BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults commencing or maintaining antidepressants, what is the risk of developing hyponatraemia? Are there any recommendations for best practice?"

Clarification of question using *PRO* structure

Patients:	Adults commencing or maintaining antidepressants
Risk:	Commencing or maintaining antidepressants
Outcome:	Hyponatraemia

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Clinical and research implications

No definite clinical implications can be made from the available evidence. There is, however, consistent evidence that selective serotonin reuptake inhibitors (SSRIs) are associated with an increased risk of developing hyponatraemia in depressed elderly adults, but there is inconsistency in the incidence (or prevalence) between studies. Due to methodological shortcomings in the evidence, and the lack of head to head studies, it is not possible to determine which antidepressants may be best to use in clinical practice.

Common recommendations were suggested:

1) Monitoring of sodium concentrations in elderly patients prescribed a SSRI or a serotonin–norepinephrine reuptake inhibitor (SNRI) should be done - including before, and 1 to 2 weeks after, initiating treatment. This is especially important for patients who present with additional risk factors such as female sex, low BMI, baseline plasma sodium level of 138 mEq/L or less, or patients with comorbid medical illness or concomitant medications known to alter ADH or cause hyponatraemia (e.g. diuretics).

2) A sodium level should be obtained in all elderly patients who exhibit abrupt changes in mental status (e.g. lethargy, confusion) any time during treatment with an SSRI.

Many authors recommended that further research, including long-term randomised controlled trials, are needed to compare the benefits and risks of different anti-depressants in elderly people with depression. More research is also needed to assess the association between antidepressants and hyponatraemia in different age groups.

What does the evidence say?

Number of included studies/reviews (number of participants)
Eight studies met the inclusion criteria for this BEST summary. Four were retrospective cohort studies (Coupland et al. 2011; Jung et al. 2011; Letmaier et al. 2012; Strachan and Shepherd 1998), three were prospective cohort studies (Fabian et al. 2003; 2004; Roxanas et al. 2007), and one was a prospective controlled study (Kirby et al. 2002).

Main Findings
The included studies evaluated associations between classes of antidepressants, and/or specific anti-depressants, and hyponatraemia. All but one study included only older patients with depression. One large retrospective cohort study (n=60,746) of older patients reported that those who took SSRIs were more likely to experience hyponatraemia than patients who took no antidepressants, with an adjusted hazard ratio of 1.52 (95% CI 1.33 to 1.75) (Coupland et al. 2011). In this same study, tricyclic antidepressants had an adjusted HR of 1.05 (95% CI 0.87 to 1.27) and 'other' antidepressants had an adjusted HR of 1.28 (95% CI 0.98 to 1.67). SSRIs were also associated with significantly higher rates of hyponatraemia compared with tricyclic antidepressants: HR 1.44 (95% CI 1.19 to 1.75), but 'other' antidepressants were not significantly different to tricyclic antidepressants: HR 1.21 (95% CI 0.90 to 1.64). Three SSRIs that were associated with the greatest increases in hyponatraemia were citalopram, escitalopram, and fluoxetine.

In a long-term (1993 to 2007) retrospective analysis of German psychiatric inpatients 28 (0.06%) of those treated with SSRIs (n=50,297) developed hyponatraemia, and 16 (0.08%) of those patients treated with SNRIs (n=19,807) developed hyponatraemia (Letmaier et al. 2012).

Two studies evaluated venlafaxine. One was a prospective study of elderly patients (Roxanas et al. 2007). In this study, 17.2% of patients developed hyponatraemia after 6 months. The other study was a retrospective controlled trial (Kirby et al. 2002). This study evaluated the prevalence of hyponatraemia in elderly psychiatric patients prescribed SSRIs and venlafaxine. In this study, 39% (29/74) developed hyponatraemia, and the authors reported that the odds of the patients having hyponatraemia was five times greater than patients who did not receive SSRIs or venlafaxine.

Two prospective studies investigated the incidence of paroxetine-induced hyponatraemia in older adults with major depression (Fabian et al. 2003; 2004). The earlier study was a pilot study which included 15 men and women with a mean age of 75.7 (SD 5.3). After 2 weeks' treatment with 10 mg/day paroxetine, 6 (40%) patients developed hyponatraemia. The later study included 75 men and women, with a mean age of 75.3 (SD 6.0) years of age. In this study, 9 (12%) of patients developed hyponatraemia, with a mean time to development of 9.3 (SD 4.7) days. Multivariate analysis demonstrated that lower body mass index and lower baseline plasma sodium level were significant risk factors for the development of hyponatraemia.

