NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Clinical guideline
CG90: Depression in adults: treatment and management (update)

Publication date
September 2010

Previous review dates
3 year review: 2012 (no update)

Surveillance report for GE
November 2013

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from evidence update			✓	
Evidence identified from literature search			✓	
Feedback from Guideline Development Group			✓	
Anti-discrimination and equalities considerations				✓
No update	Rapid update	Standard update	Transfer to static list	Change review cycle
		✓		

Surveillance recommendation
GE is asked to consider the proposal to update the guideline as a standard update. GE are asked to note that this 'yes to update' proposal will not be consulted on.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG90: Depression in adults: management and treatment (update)

Recommendation for Guidance Executive

Background information

Guideline issue date: 2010
3 year review: 2012 (no update)

NCC: Mental Health

CG23
Guideline issue date: 2004
Republished: 2007 (amended)
Republished: 2010 (standard update published as CG90)

Main conclusions from previous surveillance review

1. CG90 was previously reviewed for update in 2012. At that review point, limited new evidence was identified which would could potentially change the direction of guideline recommendations. However, the new evidence was considered to be insufficient to warrant an update hence the review recommendation was that the guideline should not be considered for an update.

Current (four year) surveillance review

2. A literature search for randomised controlled trials and systematic review was used as the primary source of evidence for this surveillance review. New evidence since the last surveillance review was considered (April 2012 (the end of the search period for the surveillance review) and September 2013) and relevant abstracts were assessed. The identified evidence from the previous 3 year surveillance review

and the Evidence Update on CG90: Depression (published April 2012) were also used as sources of evidence to ensure that the evidence base reflected the lifetime of the guideline. Clinical feedback on the guideline was obtained from 7 members of the GDG through a questionnaire and the chair was also contacted for his opinion on the surveillance decision.

3. New evidence that may impact on recommendations was identified relating to 4 clinical areas within the guideline:

<table>
<tr><th colspan="3">Clinical area 1:Service delivery– recommendation 1.2</th></tr>
<tr><td colspan="3">Q: In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which models of care produce the best outcomes?
collaborative care
stepped care
case management
stratified (matched) care
attached professional model</td></tr>
<tr><th>Evidence summary</th><th>GDG/clinical perspective</th><th>Impact</th></tr>
<tr><td><u>Evidence identified from literature search</u>
1 Cochrane review demonstrated significantly greater improvement in a range of depression outcomes for adults with depression treated with the collaborative care model in the short-term and long-term compared to a range of controls[1].

A RCT found that a multi-component programme for managing depression in primary care was more effective in improving treatment response and remission rates than usual care[2].

In addition there were two RCTs that reported on different approaches to offering collaborative care[3,4]. All approaches were equivalent in their effectiveness.

A cost-effectiveness analysis of depression case management undertaken by healthcare assistants in</td><td>The GDG highlighted the CADET trial, a RCT which compares the clinical effectiveness of collaborative care with usual care (GP decided care-non specified) in the management of patients with moderate to severe depression within UK in primary care had published. Mean depression were significantly lower in participants receiving collaborative care than in those receiving usual care at four months, and at 12 months. Participants receiving collaborative care were significantly more satisfied with treatment than those receiving usual care.

However a GDG member indicated that they felt the effect size was fairly small and unlikely to overturn the current recommendations.</td><td>The basis of provision of care recommended in CG90 is by a stepped care approach which was established in the original 2004 guideline. Collaborative care is recommended for those with a chronic condition only in CG91 (Depression in a chronic physical health problem). However, for severe depression individuals should be referred to a specialist mental health team for a programme or coordinated multi-professional care.

Within CG90 collaborative care was found to be marginally more effective than other comparators (28 RCTs). However, the GDG expressed a desire to see stronger evidence and a cost effectiveness analysis with a comparison to stepped care-before a recommendation for collaborative care could be made. The GDG highlighted the publication of the CADET trial</td></tr>
</table>

small primary care practices in Germany concluded that this approach was cost-effective[5]. A RCT of a web-delivered care management and patient self-management program for recurrent depression was found to more effective in reducing symptoms compared to specialist mental health care[6].		as a time point when to reconsider this area for update. A research recommendation 4.8 was also made in relation to collaborative care setting duration minimums and comparator profile. The CADET trial has now published and indicates that collaborative care is more effective than usual care. This study does not fully meet the research recommendation in the guideline that required a RCT to be of 18 months duration and have a clearly defined stepped care comparator. The Cochrane review identified in the literature search is likely to contain many of the original RCTS identified in CG90 from 2009 and also contains some trials from individuals with chronic conditions. Collaborative care has a greater effect size for those with a chronic condition.
Clinical area 2: Low intensity psychosocial interventions-recommendation 1.4.2 (1.4.2.1-1.4.2.4)		
Q. In depression, does self-guided self-help or peer support improve outcomes compared with other interventions?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence identified from Evidence Update A meta-analysis of 7 RCTs of self-guided psychological treatment demonstrated a small but significant effect of self-guided self-help on depression at follow up[7].	No GDG feedback was provided for this clinical area.	CG90 recommends offering one or more low-intensity psychosocial interventions (specifically, individual guided self-help based on CBT, CCBT or structured group physical activity). The current guidance does not include mention of self-help interventions without involvement of a professional coach or therapist to guide the patient (that is, self-guided self-help). This is potentially a low cost, low intensity intervention that could be included. The Evidence Update concluded that there was possible benefits from peer support, self-help delivered

		without professional support and other low cost, low intensity psychosocial interventions that are not currently included in guidance and these areas should be considered for update.
Clinical area 3: High intensity psychosocial interventions-recommendations 1.4.3, 1.5.1.1., 1.5.1.2, 1.5.1.4, 1.5.3.1-1.5.3.7		
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following (either alone or in combination with pharmacotherapy)improve outcomes compared with other interventions (including treatment as usual): CBT, BT/behavioural activation, Interpersonal therapy (IPT), counselling, problem solving, psychodynamic psychotherapy, family interventions/couples therapy, acceptance and commitment therapy, psychoeducation, systemic interventions, cognitive analytic therapy, solution focussed therapy, self-help (guided).		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence identified from Evidence update Two systematic reviews which supported guideline recommendations for psychological interventions for depression were identified [8,9]. **Evidence identified from literature search** **3 year** Through the high level RCT search 13 studies relevant to the clinical question were identified. The majority of studies supported current guideline recommendations and provided evidence of the effectiveness of CCBT, MBCT and group CBT (in older individuals)[10,11-14]. Additionally new evidence which was judged to be in line with current recommendations on behavioural activation, problem solving and short-term psychodynamic psychotherapy were identified [15,16 17-19,20]. The evidence on manualised narrative therapy was inconclusive on its effectiveness when compared to wait list control[21]. However, 1 RCT showed that sertraline was effective in primary-care patients with milder forms of	One GDG member highlighted that the existing guideline has endorsed access to CBT at the expense of access to other equally effective therapies and by depriving patients of choice has also led to continued increases in anti-depressant prescribing which the guideline did not recommend this impact has potentially limited the benefits that the guideline could have achieved.	NICE CG90 recommends group-based CBT at Step 2 for people who decline low-intensity psychosocial interventions. For people with persistent sub threshold depressive symptoms or mild to moderate depression who have not benefited from low level intensity interventions CG90 recommends either an antidepressant or one of the following: • CBT • IPT • Behavioural activation • behavioural couples therapy For those who decline these options then counselling or short term psychodynamic psychotherapy should be considered. There is evidence that numerous psychotherapies have similar efficacy. The NMA included 7 therapies and indicated these all were very similar with regard to their effectiveness. This may indicate that the guideline could reflect a greater choice of therapy for Step 2 treatment. This is confirmed by the GDG response that

