

Best Evidence Summaries of Topics in Mental Healthcare

BEST in MH *clinical question-answering service*

Question

How effective is CBT compared to SSRI (Selective Serotonin Reuptake Inhibitor) for treating Anxiety disorders in adults?

Clarification of question using *PICO* structure

Patients: Adults with Anxiety disorders
Intervention: CBT
Comparator: SSRI medication
Outcome: Any patient outcomes

Plain language summary

Most of the research found suggests that CBT and SSRI's have similar effects in improving symptoms of anxiety. One study suggests that SSRI's are significantly better than CBT at reducing frequency of panic attacks in people with Panic Disorder, however this particular study was of poor quality.

Clinical and research implications

Overall there was a small amount of moderate quality evidence to suggest that CBT and SSRIs have similar effects in improving symptoms of hypochondriasis, anxiety and worry after up to 16 weeks of treatment in adults with anxiety disorders. However one poor quality RCT found that SSRIs were better than CBT in reducing the frequency of panic attacks in adults with panic disorder, with or without agoraphobia. It recommended that for those with moderate or severe agoraphobia combined CBT and SSRI is advised but that SSRIs alone could be used for milder cases.

As most of these RCTs only measured outcomes in the short-term (up to 16 weeks) further research is needed to evaluate whether the positive effects of CBT and SSRIs are maintained over a longer time period. One of the RCTs in older adults aged 60 years or more also stated that there has been a lack of research into the treatment of later life anxiety with SSRIs and more research is needed into other psychological interventions such as reminiscence therapy.

What does the evidence say?

Number of included studies/reviews (number of participants)

Four randomised controlled trials (RCTs) were included with a total of 323 participants (range 49 to 112); all were conducted in the Netherlands. All of the RCTs included additional control groups (placebo or waiting list controls). Participants were adults with hypochondriasis (one RCT); older adults aged 60 or over with panic disorder with or without agoraphobia, or other anxiety disorders (two RCTs); and adults with panic disorder with or without agoraphobia (one RCT).

Main findings

Three RCTs found no statistically significant differences between CBT and SSRIs. One in participants with hypochondriasis found no significant difference between CBT and paroxetine after 16 weeks of treatment on measures of hypochondriasis, anxiety and depression. Two RCTs in older adults also found no significant differences in anxiety, depression, severity of agoraphobia or worry after up to 15 weeks of treatment for CBT compared to paroxetine or sertraline.

The final RCT found that CBT was less effective than SSRIs (a choice of fluoxetine, paroxetine, sertraline, citalopram, or fluvoxamine) in reducing the frequency of panic attacks in people with panic attacks with or without agoraphobia, with SSRIs being significantly better than CBT after 6 weeks of treatment.

Author's conclusions

The RCT in people with hypochondriasis concluded that: "CBT or paroxetine are effective in the treatment of hypochondriasis in a severe and heterogeneous outpatient population" (Greeven et al.)

The two RCTs in older adults concluded that: “Despite its drawbacks, the SSRI paroxetine and CBT are effective in the treatment of panic disorder in elderly patients”(Hendriks et al.) and “Both CBT and sertraline led to significant improvements on all outcomes, but sertraline completers had a greater improvement in symptoms of worry” (Schuurmans et al.)

The final RCT which included different SSRIs concluded that: “Patients with panic disorder responded well to each treatment (CBT, SSRI, CBT and SSRI) with a significant decline in panic attacks, CBT showed a slower rate of improvement compared to SSRI, and CBT and SSRI” (Van Apeldoorn et al).

Reliability of conclusions/Strength of evidence

Overall two RCTs were considered to be at a moderate risk of bias (Greeven et al. and Hendicks et al.) and two were at high risk of bias (Schuurmans et al. and Van Apeldoorn et al.). The two better quality trials both used appropriate methods of randomisation and allocation concealment, included all participants in the analysis and appeared to have clearly reported on all the outcome measures. The main limitation was the lack of blinding but it would not be possible to blind participants and therapists due to the nature of the CBT and SSRI treatments (although if a placebo was included that was blinded). It should be possible to blind the outcome assessors but in one trial this was not done and in the other it was not clear.

The two lower quality RCTs also did not use any blinding, and had high rates of participant drop-out who were excluded from the analyses. They also did not report all the outcome measures clearly, often focussing on the change within each treatment group rather than the difference between them. The numbers included in the analyses were also low (30 to 32 CBT, 17 to 24 SSRI).