A further retrospective study found associations between hyponatraemia and two SSRIs: five out of 18 patients (28%) treated with fluoxetine developed hyponatraemia, and of 8/37 patients (22%) treated with paroxetine were, or became, hyponatraemic (Strachan and Shepherd 1998).

A retrospective study by Jung et al. (2011) investigated the incidence of hyponatraemia associated with SSRIs, mirtazapine or venlafaxine in Korean patients, 18 years of age and older, with major depressive order. After 4 weeks' treatment, the incidence of hyponatraemia was significantly higher (8.6%) in patients treated with SSRIs compared with venlafaxine (4.2%) or mirtazapine (0%), p=0.029)

Authors Conclusions

Coupland et al. (2011) concluded that SSRIs may be associated with an increased risk of certain outcomes, including all-cause mortality, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures and hyponatraemia compared with tricyclic antidepressants. Letmaier et al. (2012) did not make specific conclusions regarding SSRIs alone. They stated that patients who received drugs such as diuretics or ACE inhibitors, in addition to their treatment with SSRI or venlafaxine, were at the highest risk of developing hyponatraemia. Roxanas et al. (2007) concluded that patients greater than 65 years of age should have their electrolytes measured 3-5 days after starting venlafaxine therapy. If hyponatraemia develops, it can be managed with modest fluid restriction without discontinuing drug treatment, subject to close continued clinical observation and biochemical monitoring. Kirby et al. (2002) concluded that prescription of SSRIs and venlafaxine had a significant association with hyponatraemia in a population of elderly psychiatric inpatients, and the association is not due to confounding by age, sex, depression, medical illness severity or consumption of other drugs. Fabian et al. (2013; 2014) concluded that hyponatraemia is a common and potentially serious adverse event in elderly patients prescribed paroxetine. Fabian et al. (2013) also concluded that inappropriate secretion of antidiuretic hormone may be the potential

mechanism. Strachan and Shepherd (1998) concluded that hyponatraemia may be a relatively common early asymptomatic side effect of SSRIs, especially in older women. Jung et al. (2011) concluded that SSRIs may be associated with decreased sodium levels and a higher incidence of hyponatraemia.

Reliability of conclusions/Strength of evidence

All of the included studies used designs that have some inherent risk of bias, and many of the studies had small sample sizes. The reported incidence and prevalence figures need to be considered in context (e.g. mean age, proportion of females, length of study etc.) and may not be comparable between studies, or generalizable. Three of the included studies appeared to have a 'low' risk of bias and adequate sample sizes, so that their results are likely to be reliable (Coupland et al. 2011; Kirkby et al. 2002; Letmaier et al. 2012).

What do guidelines say?

SIGN guidelines do not make recommendations regarding hyponatraemia and antidepressants.

NICE guidelines for depression in adults with a chronic physical health problem (CG91, 2009) suggest the following:

"When an antidepressant is to be prescribed for a patient with depression and a chronic physical health problem, take into account the following: the side effects of antidepressants, which may impact on the underlying physical disease (in particular, SSRIs may result in or exacerbate hyponatraemia, especially in older people)" (p.10)

However, no recommendations are made regarding monitoring patients who have been prescribed antidepressants.

Date question received: 23/07/2014
Date searches conducted: 25/07/2014
Date answer completed: 08/08/2014

References

Cohort studies

Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G., & Hippisley-Cox, J. (2011). Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. *British Medical Journal, 343*(7819), 1-15.

Fabian, T. J., Amico, J. A., Kroboth, P. D., Mulsant, B. H., Corey, S. E., Begley, A. E., … Pollock, B. G. (2003). Paroxetine-induced hyponatremia in the elderly due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Journal of Geriatric Psychiatry & Neurology, 16*(3), 160-164.

Fabian, T. J., Amico, J. A., Kroboth, P. D., Mulsant, B. H., Reynold, C. F., & Pollock, B. G. (2004). Paroxetine-Induced Hyponatremia in Older Adults: A 12-Week Prospective Study. *Archives of Internal Medicine, 164*(3), 327-332.

Jung, Y. E., Jun, T. Y., & Bahk, W. M. (2011). Hyponatremia associated with selective serotonin reuptake inhibitors, mirtazapine, and venlafaxine in Korean patients with major depressive disorder. *International Journal of Clinical Pharmacology & Therapeutics, 49*(7), 437-443.