depression when compared to CBT or placebo[22]. **4 year** A network meta-analysis (NMA) which compared the efficacy of 7 psychotherapeutic interventions (198 studies) found that psychotherapeutic interventions was superior to a wait list control[23]. However, relative effects of different psychotherapeutic interventions on depressive symptoms were absent or small. Likewise, a meta-analysis of 115 studies for CBT for the treatment of adult depression, alone and in comparison with other treatments indicated that CBT is effective [24]. However, CBT was no more or less effective than other psychotherapies or pharmacotherapy. Combined treatment was significantly more effective than pharmacotherapy or psychotherapy alone. A RCT investigated the effect of telephone-administered vs face-to-face CBT on adherence to therapy and depression outcomes among primary care patients with a major depressive disorder (MDD)[25]. CBT over the telephone compared with face-to-face resulted in lower attrition and close to equivalent improvement in depression at post treatment. In addition 3 studies provided evidence which was in line with current recommendations for the effectiveness of CBT, psycho-educational group program [26] [27] [28].		a greater choice of therapy could enhance service provision. In addition there is new evidence relating to the mode of delivery for CBT therapy (either face-to-face or via telephone) which was not addressed in the guideline for this level of care. This new evidence may impact on clinical practice. The 3 year literature review found a RCT which potentially may address a research recommendation 4.5. The efficacy of CBT compared with anti-depressants and placebo for persistent sub threshold depressive symptoms. Currently medication is not usually given to these individuals until they have had a Step 1 intervention or had symptoms for greater than 2 years.
Clinical area 4: Pharmacological interventions-recommendations 1.5.2.2-1.5.2.4		

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which drugs (either not covered by the previous guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo?
– TCAs
– duloxetine
– desvenlafaxine
– escitalopram
– agomelatine
– St John's wort
– antipsychotics (for example, quetiapine)

Evidence summary	GDG/clinical perspective	Impact
Evidence identified from Evidence Update The evidence update highlighted 5 systematic reviews that potentially impact on the guideline recommendations regarding the use of pharmacological therapies. • A meta-analysis indicated that there was no clinically relevant differences in efficacy or effectiveness for the treatment of acute, continuation and maintenance phases of MDD using second generation antidepressants[29]. • A systematic review found escitalopram to be marginally more effective than other antidepressants in MDD [30]. • A systematic review on the harms and benefits of reboxetine which included both published and unpublished RCTs indicated that reboxetine showed no significant difference in remission rates compared to placebo and was inferior to selective serotonin reuptake inhibitor SSRIs (fluoxetine, paroxetine and citalopram) for remission rates and response rates[31]. Reboxetine was inferior to placebo for both harm outcomes and was shown to	Health economic advice from within CCP indicates that the costs of some of the pharmaceuticals have changed significantly which may affect the results of the health economic model. However, whilst a GDG member noted that there are some new antidepressants on the horizon nothing was currently changing clinical practice.	When an antidepressant is to be prescribed, NICE CG90 advises that it should normally be a SSRI in a generic form. This was based on the evidence presented in CG90 that indicated SSRIs are as effective as other antidepressants and have a favourable risk–benefit ratio. A NMA by Cipriani et al. (2009) identified within CG90 indicated that sertraline had superior efficacy to other SSRIs and other pharmaceutical options, but the study had various limitations and the clinical difference was deemed to be small. This data formed the basis of a health economic model within CG90 the results of which did not take into account adverse events. The health economic analysis indicated that seraltine should be potentially first choice as it was the most cost effective. However the GDG did not make a recommendation for a specific SSRI. The studies identified by the Evidence Update indicate: • There is some support for the current guidance that a generic SSRI is usually the preferred first choice of antidepressant drug. However, there is

be inferior to fluoxetine for withdrawals due to adverse events. • A systematic review on venlafaxine and duloxetine in MDD treatment found both were significantly more effective than placebo [32]. Compared with SSRIs, venlafaxine showed significantly improved response rate but not remission rate; there were no significant differences between venlafaxine and tricyclic antidepressants (TCAs) for efficacy outcomes. Discontinuation due to adverse events was significantly higher with venlafaxine compared with SSRIs but was similar to TCAs. There was no significant difference in efficacy between duloxetine and SSRIs, although there were significantly more discontinuations due to adverse events. Duloxetine resulted in significantly higher discontinuation rates due to adverse events than venlafaxine. • A Cochrane review of treatment with second-generation antipsychotics in MDD or dysthymia identified 4 RCTs that compared quetiapine monotherapy with placebo [33]. Although significant efficacy benefits of treatment were noted, the authors suggested that the results should be interpreted with caution. Furthermore, acceptability to patients was significantly reduced because of increased adverse events. **<u>Evidence identified from literature search</u>** **3 Year** Two systematic reviews indicated that both TCAs and SSRIs are effective for depression treated in primary care and that the benefit of antidepressant medication compared with placebo increases with severity of		new evidence which may suggest a more specific choice could be made. • There is evidence to suggest additional advice on reboxetine may be appropriate. • There is evidence to support NICE CG90 advice that there is an increased likelihood of discontinuation due to tolerability issues with venlafaxine and duloxetine compared with SSRIs. This evidence may also have implications for sequencing of treatments. In addition new evidence identified from the high level literature search indicates that; • There are very little, if any, differences in efficacy between classes of pharmaceuticals such as SNRIs, SSNIs and third generation drugs. To date there has been no full analysis comparing all different classes of drugs let alone the individual drugs within each class. • New agents are available that should be considered for Step 2 therapy • There are new physical treatments and adjunctive treatments that are potentially effective in treating depression. Other identified evidence indicates that the cost of certain drugs (particularly venaflaxine) have changed since the guideline was published. This may well impact on the cost-effectiveness of certain pharmacological options.

depression symptoms and may be minimal or non-existent, in patients with mild or moderate symptoms[34,35]. 4 RCTs were identified on the effectiveness of SSRIs in the treatment of adults with depression[36-39]. These provided an equivocal evidence base for the effectiveness of these agents. As such, the identified new evidence was considered unlikely to change the current guideline recommendations at this time point. **4 year** **New antidepressant since guideline 2011** • **Agomelatine:** 2 studies have meta-analysed the evidence for agomelatine (a melatonergic antidepressant) for treatment of depression[40,41]. Both analyses indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venaflaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression. • **Levomilnacipran sustained release:** 1 RCT demonstrated that levomilnacipran sustained release improves depressive symptoms and functioning relative to placebo in patients with MDD[42]. • **Quetiapine** A meta-analysis of 3 RCTs of quetiapine extended release (XR) in adults with MDD indicated that the overall response and remission rates were higher for individuals treated with quetiapine than those with placebo[43]. Discontinuation rate due to adverse event were greater in the quetiapine group.		