Overall there was a small amount of moderate quality evidence to suggest that CBT and SSRIs have similar effects on hypochondriasis, anxiety and worry in adults with anxiety disorders after treatment for up to 16 weeks.

What do guidelines say?

Neither NICE or SIGN guidelines comment on specific research conducted about CBT vs SSRI's for treating anxiety disorders in adults. However two NICE guidelines do make recommendations for how each intervention should be administered for Social or General anxiety disorders and recommendations on research that should be conducted on this topic.

Date question received:	27/10/15
Date searches conducted:	10/11/15, 24/11/15
Date answer completed:	08/12/15

References

Randomised controlled trials

1. Greeven, A., van Balkom, A. J., Visser, S., Merkelbach, J. W., van Rood, Y. R., Richard van Dyck, M. D., ... & Spinhoven, P. (2007). Cognitive behavior therapy and paroxetine in the treatment of hypochondriasis: a randomized controlled trial. *The American journal of psychiatry*, 164(1), 91-99.
2. Hendriks, G. J., Keijsers, G. P. J., Kampman, M., Oude Voshaar, R. C., Verbraak, M. J. P. M., Broekman, T. G., & Hoogduin, C. A. L. (2010). A randomized controlled study of paroxetine and cognitive-behavioural therapy for late-life panic disorder. *Acta psychiatrica Scandinavica*, 122(1), 11-19.
3. Schuurmans, J., Comijs, H., Emmelkamp, P. M., Gundy, C. M., Weijnen, I., Van Den Hout, M., & Van Dyck, R. (2006). A randomized, controlled trial of the effectiveness of cognitive-behavioral therapy and sertraline versus a waitlist control group for anxiety disorders in older adults. *The American journal of geriatric psychiatry*, 14(3), 255-263.
4. Van Apeldoorn, F. J., Van Hout, W. J., Timmerman, M. E., Mersch, P. P. A., & den Boer, J. A. (2013). Rate of improvement during and across three treatments for panic disorder with or without agoraphobia: Cognitive behavioral therapy, selective serotonin reuptake inhibitor or both combined. *Journal of affective disorders*, 150(2), 313-319.

Guidelines

The National Institute for Health Care Excellence (2013). Social anxiety disorder: recognition, assessment and treatment – guidance. NICE Clinical Guidance (CG159).

<http://www.nice.org.uk/guidance/cg159>

The National Institute for Health Care Excellence (2011). Generalised Anxiety Disorder and Panic Disorder in adults: management guidance. NICE Clinical Guidance (CG113).

<http://www.nice.org.uk/guidance/cg113>

Results

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Greeven et. al. (2007)	<p>Participants: Adults aged 18 years and older with a primary diagnosis of Hypochondriasis (health anxiety disorder- the fear of being seriously ill)</p> <p>Intervention: CBT: 6 to 16 weeks of individual CBT</p> <p>Comparators:</p> <ul style="list-style-type: none"> - Paroxetine: 10 mg daily in the first week, 20mg daily in the second week, then weekly increases in increments of 20 mg per day to a maximum dosage of 60 mg per day, for 16 weeks - Placebo: for 16 weeks <p>Outcome: Primary Outcome:</p> <ul style="list-style-type: none"> - Hypochondriasis (The Whiteley Index) 	<p>N=112 (40 CBT, 37 paroxetine, 35 placebo)</p> <p>Outpatients, Netherlands.</p>	<p>At baseline 61% of the participants were female, with a mean age of 42 years and a mean duration of hypochondriasis of 10 years. More of the paroxetine participants had hypochondriasis without comorbid psychiatric diagnoses (29.7% vs. 17.5% for CBT), but more CBT participants had major depressive disorder (27.5% vs. 16.2%) and social anxiety disorder (22.5% vs. 8.1%), approximately 42% of participants overall had panic disorder, and 23% had generalized anxiety disorder. Ten patients withdrew from the CBT group (but only three were excluded from the analysis) and 11 from the paroxetine group (all were included in the analysis).</p> <p>There was no statistically significant difference between the CBT and paroxetine groups after 16 weeks of treatment on any of the outcome measures. The mean differences for CBT compared to paroxetine were: hypochondriasis measured by the Whiteley Index (-1.92, 95% CI -4.79 to 0.95; $p = 0.19$); Health Anxiety (-0.51, -4.00 to -2.98; $p = 0.77$); Illness Behaviour (0.46, 95% CI -1.15 to 2.06; $p = 0.58$);</p>	<p>Moderate</p> <p>Randomisation and allocation concealment used appropriate methods.</p> <p>Although there was a placebo group, participants and researchers were not blinded to the CBT group.</p> <p>It was unclear if all outcome assessments were made blind to treatment.</p> <p>An ITT analysis was</p>