Kirby, D., Harrigan, S., & Ames, D. (2002). Hyponatraemia in elderly psychiatric patients treated with Selective Serotonin Reuptake Inhibitors and venlafaxine: A retrospective controlled study in an inpatient unit. *International Journal of Geriatric Psychiatry, 17*(3), 231-237.

Letmaier, M., Painold, A., Holl, A. K., Vergin, H., Engel, R., Konstantinidis, A., … Grohmann, R. (2012). Hyponatraemia during psychopharmacological treatment: Results of a drug surveillance programme. *International Journal of Neuropsychopharmacology, 15*(6), 739-748.

Roxanas, M., Hibbert, E., & Field, M. (2007). Venlafaxine hyponatraemia: Incidence, mechanism and management. *Australian & New Zealand Journal of Psychiatry, 41*(5), 411-418.

Strachan, J. & Shepherd, J. (1998). Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. *Australian & New Zealand Journal of Psychiatry, 32*(2), 295-298.

Guidelines

National Institute for Health and Care Excellence. (2009). *Depression in adults with a chronic physical health problem*. CG91. London: National Institute for Health and Care Excellence.

Results

Cohort studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Coupland et al. (2014)	*Participants*: Adults aged 65-99 with a diagnosis of depression. Exclusion criteria: diagnosis of schizophrenia, bipolar disorder, or other types of psychosis. *Risk Factor*: Antidepressant drugs, classed according to the British National Formulary: tricyclic and related antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and other antidepressants. *Outcome*: Adverse outcomes (including hyponatraemia). *Study design*: Retrospective cohort study.	N=60,746	The associations with the adverse outcomes differed significantly between the antidepressant classes for seven outcomes: all-cause mortality, attempted suicide/self- harm, stroke/transient ischaemic attack, falls, fracture epilepsy/seizures, and hyponatraemia. Only the outcome relevant to this BEST summary has been data extracted. For hyponatraemia, selective serotonin reuptake inhibitors were associated with the highest adjusted hazard ratio: 1.52 (95% CI: 1.33 to 1.75) compared with not taking antidepressants. Tricyclic antidepressants had an adjusted HR of 1.05 (95%CI: 0.87 to 1.27) and 'other' antidepressants had an adjusted HR of 1.28 (95% CI: 0.98 to 1.67). Selective serotonin reuptake inhibitors were associated with significantly higher rates of hyponatraemia compared with tricyclic antidepressants: HR 1.44 (95% CI: 1.19 to 1.75). 'Other' antidepressants were not significantly different to tricylic antidepressants: HR 1.21 (95% CI: 0.90 to 1.64). Three selective serotonin reuptake inhibitors (citalopram, escitalopram, and fluoxetine) were associated with significantly increased risks of hyponatraemia, but paroxetine	Low

			and sertraline were not (hazard ratios were shown in a figure only).	
Fabian et al. (2003)	*Participants*: Adults aged 70-88 with a DSM-IV diagnosis of major depressive disorder, determined to be normonatraemic at baseline (plasma sodium level greater than or equal to 135 mEq/L). *Risk Factor*: Peroxetine (at least 10 mg a day). *Outcome*: Blood samples for measurement of plasma sodium, antidiuretic hormone, serum urea nitrogen, creatinine, glucose, and osmolality. *Study Design*: Prospective cohort study (12 weeks).	N=15	After 2 weeks' treatment with paroxetine, 6 patients developed hyponatraemia. The authors reported that inappropriate section of antidiuretic hormone may be a potential mechanism.	High (short duration and small sample size)
Fabian et al. (2004)	*Participants*: Adults aged 63-90 with a diagnosis of depression, with normal blood sodium levels at baseline. Exclusion criteria: Any medical illness or medications known to cause hyponatraemia; abnormal glucose or blood urea nitrogen levels at baseline. *Risk Factor*: Peroxetine (at least 10 mg a day). *Outcome*: Blood samples for measurement of plasma sodium, antidiuretic hormone, blood urea nitrogen,	N=75	After 12 weeks' treatment with paroxetine, 9 (12%) of patients developed hyponatraemia, with a mean time to development of 9.3 (SD 4.7) days. Multivariate regression analysis demonstrated that lower BMI and lower baseline plasma sodium level to be significant independent predictors of hyponatraemia.	Low (but small sample size)