An RCT found that long-term functioning and sleep quality in patients with MDD on extended-release quetiapine maintenance treatment following stabilisation with quetiapine XR was significantly improved compared to placebo[44]. In addition 9 RCTS for unlicensed drugs were identified: 5 RCTs for vortioxetine (Technology Appraisal due to start in 2014)[45 46 47 48 49], 1 RCT for GSK372475[50], 1 RCT for ziprasidone[51] and 2 studies on desvenlafaxine[52,53] . **Antidepressant v active comparator +/placebo** • 1 Cochrane systematic review which assessed the efficacy of fluoxetine in comparison to monoamine oxidase inhibitors (MOIAs), TCA, SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs) and newer agents (171 studies in total) in individuals with MDD was identified[54]. The review indicated that there may be differences in terms of relative efficacy and tolerability within classes and individual antidepressants particularly in regards to sertraline (more effective) and venlafaxine (less tolerable). • 1 study indicated that milnacipran (SNRI) and paroxetine (SSRI) showed comparable efficacy in terms of improvement in symptoms of depression in individuals with MDD[55]. New evidence that was in line with the evidence presented within CG90 was identified for the following antidepressants:		

• 1 Cochrane systematic review indicated that amitriptyline is effective in patients with MDD[65]. • 1 RCT indicated that duloxetine was effective in reducing symptoms in individuals with non MDD compared to placebo[66]. • A meta-analysis comparing desvenlafaxine with venlafaxine indicated that the two drugs were comparable in terms of safety and efficacy in the treatment of depression[51]. • 4 RCTs indicate that pioglitazone[67] oral scopolamine[68], triiodothyronine[69] or gaboxadol[70] provide no additional benefit compared to antidepressant alone in the treatment of depression.		
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which other drugs or physical therapies are effective in treating depression (as monotherapy or augmentation of antidepressants)?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence identified from 4 year literature search</u> **New Physical treatments (monotherapy)** • A RCT indicated that laser acupuncture may show some clinical benefit compared to placebo acupuncture for the treatment of major depression[56]. • A RCT found that individuals with MDD treated with a single injection of botulinum toxin were significantly less depressed at 6 weeks compared to placebo[57]. **Augmentation with physical therapy** • One RCT indicated that augmentation of pharmacological treatment with electrical	No GDG feedback was provided for this clinical area.	A small number of trials have been identified that have looked at therapies not reviewed within the guideline for depression. It may be worth considering these areas within the scoping process when the guideline is updated.

acupuncture may have some clinical benefit in patients with MDD[58]. • A RCT indicated that achronotherapeutic intervention (wake and light therapy) was more effective in treating depression symptoms in patients treated duloxetine than exercise [59]. The patients treated with exercise also showed a clinically relevant antidepressant response. • 2 RCTs and 1 systematic review indicated that facilitated physical activity as an adjunctive treatment for adults with depression in individuals with symptoms of depression was no more effective than usual care[60,61,62]. **Combination therapy with other agents** • Two RCTS indicated that augmentation of an antidepressant with another agent (vitamin D[63], oral creatine monohydrate[64] was effective in improving depression measures.		

On-going research

4. The IAPT pbr pilot (payment by results) has published and is now been extended with final results expected by 2016 therefore it is not possible to determine any potential impact on guideline recommendations. However, data from this trial may contribute towards the evidence base relating to management of depression in adults in future surveillance reviews.

Anti-discrimination and equalities considerations

5. None identified.

Implications for other NICE programmes

6. This guideline relates to a Quality Standard on depression in adults (published 2011).
7. Two of the quality statements are likely to be affected by the proposed areas for update.

Conclusion

8. Through the review of CG90 new evidence which may potentially change the direction of guideline recommendations was identified in the following areas:
    a. Service delivery (collaborative care)
    b. Low level psychosocial interventions for depression
    c. High level psychosocial interventions for depression
    d. Pharmacological interventions for moderate to severe depression

9. For all other areas of the guideline no evidence was identified which would impact on recommendations.

Surveillance recommendation

10. GE is asked to consider the proposal to update the guideline as a standard update. GE are asked to note that this 'yes to update' proposal will not be consulted on.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Katy Harrison– Technical Analyst

Centre for Clinical Practice
November 2013

References

1. Archer J, Bower P, Gilbody S et al. (2012) Collaborative care for depression and anxiety problems. Cochrane database of systematic reviews (Online) 10:2012.

2. Aragones E, Lluis PJ, Caballero A et al. (2012) Effectiveness of a multi-component programme for managing depression in primary care: A cluster randomized trial. The INDI project. Journal of Affective Disorders 142:15.

3. Fortney JC, Pyne JM, Mouden SB et al. (1-4-2013) Practice-based versus telemedicine-based collaborative care for depression in rural federally qualified health centers: a pragmatic randomized comparative effectiveness trial. American Journal of Psychiatry 170:414-425.

4. Cooper LA, Ghods Dinoso BK, Ford DE et al. (2013) Comparative effectiveness of standard versus patient-centered collaborative care interventions for depression among African Americans in primary care settings: The BRIDGE study. Health Services Research 48:February.

5. Gensichen J, Petersen JJ, Von KM et al. (2013) Cost-effectiveness of depression case management in small practices. British Journal of Psychiatry 202:June.

6. Hunkeler EM, Hargreaves WA, Fireman B et al. (2012) A web-delivered care management and patient self-management program for recurrent depression: A randomized trial. Psychiatric Services 63:01.

7. Cuijpers P, Donker T, Johansson R et al. (2011) Self-guided psychological treatment for depressive symptoms: a meta-analysis. PLoS ONE [Electronic Resource] 6:e21274.

8. Cuijpers P, Clignet F, van MB et al. (2011) Psychological treatment of depression in inpatients: A systematic review and meta-analysis. Clinical Psychology Review 31 :(3) (pp 353-360).

9. Cuijpers P, Geraedts AS, Van OP et al. (2011) Interpersonal psychotherapy for depression: A meta-analysis. American Journal of Psychiatry 168 :(6) (pp 581-592).

10. Krishna M, Jauhari A, Lepping P et al. (2011) Is group psychotherapy effective in older adults with depression? A systematic review. International Journal of Geriatric Psychiatry.26 (4) (pp 331-340), 2011.Date of Publication: April 2011. 331-340.

11. Kojima R, Fujisawa D, Tajima M et al. (2010) Efficacy of cognitive behavioral therapy training using brief e-mail sessions in the workplace: a controlled clinical trial. Industrial Health 48:495-502.

12. Godfrin KA and van HC. (2010) The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: A randomized controlled study.[Erratum appears in Behav Res Ther. 2011 Feb;49(2):144]. Behaviour Research & Therapy 48:738-746.

13. Geschwind N, Peeters F, Drukker M et al. (2011) Mindfulness training increases momentary positive emotions and reward experience in adults vulnerable to depression: A randomized controlled trial. [References]. Journal of Consulting and Clinical Psychology 79:618-628.

14. Clarke G, Kelleher C, Hornbrook M et al. (2009) Randomized effectiveness trial of an Internet, pure self-help, cognitive behavioral intervention for depressive symptoms in young adults. [References]. Cognitive Behaviour Therapy 38:222-234.