	Secondary Outcomes: <ul style="list-style-type: none"> - Health Anxiety and illness behaviour (Illness attitudes scales – Dutch Version) 		<p>Symptom Checklist-90 (-1.26, 95% CI -18.68 to 16.16; $p = 0.89$); Montgomery Asberg Depression Rating Scale (-4.68, 95% CI -9.52 to 0.61; $p = 0.06$) and the Brief Anxiety Scale (-0.77, 95% CI -2.89 to 1.35; 0.47).</p> <p>Responders were classified as those with a change in Whiteley Index score greater than one standard deviation, but there was no significant difference between CBT and paroxetine (45% vs. 30%; $p = 0.17$).</p>	performed, and all outcomes were reported.
Hendricks et.al. (2010)	<p>Participants: Adults aged 60 years and older with a diagnosis of Panic disorder with Agoraphobia (PDA).</p> <p>Intervention: CBT – 14 weekly sessions of individual CBT which was then tapered off within a maximum of six sessions during the 12-week follow-up period.</p> <p>Comparator:</p> <ul style="list-style-type: none"> - Paroxetine: 10mg daily in the first week then increased in 10mg weekly increments to 40mg/day including 30 minute weekly consultations. From weeks 5 to 14, all patients attended five 30 min 	<p>N=49 (20 CBT, 17 paroxetine, 12 waiting list control)</p> <p>Specialist outpatient anxiety clinic, Netherlands</p>	<p>The mean participant age was 69 years, 57% were female, and the mean duration of anxiety was 12.3 years. The numbers with a co-morbid psychiatric diagnosis were lower in the CBT group (10% vs. 47% paroxetine) and also for a co-morbid somatic disorder (60% vs. 76.5%). Three patients withdrew from the CBT group and one from the paroxetine group.</p> <p>After 14 weeks of treatment there were no statistically significant differences between CBT and paroxetine on any outcome measure. Mean (standard deviation) scores were: ACQ (CBT 1.4 (0.4), paroxetine 1.4 (0.4)); MI-A (CBT 1.7 (0.9), paroxetine 1.9 (0.7)); and SCL-90 (CBT 145.4 (32.8), paroxetine 135.9 (24.8)). At the 26 week follow-up assessment there were also no statistically significant differences between CBT and paroxetine for any outcome measures.</p>	<p>Moderate</p> <p>Randomisation and allocation concealment used appropriate methods.</p> <p>Participants and researchers were not blinded to the treatment group, and as outcomes were self-reported, these were also not blinded.</p> <p>The analysis</p>

























	<p>medical consultations once every 2 weeks. Paroxetine was maintained at 40 mg/day during weeks 14–26.</p> <ul style="list-style-type: none"> - Waiting list control: could get CBT or paroxetine after week 14. <p>Outcome:</p> <ul style="list-style-type: none"> - Severity of agoraphobic/anxiety cognitions; Agoraphobic Cognitions Questionnaire (ACQ) Dutch version - Severity of phobic avoidance; Mobility Inventory Avoidance scale (MI-A) Dutch Version <p>Outcomes were measured at baseline, 8, 14 and 26 weeks.</p>			method meant that all participants were included, and all the outcomes were reported.
Schuurmans et. al. (2006)	<p>Participants:</p> <p>Adults aged 60 years and older with a diagnosis of generalized anxiety disorder (GAD), panic disorder (with or without agoraphobia), agoraphobia without a history of panic disorder or social phobia</p> <p>Intervention:</p> <p>CBT – 15 weekly sessions of individual CBT lasting 1 hour each consisting of relaxation, cognitive restructuring and exposure.</p>	<p>N=84 (42 CBT, 29 sertraline, 13 waiting list control)</p> <p>Referrals to GPs, community mental health centres and outpatient clinics in the</p>	<p>The mean participant age was 70 years, 75% were female, and the mean duration of anxiety was 25 years. The most common disorder was panic disorder (40.5% CBT, 55.2% sertraline), followed by generalized anxiety disorder (33.3% CBT, 34.5% sertraline), agoraphobia (16.7%, 3.4% sertraline) and social phobia (9.5% CBT, 6.9% sertraline).</p> <p>Drop-out rates were high with 12 (29%) CBT and 12 (41%) sertraline participants being excluded from the analyses.</p> <p>Both the CBT and sertraline groups showed significant</p>	<p>High</p> <p>Treatment allocations were selected blindly and at random by a researcher.</p> <p>Due to the nature of the interventions it was not possible to blind the participants or</p>