	creatinine, glucose, and osmolality. *Study Design*: Prospective cohort study (12 weeks).			
Jung et al. (2011)	*Participants*: Korean patients in a psychiatric inpatient unit, aged 18 and over, with a DSM-IV diagnosis of major depressive disorder. Exclusion criteria: taking 2 or more antidepressants, mood stabilisers, psychostimulants, or antipsychotics; any psychiatric comorbidity; history of severe physical illness or any condition affecting sodium and water metabolism; abnormal serum sodium level at baseline. *Risk Factor*: An SSRI, Mirtazapine, or Venlafaxine. *Outcome*: Hyponatraemia (serum sodium level, mmol/L) *Study Design*: Retrospective cohort study.	N=240 (93 treated with an SSRI, 76 treated with mirtazapine, and 71 treated with venlafaxine)	After 4 weeks' treatment, the incidence of hyponatraemia was significantly higher (8.6%) in patients treated with SSRIs compared with venlafaxine (4.2%) or mirtazapine (0%), p=0.029. The incidence of hyponatraemia in patients 60 years or older was 21.9% (7/32).	Acceptable (but only patients who received treatment for the full 4 weeks were included in the analysis)
Kirby et al. (2002)	*Participants*: Older adults in a psychogeriatric inpatient unit, aged 65 and over, with a diagnosis of depression. *Risk Factor*: An SSRI or venlafaxine. *Outcome*: Hyponatraemia (sodium less than 135 mmol/L). *Study Design*: Retrospective controlled study (Condition 1, prescribed an SSRI or venlafaxine; Condition 2, not prescribed an SSRI or venlafaxine).	N=199 (74 antidepressant condition, 125 control condition)	Of 74 patients treated with an SSRI or venlafaxine, 29 (39%) developed hyponatraemia compared with 13 (10%) in the control condition, p<0.001: OR 5.6 (95% CI 2.6 to 11.6). Of these 74 patients, 25 were treated with paroxetine, and 32% became hyponatraemic; 28 were treated with sertraline, and 27% became hyponatraemic; 5 were treated with fluoxetine, and 60% became hyponatraemic; 2 were treated with fluvoxamine, and 0% became hyponatraemic; 14 were treated with venlafaxine, and 71% became hyponatraemic.	Low

			For the sample of 199, 159 (80%) were on other causal drugs including thiazides. There was no evidence of a statistically significant association between hyponatraemia and being on all causal drugs, including thiazides. Thirty-seven patients were on thiazides alone, of whom 13 developed hyponatraemia (35%). Thus, in this group there was a significant association between hypnatraemia status and thiazides (p=0.020). Patients who were on thiazides had a higher rate of hyponatraemia, particularly if also on SSRIs or venlafaxine (73% vs 19% not on SSRIS or venlafaxine) – OR: 11.2 (95% CI 2.2 to 58.1).	
Letmaier et al. (2012)	*Participants*: Adult inpatients in a psychiatric unit (from 80 hospitals). *Risk Factor*: Psychopharmacological treatment (including antidepressants). *Outcome*: Hyponatraemia (sodium less than 130 mmol/L). *Study Design*: Retrospective cohort study.	N=263,864	A total of 93 (0.04%) patients developed hyponatraemia from 1993 to 2007 (including all psychopharmacological treatment). Of those patients treated with SSRIs (n=50,297), 28 (0.06%) had hyponatraemia and of those patients treated with SNRIs (n=19,807), 16 (0.08%) had hyponatraemia. Of those treated with tricyclic antidepressants (n=41, 587), 2 (0.005%) had hyponatraemia. Data were reported for other drugs classes (anticonvulsants, antipsychotics), but have not been data extracted.	Low
Roxanas et al.	*Participants*: Adults aged 65 years and over (actual ages: 67-88) with a DSM-IV	N=58	After 6 months, 10 patients (17.2%) developed hyponatraemia.	Acceptable (but small