15. Bohlmeijer ET, Fledderus M, Rokx TAJJ et al. (2011) Efficacy of an early intervention based on acceptance and commitment therapy for adults with depressive symptomatology: Evaluation in a randomized controlled trial. [References]. Behaviour Research and Therapy 49:62-67.

16. Samad Z, Brealey S, and Gilbody S. (2011) The effectiveness of behavioural therapy for the treatment of depression in older adults: A meta-analysis. International Journal of Geriatric Psychiatry.26 (12) (pp 1211-1220), 2011.Date of Publication: December 2011. 1211-1220.

17. Arean PA, Raue P, Mackin RS et al. (2010) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. [References]. The American Journal of Psychiatry 167:1391-1398.

18. Cape J, Whittington C, Buszewicz M et al. (2010) Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. [Review] [86 refs]. BMC Medicine 8:38.

19. Cuijpers P, van Straten A, Bohlmeijer E et al. (2010) The effects of psychotherapy for adult depression are overestimated: A meta-analysis of study quality and effect size. [References]. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences 40:211-223.

20. Cuijpers P, van Straten A, Smit F et al. (2009) Is psychotherapy for depression equally effective in younger and older adults? A meta-regression analysis. [References]. International Psychogeriatrics 21:16-24.

21. Vromans LP and Schweitzer RD. (2011) Narrative therapy for adults with major depressive disorder: improved symptom and interpersonal outcomes. SO: Psychotherapy research : journal of the Society for Psychotherapy Research 21:4-15.

22. Hegerl U, Hautzinger M, Mergl R et al. (2010) Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. International Journal of Neuropsychopharmacology 13:31-44.

23. Barth J, Munder T, Gerger H et al. (2013) Comparative Efficacy of Seven Psychotherapeutic Interventions for Patients with Depression: A Network Meta-Analysis. PLoS Medicine 10:e1001454.

24. Cuijpers P, Berking M, Andersson G et al. (2013) A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Canadian Journal of Psychiatry 58:July.

25. Mohr DC, Ho J, Duffecy J et al. (2012) Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: A randomized trial. JAMA - Journal of the American Medical Association 307:30.

26. Gould RL, Coulson MC, and Howard RJ. (2012) Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. Journal of the American Geriatrics Society 60:1817-1830.

27. Casanas R, Catalan R, del Val JL et al. (2012) Effectiveness of a psycho-educational group program for major depression in primary care: A randomized controlled trial. BMC Psychiatry 12.

28. Cuijpers P, Hollon SD, Van SA et al. (2013) Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open 3:e002542.

29. Gartlehner G, Hanse R, Morgan L et al. (2011) Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder. Annals of Internal Medicine 155:772-785.

30. Ali MK and Lam RW. (2011) Comparative efficacy of escitalopram in the treatment of major depressive disorder. Neuropsychiatric Disease and Treatment 7 :(1) (pp 39-49).

31. Eyding D, Lelgemann M, Grouven U et al. (16-10-2010) Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 341 :(7777) (pp 816).

32. Schueler Y-B, Koesters M, Wieseler B et al. (2011) A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. Acta Psychiatrica Scandinavica 123 :(4) (pp 247-265).

33. Komossa K, Depping AM, Gaudchau A et al. (2010) Second-generation antipsychotics for major depressive disorder and dysthymia. Komossa.Katja., Depping.Anna.M., Gaudchau.Andrea., Kissling.Werner., Leucht.Stefan.Second generation.antipsychotics.for major.depressive.disorder.and dysthymia.Cochrane Database of Systematic Reviews: Reviews 2010 Issue.12 John Wiley & Sons., Ltd Chiche .

34. Arroll B, Elley CR, Fishman T et al. (2009) Antidepressants versus placebo for depression in primary care. [Review] [66 refs]. Cochrane Database of Systematic Reviews CD007954.

35. Fournier JC, DeRubeis RJ, Hollon SD et al. (6-1-2010) Antidepressant drug effects and depression severity: a patient-level meta-analysis. [Review] [30 refs]. JAMA 303:47-53.

36. Fang Y, Yuan C, Xu Y et al. (2011) A pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or thyroid hormone in adult Chinese patients with treatment-resistant major depression. [References]. Journal of Clinical Psychopharmacology 31:638-642.

37. Kasper S, Baldwin DS, Larsson LS et al. (2009) Superiority of escitalopram to paroxetine in the treatment of depression. European Neuropsychopharmacology 19:229-237.

38. Kendrick T, Chatwin J, Dowrick C et al. (15-1-2009) Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. Health Technology Assessment (Winchester, England) 13:iii-iiv.

39. Martinez JM, Katon W, Greist JH et al. (2012) A pragmatic 12-week, randomized trial of duloxetine versus generic selective serotonin-reuptake inhibitors in the treatment of adult outpatients in a moderate-to-severe depressive episode. International Clinical Psychopharmacology 27:17-26.

40. Demyttenaere K, Corruble E, Hale A et al. (2013) A pooled analysis of six month comparative efficacy and tolerability in four randomized clinical trials: agomelatine versus escitalopram, fluoxetine, and sertraline. CNS spectrums 18:Jun.

41. Kasper S, Corruble E, Hale A et al. (2013) Antidepressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control. International Clinical Psychopharmacology 28:12-19.

42. Asnis GM, Bose A, Gommoll CP et al. (2013) Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: A phase 3, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 74:March.

43. Maneeton N, Maneeton B, Srisurapanont M et al. (2012) Quetiapine monotherapy in acute phase for major depressive disorder: A meta-analysis of randomized, placebo-controlled trials. BMC Psychiatry 12.

44. Sheehan DV, Locklear J, Svedsater H et al. (2012) Long-term functioning and sleep quality in patients with major depressive disorder treated with extended-release quetiapine fumarate. International Clinical Psychopharmacology 27:September.

45. Katona C, Hansen T, and Olsen CK. (2012) A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. International Clinical Psychopharmacology 27:215-223.

46. Alvarez E, Perez V, Dragheim M et al. (2012) A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. International Journal of Neuropsychopharmacology 15:June.

47. Baldwin DS, Loft H, and Dragheim M. (2012) A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). European Neuropsychopharmacology 22:July.

48. Jain R, Mahableshwarkar AR, Jacobsen PL et al. (2013) A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5A mg vortioxetine in adults with major depressive disorder. International Journal of Neuropsychopharmacology 16:March.

49. Mahableshwarkar AR, Jacobsen PL, and Chen Y. (2013) A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Current Medical Research and Opinion 29:March.

50. Learned S, Graff O, Roychowdhury S et al. (2012) Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder: Two randomized, placebo- and active-controlled clinical trials. Journal of Psychopharmacology 26:May.

51. Papakostas GI, Vitolo OV, IsHak WW et al. (2012) A 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder. Journal of Clinical Psychiatry 73:December.

52. Liebowitz MR, Tourian KA, Hwang E et al. (2013) A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry 13.

53. Papakostas GI, Culpepper L, Fayyad RS et al. (19-7-2013) Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol.

54. Magni LR, Purgato M, Gastaldon C et al. (2013) Fluoxetine versus other types of pharmacotherapy for depression. SO: Cochrane Database of Systematic Reviews .