	<p>Comparator:</p> <ul style="list-style-type: none"> - Sertraline: 8, 20 minute sessions over 15 weeks with a starting dose of less than 25mg up to a minimum dose of 100mg and maximum of 150mg within 4 weeks. - Wait-list control: 15 week waiting period, who could then receive either treatment. <p>Outcome:</p> <p>Primary Outcomes</p> <ul style="list-style-type: none"> - Anxiety: Hamilton Anxiety Rating Scale (HARS), Beck Anxiety Inventory (BAI) <p>Secondary Outcomes</p> <ul style="list-style-type: none"> - Worry: Worry Domain Questionnaire (WDQ) - Depressive Symptoms;: Centre of Epidemiological Studies Depression Scale (CES-D) <p>Outcomes were measured at baseline, post-treatment (15 weeks) and at 3 months follow-up.</p>	Netherlands.	<p>improvements on all outcome measures over time. There was a significant difference between all three treatment groups for anxiety measured by the HARS ($p < 0.05$) but there was no significant difference between sertraline and CBT, only between sertraline and the waiting list control. No significant between group differences were seen for worry or depressive symptoms.</p> <p>After 15 weeks of treatment 44% of CBT participants and 57% of sertraline participants were treatment responders (an improvement of 20% on the BAI and HARS). There was no significant difference between CBT and sertraline ($p = 0.33$). A considerable number of moderate to severe adverse effects were reported with sertraline.</p>	<p>therapists. As some outcomes were self-reported their assessment would also be un-blinded.</p> <p>Dropout rates were high, and although an intent-to-treat analysis was reported, full details were not given and it was not the main analysis.</p> <p>Results were poorly reported and focussed on the changes within groups.</p>
Van Apeldoorn et.al. (2013)	<p>Participants:</p> <p>Adults (18 to 65 years old) who met the diagnosis criteria for panic disorder (PD) with or without agoraphobia (AG).</p>	N=160 (55 CBT, 53 SSRI, 52 CBT + SSRI)	<p>Only those participants who completed treatment were included in the analysis (32 CBT, 24 SSRI, 22 CBT + SSRI). The mean participant age was 36.6 years, 56.6% were female, and they had suffered from panic</p>	<p>High</p> <p>No details were reported about the</p>


	<p>Intervention: CBT – up to 21 treatment sessions of approximately 50 minutes each over the course of 12 months.</p> <p>Comparator:</p> <ul style="list-style-type: none"> - SSRI medication alone: SSRI's used were chosen by clinicians out of the following; Fluoxetine, paroxetine, sertraline, citalopram or fluvoxamine. Participants had 9 sessions lasting 20 minutes with clinicians during the 12 month treatment period. - CBT and SSRI combined: Both treatments started simultaneously and were delivered alongside each other. <p>Outcome: Frequency of panic attacks (recorded by patients in panic plots and used to calculate weekly frequencies).</p>	<p>University research centres/clinics and mental health clinics in the Netherlands.</p>	<p>disorder for a mean of 7.4 years. Around 50% had moderate or severe agoraphobia.</p> <p>The rate of improvement in panic attacks was significantly faster for SSRI and CBT + SSRI compared with CBT alone. Significant differences between all three treatments emerged after week 6 showing that SSRI was significantly better than CBT at specific time-points.</p>	<p>methods of randomisation and allocation concealment.</p> <p>Participants, therapists and outcome assessors (the participants) were not blinded to treatment.</p> <p>The analysis only included those who completed treatment (55%) so is likely to have been biased..</p> <p>Results were poorly reported without any descriptive summaries of the main outcome.</p>
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Risk of bias

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
Greeven et al. (2007)						
Hendricks et.al. (2012)						
Schuurmans et al. (2015)						
Van Apeldoorn et al. (2013)						