(2007)	diagnosis of depression, and normal baseline plasma sodium levels. *Risk Factor*: Venlafaxine (75 mg a day, titrated up to 150 mg a day). *Outcome*: Hyponatraemia (sodium less than 135 mmol/L), plasma osmolality, antidiuretic hormone, urinary osmolality, urinary socium. *Study Design*: Prospective cohort study (6 months).			sample size)
Strachan et al. (1998)	*Participants*: Older adults in a psychogeriatric inpatient unit, aged 70-83. *Risk Factor*: Fluoxetine or paroxetine. *Outcome*: Hyponatraemia (serum sodium of 134 mmol/L or below). *Study Design*: Retrospective cohort study.	N=53	Of 18 patients treated with fluoxetine 5 (28%) developed hyponatraemia, and of 37 patients treated with paroxetine 8 (22%) were, or became, hyponatraemic. For eight of the patients, the time from commencement of the SSRI as an inpatient to the lowest serum sodium was known and ranged from 4 days to 28 days (mean 12.5 days). Five patient had received an SSRI before admission and the time to discovery of hyponatraemia ranged from 27 days to 2 years.	Acceptable (but small sample size)

Risk of Bias

Study	RISK OF BIAS (ASSESSED USING SIGN GUIDANCE FOR COHORT STUDIES)					
	Question (clearly focussed)	Subject selection (comparable groups, loss to follow-up)	Outcome assessment (clearly defined, reliable and blinded to exposure)	Confounding (accounted for in design and analysis)	Statistical analysis (reporting of confidence intervals)	Overall assessment
Coupland et al. (2014)	☺	☺	☺	☺	☺	☺
Fabian et al. (2003)	☺	☺	☺	☹	☺	☹
Fabian et al. (2004)	☺	☺	☺	☺	☺	☺
Jung et al. (2011)	☺	?	☺	☺	☹	Acceptable
Kirby et al. (2002)	☺	☺	☺	☺	☺	☺
Letmaier et al. (2012)	☺	☺	☺	☺	☺	☺
Roxanas et al. (2007)	☺	☺	☺	☺	☹	Acceptable
Strachan et al. (1998)	☺	☺	☺	?	☹	Acceptable

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Hyponatremia (1) Hyponatraemia (11) antidiuretic hormone secretion (2) SIADH (0)	14	1
DARE	(inappropriate ADJ3 (ADH OR vasopressin)) IN DARE 0 Delete 2 ((ADH OR vasopressin) ADJ2 syndrome*) IN DARE 0 Delete 3 (hyponatremia) IN DARE 12 Delete 4 MeSH DESCRIPTOR Hyponatremia EXPLODE ALL TREES 9 Delete 5 (hyponatr*emia*) IN DARE 22 Delete 6 (antidepress* OR anti-depress*) IN DARE 769 Delete 7 MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES 661 Delete 8 MeSH DESCRIPTOR Antidepressive Agents, Second-Generation EXPLODE ALL TREES 109 Delete 9 MeSH DESCRIPTOR Antidepressive Agents, Tricyclic EXPLODE ALL TREES 113 Delete 10 #1 OR #2 OR #3 OR #4 OR #5 23 Delete 11 #6 OR #7 OR #8 OR #9 980 Delete 12 #10 AND #11	1	0
Primary studies			
CENTRAL	#1 MeSH descriptor: [Antidepressive Agents] explode all trees 4886 #2 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees 2373 #3 SSRI 1108 #4 antidepressant 7903 #5 #1 or #2 or #3 or #4 11653 #6 MeSH descriptor: [Hyponatremia] explode all trees 107	4	0

	#7 hyponatraemia or hyponatremia 536 #8 #6 or #7 536 #9 #5 and #8 22 Central only 4		
PsycINFO	1. PsycINFO; exp ANTIDEPRESSANT DRUGS/; 31994 results. 2. PsycINFO; exp HYPONATREMIA/; 212 results. 3. PsycINFO; hyponatraemia.ti,ab; 84 results. 4. PsycINFO; 2 OR 3; 269 results. 5. PsycINFO; 1 AND 4; 59 results. 6. PsycINFO; exp SEROTONIN REUPTAKE INHIBITORS/; 10553 results. 7. PsycINFO; SSRI's.ti,ab; 3404 results. 8. PsycINFO; antidepressant*.ti,ab; 29301 results. 9. PsycINFO; 1 OR 6 OR 7 OR 8; 46405 results. 10. PsycINFO; 4 AND 9; 84 results. 11. PsycINFO; CLINICAL TRIALS/; 7751 results. 12. PsycINFO; random*.ti,ab; 131689 results. 13. PsycINFO; groups.ti,ab; 370342 results. 14. PsycINFO; (double adj3 blind).ti,ab; 17962 results. 15. PsycINFO; (single adj3 blind).ti,ab; 1422 results. 16. PsycINFO; EXPERIMENTAL DESIGN/; 9210 results. 17. PsycINFO; controlled.ti,ab; 81762 results. 18. PsycINFO; (clinical adj3 study).ti,ab; 8032 results. 19. PsycINFO; trial.ti,ab; 69282 results. 20. PsycINFO; "treatment outcome clinical trial".md; 27392 results. 21. PsycINFO; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 573727 results. 22. PsycINFO; (cohort OR observational OR longitudinal).ti,ab; 114221 results. 23. PsycINFO; 21 OR 22; 663149 results. 24. PsycINFO; 10 AND 23; 8 results.	8	
Embase	23. EMBASE; exp ANTIDEPRESSANT DRUGS/; 0 results.	198	