55. Kamijima K, Hashimoto S, Nagayoshi E et al. (2013) Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression. Neuropsychiatric Disease and Treatment 9:24.

56. Quah-Smith I, Smith C, Crawford JD et al. (2013) Laser acupuncture for depression: A randomised double blind controlled trial using low intensity laser intervention. Journal of Affective Disorders 148:June.

57. Wollmer MA, De BC, Kalak N et al. (2012) Facing depression with botulinum toxin: A randomized controlled trial. Journal of Psychiatric Research 46:May.

58. Qu S-S, Huang Y, Zhang Z-J et al. (2013) A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. Journal of Psychiatric Research 47:June.

59. Martiny K, Refsgaard E, Lund V et al. (2012) A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. Journal of Clinical Psychiatry 73:September.

60. Chalder M, Wiles NJ, Campbell J et al. (2012) Facilitated physical activity as a treatment for depressed adults: Randomised controlled trial. BMJ (Online) 344:e2758.

61. Pfaff JJ, Alfonso H, Newton RU et al. (6-7-2013) ACTIVEDEP: a randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. Br J Sports Med .

62. Danielsson L, Noras AM, Waern M et al. (22-3-2013) Exercise in the treatment of major depression: A systematic review grading the quality of evidence. Physiother Theory Pract .

63. Khoraminya N, Tehrani-Doost M, Jazayeri S et al. (2013) Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Australian and New Zealand Journal of Psychiatry 47:March.

64. Lyoo IK, Yoon S, Kim T-S et al. (2012) A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. American Journal of Psychiatry 169:01.

65. Leucht C, Huhn M, and Leucht S. (2012) Amitriptyline versus placebo for major depressive disorder. Cochrane database of systematic reviews (Online) 12:2012.

66. Hellerstein DJ, Stewart JW, McGrath PJ et al. (2012) A randomized controlled trial of duloxetine versus placebo in the treatment of nonmajor chronic depression. Journal of Clinical Psychiatry 73:July.

67. Sepanjnia K, Modabbernia A, Ashrafi M et al. (2012) Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: Randomized double-blind placebo-controlled trial. Neuropsychopharmacology 37:August.

68. Khajavi D, Farokhnia M, Modabbernia A et al. (2012) Oral scopolamine augmentation in moderate to severe major depressive disorder: A randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 73:November.

69. Garlow SJ, Dunlop BW, Ninan PT et al. (2012) The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. Journal of Psychiatric Research 46:November.

70. Kasper S, Ebert B, Larsen K et al. (2012) Combining escitalopram with gaboxadol provides no additional benefit in the treatment of patients with severe major depressive disorder. International Journal of Neuropsychopharmacology 15:July.

Appendix 1 Decision matrix

Surveillance and identification of triggers for updating CG90. The table below provides summaries of the new evidence identified for the clinical questions.

Chapter 5- Case identification				
Q. What methods are effective in identifying people with depression in primary care and community settings, including sexual health clinics, emergency departments, and drug and alcohol services?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. In which populations (excluding those with chronic physical health problems) should identification methods be used?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. What are appropriate ways to promote adherence?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. What are appropriate ways to promote adherence?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), how can equal access to services for all be ensured? [What promotes access to effective care particularly for people with learning difficulties, acquired cognitive impairment and language difficulties?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence	No relevant evidence	No relevant evidence	None	No relevant evidence

identified	identified	identified		identified
Q. In the treatment of depression, are there specific clinician approaches that improve outcomes?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Chapter 5- Service delivery				
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which models of care produce the best outcomes? • **collaborative care** • **stepped care** • **case management** • **stratified (matched) care** • **attached professional model**				

Evidence update	3 year review	4 year review	Other evidence	Comments Recs 5.5.9.1-2
No areas that would 'impact' were identified • A number of areas not specifically covered by CG90 were highlighted: • The EU also reported that although unlikely to affect current guidance, limited evidence suggests that there is value in psychiatric assessments to support GPs. • NICE CG90 does not explicitly discuss referral pathways. Although referral of patients who have not responded to treatment to a practitioner with a specialist interest in treating depression is recommended, there is no mention of referral to specialist services to aid assessment and diagnosis. Such issues were considered in a systematic review[1]. • The EU also found evidence in a systematic review that suggests that pharmacist interventions could improve adherence to antidepressants. • • In addition an RCT on stepped care and an analysis of medication management that supports, CG90 were highlighted[2,3]. •	**None identified**	**New evidence which could potentially impact recommendations** **Collaborative care** 1 Cochrane review[4] (which included 79 trials) demonstrated significantly greater improvement in depression outcomes for adults with depression treated with the collaborative care model in the short-term and long-term. There was evidence of benefit in secondary outcomes including medication use, mental health, quality of life, and patient satisfaction, although there was less evidence of benefit in physical quality of life. A cluster RCT found that a multi-component programme for managing depression in primary care was more effective in improving treatment response and remission rates than usual care[5]. However, the severity of depression was not significantly different between the groups at the end of treatment. In addition there were two RCTs that reported on different approaches to offering collaborative care[6,7]. All approaches were equivalent in their effectiveness.	**New evidence which could potentially impact recommendations** **Collaborative care** The GDG highlighted the CADET trial a RCT which compares the clinical effectiveness of collaborative care with usual care (GP decided care-non specified) in the management of patients with moderate to severe depression within UK in primary care. Short term outcomes were measured at 4 months and medium term at 12 months. Mean depression scores were significantly lower in in participants receiving collaborative care than in those receiving usual care at four months, and at 12 months. Participants receiving collaborative care were significantly more satisfied with treatment than those receiving usual care.	**New evidence which could potentially impact recommendations?** The basis of provision of care in CG90 is by a stepped care approach which was established in the original 2004 guideline. Collaborative care is recommended for those with a chronic condition (CG91). However, for severe depression individuals should be referred to a specialist mental health team for a programme or coordinated multi-professional care. Within CG90 collaborative care was marginally more effective than other comparators in CG90 (28 RCTS) but the GDG expressed a desire to see stronger evidence and cost effectiveness with a comparison to stepped care- before a recommendation for collaborative care could be made. They highlighted the on-going CADET trial for when to reconsider this area

		A cost-effectiveness analysis of depression case management undertaken by healthcare assistants in small primary care practices in Germany concluded that this approach was cost-effective[8]. A RCT of a web-delivered care management and patient self-management program for recurrent depression was found to more effective in reducing symptoms compared to specialist mental health care[9].	However a GDG member indicated that they felt the effect size was fairly small and unlikely to overturn the recommendation.	for update. This study has just published. A research recommendation was also made in relation to collaborative care setting duration minimums and comparator profile. The CADET trial has now published and indicates that collaborative care is more effective than usual care. This study does not fully meet the research recommendation in the guideline that required a RCT to be of 18 months duration and have a clearly defined stepped care comparator. It should also be noted that Cochrane review is likely to contain many/all of the original RCTS identified in CG90 from 2009. It seems likely given the time difference that many of the studies may also include those with chronic conditions. It should be noted that collaborative care **is** recommended in CG91 for those with a chronic condition as the effect size is greater in this population.