 Low risk

 High risk

 Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>Guidelines</i>			
NICE	CBT, SSRI, ANXIETY	14	2
SIGN	CBT, SSRI, ANXIETY	9	0
<i>Systematic Reviews0</i>			
MEDLINE	<ol style="list-style-type: none"> 1 exp Serotonin Uptake Inhibitors/ (33265) 2 exp Citalopram/ (4086) 3 exp Fluoxetine/ (8127) 4 exp Fluvoxamine/ (1769) 5 exp Paroxetine/ (3674) 6 exp Sertraline/ (2606) 7 SSRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5036) 8 (serotonin adj2 reuptake*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (12594) 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (38285) 10 exp Eating Disorders/ (23937) 11 Anorexia Nervosa/ (11276) 12 exp Bulimia/ (5046) 13 exp Suicide, Attempted/ (16073) 14 exp Self Mutilation/ (3134) 15 exp Self-Injurious Behavior/ (57859) 16 exp Mood Disorders/ (124875) 17 exp Bipolar Disorder/ (34263) 18 exp Neurotic Disorders/ (16012) 19 exp Depressive Disorder/ (87497) 	169	0

	20 exp Dysthymic Disorder/ (1060) 21 exp Depression/ or exp Depression, Postpartum/ (89741) 22 exp Seasonal Affective Disorder/ (1128) 23 exp Anxiety/ or exp Anxiety Disorders/ (131423) 24 exp Panic Disorder/ or exp Panic/ (8630) 25 exp Phobic Disorders/ (9720) 26 exp Stress Disorders, Post-Traumatic/ or exp Combat Disorders/ or exp Stress, Psychological/ (124505) 27 exp Somatoform Disorders/ (13657) 28 exp Obsessive-Compulsive Disorder/ (12165) 29 exp Hypochondriasis/ (2180) 30 exp Conversion Disorder/ (2020) 31 exp Munchausen Syndrome by Proxy/ or exp Munchausen Syndrome/ (1726) 32 exp Neurasthenia/ (1329) 33 exp Fatigue Syndrome, Chronic/ (4738) 34 exp Obsessive-Compulsive Disorder/ (12165) 35 exp Compulsive Behavior/ (8532) 36 exp Mental Disorders/ (1026799) 37 exp Schizophrenia/ (90913) 38 exp Paranoid Disorders/ (3858) 39 "schizo*".ab,ti. (115590) 40 "hebephrenic*".ab,ti. (201) 41 "oligophreni*".ab,ti. (910) 42 "psychotic*".ab,ti. (27502) 43 "psychos*".ab,ti. (119819) 44 "chronic* adj3 mental*".ab,ti. (0) 45 "sever* adj3 mental".ab,ti. (0) 46 "mental* adj3 disorder*".ab,ti. (0) 47 "mental* adj3 ill*".ab,ti. (0) 48 "emotion* adj3 disorder*".ab,ti. (0) 49 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 (1312065)		
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	50 9 and 49 (21561) 51 exp Cognitive Therapy/ (18840) 52 CBT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6324) 53 (cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (10617) 54 51 or 52 or 53 (24015) 55 50 and 54 (1296) 56 – 75 Systematic Review Filters applied (919745) 76 55 and 75 (169)		
EMBASE	1 exp Serotonin Uptake Inhibitors/ 33395 2 exp Citalopram/ 4108 3 exp Fluoxetine/ 8158 4 exp Fluvoxamine/ 1774 5 exp Paroxetine/ 3682 6 exp Sertraline/ 2621 7 SSRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5071 8 (serotonin adj2 reuptake*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 12668 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 38453	86	0

	10	exp Cognitive Therapy/ CBT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword	18953		
	11	heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6378		
	12	(cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10709		
	13	10 or 11 or 12	24187		
	14	9 and 13	1444		
	15	exp eating disorder/	24009		
	16	exp anorexia nervosa/	11310		
	17	exp bulimia/	5056		
	18	exp suicide attempt/	16121		
	19	exp mood disorder/	125359		
	20	exp bipolar disorder/	34385		
	21	exp neurosis/	0		
	22	exp depression/	86793		
	23	exp dysthymia/	0		
	24	exp seasonal affective disorder/	1131		
	25	exp anxiety/ or exp anxiety disorder/ or exp generalized anxiety disorder/	132038		

	26	exp panic/	2489		
	27	exp phobia/	9757		
	28	exp posttraumatic stress disorder/	23973		
	29	exp somatoform disorder/	13684		
	30	exp hypochondriasis/	2183		
	31	exp hysteria/	3464		
	32	exp hysteria/ or exp conversion disorder/	5275		
	33	exp Munchausen syndrome/	1252		
	34	exp Munchausen syndrome by proxy/	523		
	35	exp neurasthenia/	1330		
	36	chronic fatigue syndrome/	4749		
	37	exp obsessive compulsive disorder/	12209		
	38	exp obsession/	1104		
	39	exp compulsion/	0		
	40	exp mental stress/	0		
	41	exp paranoid schizophrenia/ or exp schizophrenia/	91243		
	42	exp paranoid psychosis/	0		
	43	*Mental Disorders/	98111		
	44	schizo\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word,	144140		

	unique identifier]		
45	hebephreni\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	277	
46	oligophreni\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1109	
47	psychotic\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	53186	
48	psychos#s.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	43611	
49	(chronic\$ adj mental\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1802	
50	(sever\$ adj mental).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6570	
51	(mental\$ adj disorder\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	157678	