	24. EMBASE; exp HYPONATREMIA/; 18685 results. 25. EMBASE; hyponatraemia.ti,ab; 2095 results. 26. EMBASE; 24 OR 25; 19012 results. 27. EMBASE; 23 AND 26; 0 results. 28. EMBASE; exp SEROTONIN REUPTAKE INHIBITORS/; 0 results. 29. EMBASE; SSRI's.ti,ab; 7429 results. 30. EMBASE; antidepressant*.ti,ab; 61074 results. 31. EMBASE; 23 OR 28 OR 29 OR 30; 64475 results. 32. EMBASE; 26 AND 31; 406 results. 33. EMBASE; (cohort OR observational OR longitudinal).ti,ab; 604025 results. 34. EMBASE; exp ANTIDEPRESSANT AGENT/; 301289 results. 35. EMBASE; 31 OR 34; 309123 results. 36. EMBASE; 26 AND 35; 1816 results. 37. EMBASE; random*.ti,ab; 884923 results. 38. EMBASE; factorial*.ti,ab; 22992 results. 39. EMBASE; (crossover* OR cross-over*).ti,ab; 68956 results. 40. EMBASE; placebo*.ti,ab; 199261 results. 41. EMBASE; (doubl* ADJ blind*).ti,ab; 141734 results. 42. EMBASE; (singl* ADJ blind*).ti,ab; 14389 results. 43. EMBASE; assign*.ti,ab; 238525 results. 44. EMBASE; allocat*.ti,ab; 83585 results. 45. EMBASE; volunteer*.ti,ab; 175654 results. 46. EMBASE; CROSSOVER PROCEDURE/; 39531 results. 47. EMBASE; DOUBLE BLIND PROCEDURE/; 114388 results. 48. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 345939 results. 49. EMBASE; SINGLE BLIND PROCEDURE/; 18551 results. 50. EMBASE; 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49; 1410724 results. 51. EMBASE; 33 OR 50; 1938754 results.		

	52. EMBASE; 36 AND 51; 198 results.		
Medline	23. MEDLINE; exp ANTIDEPRESSANT DRUGS/; 121706 results. 24. MEDLINE; exp HYPONATREMIA/; 7170 results. 25. MEDLINE; hyponatraemia.ti,ab; 1713 results. 26. MEDLINE; 24 OR 25; 7896 results. 27. MEDLINE; 23 AND 26; 217 results. 28. MEDLINE; exp SEROTONIN REUPTAKE INHIBITORS/; 31507 results. 29. MEDLINE; SSRI's.ti,ab; 4914 results. 30. MEDLINE; antidepressant*.ti,ab; 46458 results. 31. MEDLINE; 23 OR 28 OR 29 OR 30; 144735 results. 32. MEDLINE; 26 AND 31; 278 results. 33. MEDLINE; (cohort OR observational OR longitudinal).ti,ab; 450648 results. 34. MEDLINE; "randomized controlled trial".pt; 379459 results. 35. MEDLINE; "controlled clinical trial".pt; 88883 results. 36. MEDLINE; randomized.ab; 299981 results. 37. MEDLINE; placebo.ab; 156290 results. 38. MEDLINE; "drug therapy".fs; 1718784 results. 39. MEDLINE; randomly.ab; 216923 results. 40. MEDLINE; trial.ab; 311654 results. 41. MEDLINE; groups.ab; 1376962 results. 42. MEDLINE; 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 3385787 results. 43. MEDLINE; 33 OR 42; 3704688 results. 44. MEDLINE; 32 AND 43; 142 results.	142	
Summary	**NA**	**NA**	

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