Q. Are different models appropriate to the care of people in different phases of the illness, such as treatment resistant depression and relapse prevention?				
Evidence Update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
None identified	**None identified**	**Insufficient new evidence which could potentially impact recommendations** A stepped care relapse prevention program for depression in older people was found to be no more effective that care as usual in one RCT[10].	**None**	**No new evidence that impacts recommendations** No specific recommendations are made in CG90 for this group of people with regards to service delivery and relapse prevention. As the stepped care option in this RCT is not the same as that given in CG90 there is no conclusive evidence that this question within CG90 requires updating at this time.

7. Low intensity psychosocial interventions

Q. New intervention: New clinical question: In depression, does self-guided self-help improve outcomes compared with other interventions?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
New evidence which could potentially impact recommendations Evidence suggests possible benefits from peer support, self-help delivered without professional support and other low cost, low intensity psychosocial interventions that are not currently included in guidance. A meta-analysis of 7 RCTs of self-guided psychological treatment demonstrated a small but	**New evidence which could potentially impact recommendations** The same systematic review of self-guided self-help, indicated that self-guided psychological treatment has a small clinical benefit in improving depressive	**No new evidence that impacts recommendations** A RCT which compared self-help for depression via E-mails compared to emails containing depression information was identified[13]. The	**None**	**New evidence which could potentially impact recommendations** CG90 recommends offering one or more low-intensity psychosocial interventions (specifically, individual

significant effect of self-guided self-help on depression at follow up[11]. A meta-analysis examined 17 RCTs of psychological treatments in low-income to middle-income countries found an overall benefit of such therapies compared with usual care[12]. Although the implications for guidelines in the UK are limited, the low cost of some interventions (for example, use of lay counsellors and primary care workers) shown to be effective makes them worthy of further investigation in a developed healthcare setting.	symptomatology[11].	results suggest that the e-mails were able to increase participants' use of evidence-based self-help, but that this did not improve depression more than an attention control.		guided self-help based on CBT, CCBT or structured group physical activity). The current guidance does not include mention of self-help interventions without involvement of a professional coach or therapist to guide the patient (that is, self-guided self-help). This is potentially a low cost, low intensity intervention that could be included.

Q. In depression, does guided self-help improve outcomes compared with other interventions?

Evidence update	3 year review	4 year review	Other evidence	Comments
No areas that would 'impact' were identified One systematic review provides limited evidence supporting guided self-help[14].	**None identified**	**No evidence that conflicts CG90 was identified** Two RCTs which supports the effectiveness of guided self-help either CBT[15] or internet-based psychodynamic guided self-help treatment[16] were identified.	**None**	**New evidence is consistent with guideline recommendations**

Q. Does computerised CBT (CCBT) improve patient outcomes compared with other treatments?

Evidence update	3 year review	4 year review	Other evidence	Comments
None identified	**None identified**	**No evidence that conflicts CG90**	**Insufficient evidence provided**	**New evidence is consistent with**

		was identified Three studies that support the guideline recommendations in relation to CCBT were identified. • A meta-analysis found CCBT to be effective in the short term but there was no significant clinical effect at long term follow-up[17]. • A systematic review of psychotherapy for sub-clinical depression in older adults found that CCBT was an effective intervention for reducing depressive symptoms in comparison to waiting list control[18]. CCBT was at least as effective as group CBT in reducing depressive symptoms. • One RCT indicated that delivery of CCBT using a mobile application can result in clinically significant improvements in outcomes for patients with depression[19].	A GDG member indicated that there is evidence that brief dynamic therapy should be a first-line and that indicates CCBT should not be a first-line treatment. However no references were not provided and have not been identified by surveillance searches for RCTs.	**guideline recommendations**
In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following improve outcomes compared with other interventions? **– exercise** **– support including groups, befriending, and non-statutory provision** **– programmes to facilitate employment**				

Evidence update	3 year review	4 year review	Other evidence	Comments
Insufficient new evidence to justify guideline alterations. **Peer support** A systematic review assessed the efficacy of peer support compared with group-based CBT in 7 studies[20]. No significant difference was found between treatment approaches. The review also compared peer support to usual care and found benefits in reducing depressive symptoms .Although the evidence is unlikely to affect NICE CG90, in view of the low cost of peer support, further research on its value at step 2 is desirable. **Physical activity programmes** The recommendation for physical activity programmes receives some support from current evidence (2 systematic reviews)[21,22], and limited evidence also suggests that shorter programmes may be as effective as longer programmes.	**No new evidence that impacts was identified** **Physical activity programmes** Two studies relevant to the clinical question were identified on physical activity[22,23]. Generally they indicated that it may have a short term beneficial effect in adults with depression. This is in keeping with the current recommendations	**No new evidence that impacts was identified** **Physical activity programmes** Three systematic reviews, 2 in older individuals[24,25] and 1 in all ages of adulthood[26] found that exercise was associated with significantly lowering of depression severity. A systematic review also indicated that walking has a statistically significant, large effect on the symptoms of depression in some populations[27] .	**None**	**New evidence is consistent with guideline recommendations**

Chapter 8 High Intensity psychosocial interventions

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following (either alone or in combination with pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual):
CBT
BT/behavioural activation
- **Interpersonal therapy (IPT)**
- **counselling/person-centred therapy**
- **problem solving**
- **psychodynamic psychotherapy**

Family interventions/couples therapy
ACT (acceptance and commitment therapy)
Systemic interventions
Psychoeducation
Cognitive analytic therapy (CAT)
Solution-focused therapy
Self-help, including guided self-help
CCB

Evidence update	3 year review	4 year review	Other evidence	Comments Recs 8.11.2, 8.11.3
No areas that would 'impact' were identified A systematic review confirms that the psychological interventions appear to have a small but statistically significant additional effect on depression compared with alternative approaches[28]. A meta-analysis which confirms that IPT is an effective high-intensity psychological treatment, in accordance with current guidance was also	**New evidence which could potentially impact recommendations** **CBT** Through the high level RCT search numerous studies relevant to the clinical question were identified. One RCT showed that sertraline was effective in primary-care patients with milder forms of depression	**New evidence which could potentially impact recommendations** **CBT** A network meta-analysis (NMA) which compared the efficacy of 7 psychotherapeutic interventions (198 studies) found that psychotherapeutic interventions was superior to a waitlist control [42] . Relative effects of different psychotherapeutic	**New evidence which could potentially impact recommendations** **GDG feedback**. One GDG member highlighted that the existing guideline has endorsed access to CBT at the expense of access to other equally effective therapies and by	**New evidence which could potentially impact recommendations** NICE CG90 recommends group-based CBT at Step 2 for people who decline low-intensity psychosocial interventions. For people with persistent sub threshold depressive symptoms or mild to moderate depression who have not benefited from low