	<p>(mental\$ adj ill\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 34449</p> <p>(emotion\$ adj disorder\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2038</p> <p>15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 637152</p> <p>55 - 84 Systematic Review Filter applied 458760</p> <p>85 limit 84 to yr="2010 -Current" 226707</p> <p>86 14 and 54 and 85 86</p>		
PsycINFO/CINAHL	<p>1 exp Cognitive Therapy/ (18928)</p> <p>2 CBT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6349)</p> <p>3 (cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (10670)</p> <p>4 1 or 2 or 3 (24126)</p> <p>5 exp Citalopram/ (4104)</p> <p>6 exp Fluoxetine/ (8153)</p> <p>7 exp Fluvoxamine/ (1773)</p> <p>8 exp Paroxetine/ (3681)</p> <p>9 exp Sertraline/ (2618)</p> <p>10 SSRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,</p>	83	0

	<p>protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5064)</p> <p>11 (serotonin adj2 reuptake*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (12648)</p> <p>12 exp Serotonin Reuptake Inhibitors/ or exp Serotonin/ (94034)</p> <p>13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (98626)</p> <p>14 4 and 13 (1463)</p> <p>15 exp Eating Disorders/ (24000)</p> <p>16 exp Anorexia Nervosa/ (11307)</p> <p>17 exp Bulimia/ (5056)</p> <p>18 exp Attempted Suicide/ (16109)</p> <p>19 exp Self Mutilation/ (3140)</p> <p>20 exp Self Injurious Behavior/ (58004)</p> <p>21 exp Bipolar Disorder/ (34357)</p> <p>22 exp Affective Disorders/ (125250)</p> <p>23 exp Major Depression/ (0)</p> <p>24 exp Dysthymic Disorder/ (1061)</p> <p>25 exp Neurosis/ (0)</p> <p>26 exp Seasonal Affective Disorder/ (1130)</p> <p>27 exp Anxiety Disorders/ (74811)</p> <p>28 exp Panic Disorder/ (6306)</p> <p>29 exp Phobias/ (9748)</p> <p>30 exp Posttraumatic Stress Disorder/ (23947)</p> <p>31 exp Somatoform Disorders/ (13676)</p> <p>32 exp Hypochondriasis/ (2183)</p> <p>33 exp Hysteria/ (3464)</p> <p>34 exp Conversion Disorder/ (2023)</p> <p>35 exp Munchausen Syndrome/ (1252)</p> <p>36 exp Munchausen Syndrome by Proxy/ (523)</p> <p>37 exp Neurasthenia/ (1330)</p> <p>38 exp Chronic Fatigue Syndrome/ (4746)</p>		
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39	exp Obsessive Compulsive Disorder/ (12200)		
40	exp Psychological Stress/ (101996)		
41	exp Schizophrenia/ (91191)		
42	(Mood adj disorder*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (21459)		
43	(Mental adj Disorders).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (160289)		
44	schizo*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (143963)		
45	hebephrenic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (202)		
46	oligophreni*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1109)		
47	psychotic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (53117)		
48	psychos*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (141502)		
49	(chronic* adj mental*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1801)		
50	(severe* adj mental*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (7139)		
51	(mental* adj disorder*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (157500)		
52	(mental* adj ill*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (34372)		

	<p>53 (emotion* adj disorder*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2036)</p> <p>54 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (730397)</p> <p>55 14 and 54 (1231)</p> <p>56 – 65 Systematic Review Filters applied (366857)</p> <p>66 55 and 65 (83)</p>		
Primary Studies			
MEDLINE	<p>1 exp Serotonin Uptake Inhibitors/ (33265)</p> <p>2 exp Citalopram/ (4086)</p> <p>3 exp Fluoxetine/ (8127)</p> <p>4 exp Fluvoxamine/ (1769)</p> <p>5 exp Paroxetine/ (3674)</p> <p>6 exp Sertraline/ (2606)</p> <p>7 SSRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5036)</p> <p>8 (serotonin adj2 reuptake*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (12594)</p> <p>9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (38285)</p> <p>10 exp Eating Disorders/ (23937)</p> <p>11 Anorexia Nervosa/ (11276)</p> <p>12 exp Bulimia/ (5046)</p> <p>13 exp Suicide, Attempted/ (16073)</p> <p>14 exp Self Mutilation/ (3134)</p>	387	0

