>#2 "clinical depress*" 266</p> <p>#3 "clinically depress*" 110</p> <p>#4 "major depress*" 7441</p> <p>#5 clinical* near/3 depress* 4229</p> <p>#6 #1 or #2 or #3 or #4 or #5 10568</p> <p>#7 MeSH descriptor: [Serotonin] explode all trees 864</p> <p>#8 MeSH descriptor: [Dopamine] explode all trees 1031</p> <p>#9 MeSH descriptor: [Norepinephrine] explode all trees 2396</p> <p>#10 MeSH descriptor: [Epinephrine] explode all trees 4232</p> <p>#11 MeSH descriptor: [Histamine] explode all trees 1062</p> <p>#12 MeSH descriptor: [Acetylcholine] explode all trees 422</p> <p>#13 MeSH descriptor: [Neurotransmitter Agents] explode all trees 19765</p> <p>#14 serotonin near/3 decrease* or deplet* or "low level*" 7711</p> <p>#15 lower adj3 level* and serotonin 80</p> <p>#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 32883</p> <p>#17 #6 and #16 1371</p> <p>#18 2010 or 2011 or 2012 or 2013 or 2014 or 2015 329905</p> <p>#19 #17 and #18 494</p> <p>Central only 227</p>	227	0

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