highlighted[29].	when compared to CBT or placebo[30]. The remaining evidence supported the effectiveness of CCBT, indicated that MBCT showed some effectiveness and group CBT showed some effectiveness in older individuals[31-35]. Additionally studies on Behavioural activation, Problem solving short-term psychodynamic psychotherapy that were judged to be in line with current recommendations[36-41].	interventions on depressive symptoms were absent to small. A meta-analysis of 115 studies for CBT for adult depression, alone and in comparison with other treatments indicated that CBT is effective [43]. CBT was no more or less effective than other psychotherapies or pharmacotherapy. Combined treatment was significantly more effective than pharmacotherapy alone. A RCT investigated the effect of telephone-administered vs face-to-face CBT on adherence to therapy and depression outcomes among primary care patients with MDD[44]. CBT over the telephone compared with face-to-face resulted in lower attrition and close to equivalent improvement in depression at post treatment. The following evidence is in line with current recommendations: • A meta-analysis of CBT for depression in older people indicated CBT is effective compared to control[45]. • A RCT indicated that a	depriving patients of choice has also led to continued increases in anti-depressant prescribing which the guideline did not recommend this impact has potentially limited the benefits that the guideline could have achieved.	level intensity interventions CG90 recommends either an antidepressant or one of the following: • CBT • IPT • Behavioural activation • behavioural couples therapy • For those who decline these options then counselling or short term psychodynamic psychotherapy should be considered. There is evidence that numerous psychotherapies have similar efficacy. The NMA included 7 therapies this would indicate that the guideline may need updating to reflect a greater choice of therapy for Step 2 treatment. This is confirmed by the GDG response that a greater choice of therapy could enhance service provision. The mode of delivery for CBT therapy either face-to-face or via telephone was not covered in the guideline for this Step level of care. Hence this new evidence may impact

		psycho-educational group program was effective in the short and long-term in treatment for patients with mild depression symptoms[46]. • A meta-analysis[47] indicated that that CBT has an enduring effect following termination of the acute treatment. No significant difference in relapse after the acute phase CBT versus continuation of pharmacotherapy after remission was reported.		on clinical practice. In addition the 3 year review found a RCT which potentially may address a research recommendation 8.12.1.3. The efficacy of CBT compared with anti-depressants and placebo for persistent sub threshold depressive symptoms. Currently medication is not a given to these individuals at until they have had Step interventions.
Q. Does mode of delivery (group-based or individual) impact on outcomes?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. Are there specific therapist characteristics that improve outcomes?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. Are there specific patient characteristics (for example, anxiety, previous episodes) that predict outcomes?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified
Q. Are brief interventions (for example, 6 to 8 weeks) effective?				

Evidence update	3 year review	4 year review	Other evidence	Comments Recs 8.11.4 and 8.11.5
None identified	**None identified**	**New evidence which could potentially impact recommendations** A systematic review and meta-analysis of brief psychotherapy for depression was identified[48]. The systematic review found brief psychotherapies to be more efficacious than control and conclude that depression can be efficaciously treated with 6-8 to sessions of psychotherapy, particularly CBT and problem-solving therapy.	**None**	**Insufficient new evidence to impact recommendations** The guideline makes various recommendations about the duration of treatment with high intensity psychological interventions. In general 16-20 sessions over 3-4months is recommended for most therapies. For those with persistent sub threshold symptoms 6-10 treatments over 8-12 weeks is recommended. It was not clear from the abstract the type of depression included and comparisons were to control only. This evidence was therefore considered to be in line with that already detailed in the guideline.

Q. Are psychological interventions harmful?

Evidence update	3 year review	4 year review	Other evidence	Comments
No relevant evidence identified	No relevant evidence identified	No relevant evidence identified	None	No relevant evidence identified

Pharmacological interventions Chapters 9/10

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which

drugs (either not covered by the previous guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo?
– TCAs
– duloxetine
– desvenlafaxine
– escitalopram
– agomelatine
– St John's wort
– antipsychotics (for example, quetiapine)

Evidence update	3 year review	4 year review	Other evidence	Comments **Recs** 10.14.1-3
New evidence that could potentially impacts the recommendations A comprehensive meta-analysis to assess the comparative benefits and harms of second generation antidepressants in MDD was identified[49]. The review found no clinically relevant differences in efficacy or effectiveness for the treatment of acute, continuation and maintenance phases of MDD. There were some differences in relation to adverse events and discontinuation rates. Another study assessed the efficacy of escitalopram in MDD compared with other antidepressant drugs in a systematic review of 6 pooled analyses[50]. Escitalopram was marginally more effective than other antidepressants. A systematic review included both published and unpublished RCTs comparing the SNRIs, reboxetine, with placebo and/or SSRIs[51]. A total of 13 acute treatment trials were included. Reboxetine showed no significant difference in remission rates from placebo. Reboxetine was inferior to placebo for both harm outcomes. Reboxetine was shown to be inferior to SSRIs (fluoxetine, paroxetine and	**No evidence that would impact the recommendations** **Placebo-controlled RCTs of antidepressants** 2 systematic reviews indicated that both TCAs and SSRIs are effective for depression treated in primary care and that the at the benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or non-existent, on average, in patients with mild or moderate symptoms[54,55]. **SSRIs** 4 RCTs were identified. Overall, the evidence is mixed on the effectiveness of SSRIs in the treatment of adults with depression[56-59]. As such, the identified new evidence is unlikely to change the current guideline recommendations.	**New evidence which could potentially impact recommendations** **New antidepressant (not reported in CG) drugs since 2011** • **Agomelatine:** 2 studies have meta-analysed the evidence for agomelatine a melatonergic antidepressant, for treatment of depression[60,61]. Both analyses indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venaflaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression. • **Levomilnacipran sustained release**1 RCT demonstrated that levomilnacipran sustained release [62] improves depressive symptoms and functioning relative to placebo in patients with	**New evidence which could potentially impact recommendations** The costs of some of the pharmaceuticals have changed significantly which may affect the results of the health economic model. A GDG member noted that there are some new antidepressants on the horizon but nothing changing clinical practice.	**New evidence which could potentially impact recommendations** When an antidepressant is to be prescribed, NICE CG90 advises that it should normally be a SSRI in a generic form because SSRIs are as effective as other antidepressants and have a favourable risk–benefit ratio. It should be noted that a meta-analysis by Cipriani et al. (2009) also identified an antidepressant drug (sertraline) with superior efficacy to other SSNRIs and pharmaceutical options although there were limitations to this study and the clinical difference was small. This was incorporated into a health economic model within CG90 the results of which did not take into account adverse events which are a problem for some of these drugs. The HE analysis and NMA