	15	exp Self-Injurious Behavior/ (57859)		
	16	exp Mood Disorders/ (124875)		
	17	exp Bipolar Disorder/ (34263)		
	18	exp Neurotic Disorders/ (16012)		
	19	exp Depressive Disorder/ (87497)		
	20	exp Dysthymic Disorder/ (1060)		
	21	exp Depression/ or exp Depression, Postpartum/ (89741)		
	22	exp Seasonal Affective Disorder/ (1128)		
	23	exp Anxiety/ or exp Anxiety Disorders/ (131423)		
	24	exp Panic Disorder/ or exp Panic/ (8630)		
	25	exp Phobic Disorders/ (9720)		
	26	exp Stress Disorders, Post-Traumatic/ or exp Combat Disorders/ or exp Stress, Psychological/ (124505)		
	27	exp Somatoform Disorders/ (13657)		
	28	exp Obsessive-Compulsive Disorder/ (12165)		
	29	exp Hypochondriasis/ (2180)		
	30	exp Conversion Disorder/ (2020)		
	31	exp Munchausen Syndrome by Proxy/ or exp Munchausen Syndrome/ (1726)		
	32	exp Neurasthenia/ (1329)		
	33	exp Fatigue Syndrome, Chronic/ (4738)		
	34	exp Obsessive-Compulsive Disorder/ (12165)		
	35	exp Compulsive Behavior/ (8532)		
	36	exp Mental Disorders/ (1026799)		
	37	exp Schizophrenia/ (90913)		
	38	exp Paranoid Disorders/ (3858)		

	<p>39 "schizo*".ab,ti. (115590)</p> <p>40 "hebephrenic*".ab,ti. (201)</p> <p>41 "oligophreni*".ab,ti. (910)</p> <p>42 "psychotic*".ab,ti. (27502)</p> <p>43 "psychos*".ab,ti. (119819)</p> <p>44 "chronic* adj3 mental*".ab,ti. (0)</p> <p>45 "sever* adj3 mental".ab,ti. (0)</p> <p>46 "mental* adj3 disorder*".ab,ti. (0)</p> <p>47 "mental* adj3 ill*".ab,ti. (0)</p> <p>48 "emotion* adj3 disorder*".ab,ti. (0)</p> <p>49 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 (1312065)</p> <p>50 9 and 49 (21561)</p> <p>51 exp Cognitive Therapy/ (18840)</p> <p>52 CBT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6324)</p> <p>53 (cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (10617)</p> <p>54 51 or 52 or 53 (24015)</p> <p>55 50 and 54 (1296)</p> <p>56 – 63 RCT Filters applied (737923)</p>		
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	64 55 and 63 (387)		
EMBASE	1 exp Serotonin Uptake Inhibitors/ (156582) 2 exp Citalopram/ (18874) 3 exp Fluoxetine/ (39538) 4 exp Fluvoxamine/ (11712) 5 exp Paroxetine/ (24134) 6 exp Sertraline/ (21248) 7 SSRI.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (8703) 8 (serotonin adj2 reuptake*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (19922) 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (158398) 10 exp Cognitive Therapy/ (39373) 11 CBT.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (9891) 12 (cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (16625) 13 10 or 11 or 12 (44286) 14 9 and 13 (7697) 15 exp eating disorder/ (39903) 16 exp anorexia nervosa/ (17043) 17 exp bulimia/ (11630) 18 exp suicide attempt/ (23256) 19 exp mood disorder/ (385070) 20 exp bipolar disorder/ (46143) 21 exp neurosis/ (56790) 22 exp depression/ (352066) 23 exp dysthymia/ (6769) 24 exp seasonal affective disorder/ (1048) 25 exp anxiety/ or exp anxiety disorder/ or exp generalized anxiety disorder/ (285191) 26 exp panic/ (19027)	1263	4

27	exp phobia/ (24240)		
28	exp posttraumatic stress disorder/ (40221)		
29	exp somatoform disorder/ (20085)		
30	exp hypochondriasis/ (3807)		
31	exp hysteria/ (6139)		
32	exp hysteria/ or exp conversion disorder/ (7783)		
33	exp Munchausen syndrome/ (1711)		
34	exp Munchausen syndrome by proxy/ (438)		
35	exp neurasthenia/ (1647)		
36	chronic fatigue syndrome/ (7873)		
37	exp obsessive compulsive disorder/ (31000)		
38	exp obsession/ (8784)		
39	exp compulsion/ (8530)		
40	exp mental stress/ (64361)		
41	exp paranoid schizophrenia/ or exp schizophrenia/ (156550)		
42	exp paranoid psychosis/ (14529)		
43	*Mental Disorders/ (86106)		
44	schizo\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (194322)		
45	hebephreni\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (887)		
46	oligophreni\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1756)		
47	psychotic\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (42831)		
48	psychos#.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (111065)		
49	(chronic\$ adj mental\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2213)		
50	(sever\$ adj mental).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (8929)		

	<p>51 (mental\$ adj disorder\$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (58976)</p> <p>52 (mental\$ adj ill\$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (34911)</p> <p>53 (emotion\$ adj disorder\$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (14682)</p> <p>54 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (977579)</p> <p>55 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (1149409)</p> <p>56 (animals not humans).sh. (566)</p> <p>57 exp Clinical Trials/ (171079)</p> <p>58 random*.mp. (1200355)</p> <p>59 57 not 58 (72677)</p> <p>60 55 not (56 or 59) (1147333)</p> <p>61 14 and 54 and 60 (1263)</p>		
PsycINFO/CINAHL	<p>1 exp Cognitive Therapy/ (12164)</p> <p>2 CBT.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (9388)</p> <p>3 (cognitive* adj2 (behaviour* or behavior*) adj2 therap*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (22373)</p> <p>4 1 or 2 or 3 (30988)</p> <p>5 exp Citalopram/ (1133)</p> <p>6 exp Fluoxetine/ (3442)</p> <p>7 exp Fluvoxamine/ (783)</p> <p>8 exp Paroxetine/ (1583)</p> <p>9 exp Sertraline/ (1151)</p> <p>10 SSRI.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (3253)</p> <p>11 (serotonin adj2 reuptake*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (9206)</p> <p>12 exp Serotonin Reuptake Inhibitors/ or exp Serotonin/ (24162)</p> <p>13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (28127)</p> <p>14 4 and 13 (842)</p>	306	

	15 exp Eating Disorders/ (24984) 16 exp Anorexia Nervosa/ (9419) 17 exp Bulimia/ (6936) 18 exp Attempted Suicide/ (8452) 19 exp Self Mutilation/ (1100) 20 exp Self Injurious Behavior/ (3993) 21 exp Bipolar Disorder/ (21715) 22 exp Affective Disorders/ (132128) 23 exp Major Depression/ (103358) 24 exp Dysthymic Disorder/ (1413) 25 exp Neurosis/ (7534) 26 exp Seasonal Affective Disorder/ (961) 27 exp Anxiety Disorders/ (67583) 28 exp Panic Disorder/ (7041) 29 exp Phobias/ (11506) 30 exp Posttraumatic Stress Disorder/ (24478) 31 exp Somatoform Disorders/ (11343) 32 exp Hypochondriasis/ (1157) 33 exp Hysteria/ (1960) 34 exp Conversion Disorder/ (1119) 35 exp Munchausen Syndrome/ (119) 36 exp Munchausen Syndrome by Proxy/ (213) 37 exp Neurasthenia/ (300) 38 exp Chronic Fatigue Syndrome/ (1639) 39 exp Obsessive Compulsive Disorder/ (11135) 40 exp Psychological Stress/ (7936) 41 exp Schizophrenia/ (77208) 42 (Mood adj disorder*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (13575) 43 (Mental adj Disorders).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (109388)		
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44	schizo*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (116556)		
45	hebephrenic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (419)		
46	oligophreni*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (520)		
47	psychotic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (40013)		
48	psychos*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (187137)		
49	(chronic* adj mental*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (3710)		
50	(severe* adj mental*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (8249)		
51	(mental* adj disorder*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (109052)		
52	(mental* adj ill*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (45693)		
53	(emotion* adj disorder*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (4180)		
54	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 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 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (586872)		
55	(random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (170279)		
56	(animals not humans).sh. (6195)		
57	exp Clinical Trials/ (9180)		
58	random*.mp. (149023)		
59	57 not 58 (3967)		
60	55 not (56 or 59) (169675)		
61	14 and 54 and 60 (306)		

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