citalopram) for remission rates and response rates and reboxetine was inferior to fluoxetine for withdrawals due to adverse events. A systematic review which assessed 54 RCTs of venlafaxine, 14 RCTs of duloxetine and two direct comparisons in major depression was highlighted[52]. Both therapies were significantly more effective than placebo. Compared with SSRIs, venlafaxine showed significantly improved response rate but not remission rate; there were no significant differences between venlafaxine and tricyclic antidepressants (TCAs) for either efficacy outcome. Discontinuation due to adverse events was significantly higher with venlafaxine compared with SSRIs but was similar to TCAs. There was no significant difference in efficacy between duloxetine and SSRIs, although there were significantly more discontinuations due to adverse events. Duloxetine resulted in significantly higher discontinuation rates due to adverse events than venlafaxine. **Antipsychotic drugs** A Cochrane review of treatment with second-generation antipsychotics in MDD or dysthymia was highlighted[53]. Four RCTs compared quetiapine monotherapy with placebo. Although significant efficacy benefits of treatment were noted, the authors suggested that the results should		MDD. • **Quetiapine** A meta-analysis of 3 RCTs of quetiapine extended release in adults with MDD indicated that the overall response and remission rates were higher for individuals treated with quetiapine than those with placebo[63]. Discontinuation rate due to adverse event were greater in the quetiapine group. • An RCT found that long-term functioning and sleep quality in patients with MDD on extended-release quetiapine maintenance treatment following stabilisation with quetiapine XR was significantly improved compared to placebo[64]. In addition the 9 RCTS for unlicensed drugs were identified: • 5 RCTs for vortioxetine (Technology Appraisal due to start in 2014)[65 66 67 68 69], 1 RCT for GSK372475[70], 1 RCT ziprasidone [71] and 2 studies on desvenlafaxine[72 73] . **Placebo-controlled RCTs of**		indicated that seraltine should be first choice-the GDG did not make a recommendation for a specific SSRI. The studies identified by the EU indicate: • Some supports current guidance that a generic selective serotonin reuptake inhibitor is usually the preferred first choice of antidepressant drug, though new evidence may suggest a more specific choice could be made. • There is also evidence to suggest additional advice on reboxetine may be appropriate. • Whilst the evidence supports NICE CG90 advice that there is an increased likelihood of discontinuation due to tolerability issues with venlafaxine and duloxetine compared with SSRIs. This evidence may also have implications for sequencing of treatments. In addition new evidence

be interpreted with caution. Furthermore, acceptability to patients was significantly reduced because of increased adverse events. The review also included one RCT comparing quetiapine and duloxetine, which found no efficacy benefits but reduced tolerability. NICE CG90 recommendations do not include quetiapine as therapy at step 3 (although quetiapine augmentation may be considered after initial inadequate response) and this limited evidence supports this view.		**antidepressants** New evidence that was in line with the evidence presented within CG90 was identified for the following antidepressants: 1 Cochrane systematic review indicated that amitriptyline is effective in patients with major depressive disorder[74]. 1 RCT indicated that duloxetine was effective in reducing symptoms in individuals with non MDD compared to placebo [75]. **Antidepressant v active comparator +/placebo** **Fluoxetine** 1 Cochrane systematic review[76] of fluoxetine in comparison to MOIAs, TCA, SSRIs, SNRIs and newer agents (171 studies in total) in individuals with MDD was identified. The review indicated that there may be differences in terms of relative efficacy and tolerability within classes and individual antidepressants particularly in regards to sertraline and		identified from the high level literature search indicates that; • There is very little, if any differences in efficacy between classes of pharmaceuticals such as SNRIs, SSNIs and third generation drugs. To date there has been no full analysis comparing all different classes of drugs let alone the individual drugs within each class. • New agents are available that should be considered for Step 2 therapy. • There are new physical treatments and adjunctive treatments that are potentially effective in treating depression.

		venlafaxine. 1 study indicated that milnacipran (SNRI) and paroxetine (SSRI) showed comparable efficacy in terms of improvement in symptoms of depression in individuals with MDD[77] . A meta-analysis comparing desvenlafaxine with venlafaxine indicated that the two drugs were comparable in terms of safety and efficacy in the treatment of depression[78] .		

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which other drugs or physical therapies are effective in treating depression (as monotherapy or augmentation of antidepressants)?

Evidence update	3 year review	4 year review	Other evidence	Comments
No evidence that could potentially impact the recommendations	**No evidence that could potentially impact the recommendations**	**New Physical treatments - Monotherapy** A RCT indicated that laser acupuncture may show some clinical benefit compared to	**None**	A small number of trials have been identified that have looked at therapies not reviewed within the guideline for depression. It may be worth considering these areas within

		placebo acupuncture indicated for the treatment of major depression[79] . A RCT found that individuals with MDD treated with a single injection of botulinum toxin were significantly less depressed as measured on the HDRS at 6 weeks compared to placebo[80]. **Combination therapy with other agents** Two RCTS indicated that augmentation of an antidepressant with another agent (vitamin D[81], oral creatine monohydrate[82] was effective in improving depression measures. Whereas 4 RCTs indicated that pioglitazone [83] oral scopolamine[84], triiodothyronine[85] or gaboxadol[86] provided no additional benefit compared to antidepressant alone in the treatment of depression. **Augmentation with physical therapy** One RCT indicated that		the scoping process when the guideline is updated.

		augmentation of pharmacological treatment with electrical acupuncture may have some clinical benefit in patients with MDD[87]. A RCT indicated that achronotherapeutic intervention (wake and light therapy) was more effective in treating than exercise in reducing depression symptoms in patients with MDD treated with duloxetine[88]. The patients treated with exercise, also had a clinically relevant antidepressant response. 2 RCTs and 1 systematic review indicated that facilitated physical activity as an adjunctive treatment for adults with depression in individuals with symptoms of depression was no more effective than usual care[89,90,91].		
11. Factors influencing choice of anti-depressants				
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), to what extent do the following factors affect the choice of drug?				

– adverse events (in particular, cardio toxicity), including long-term adverse events, discontinuation problems				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No evidence that could potentially impact the recommendations A RCT which indicated that PST in elderly depressed patients, delivered by highly qualified or experienced therapists, appears to reduce depressive symptoms in parallel with a reduction in disability, compared with usual therapy, suggesting that such an intervention may be a consideration for future guidance reviews[92].	**No evidence that could potentially impact the recommendations** **The pharmacological management of depression with psychotic symptoms** 1 RCT indicated that mifepristone was no more effective than placebo[93].	**No evidence that could potentially impact the recommendations** **Older Patients** A systematic review of the efficacy of antidepressants older depressed patients indicated that all classes of antidepressant were more effective than placebo in achieving response[94]. In achieving remission however, only pooling all 3 classes of antidepressants showed a statistically significant difference from placebo. **The pharmacological management of depression with psychotic symptoms** A systematic review concluded that antidepressant-antipsychotic co-treatment was superior to	**None**	**New evidence is consistent with guideline recommendations**

		monotherapy with either drug class in the acute treatment of psychotic depression[95]. **Depression, antidepressants and Suicide** Results from an RCT indicate that fluoxetine increases suicide ideation less than placebo during treatment of adults with minor depressive disorder over a 12 week period[96].		
Q. In people whose depression has atypical features, what are the most effective treatment strategies?				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No relevant evidence identified	**No relevant evidence identified**	**No relevant evidence identified**	**None**	**No relevant evidence identified**
12 The pharmacological and physical management of depression that has not adequately responded to treatment, and relapse prevention				
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following improve outcomes compared with other interventions? – ECT – TMS (integrate NICE Interventional Procedure Guidance) – - light therapy – VNS – neurosurgery				

– deep brain stimulation				
Evidence update	**3 year review**	**4 year review**	**Other evidence**	**Comments**
No evidence that could potentially impact the recommendations **Sequencing treatments after initial inadequate response** Current recommendations for augmentation of antidepressant therapies with antipsychotics appear to be supported by a Cochrane review[53]. A meta-analysis indicated that adjunctive atypical antipsychotic treatment was significantly more effective than placebo for both response to treatment and remission in patients with non-psychotic unipolar MDD resistant to prior antidepressant treatment[97]. A pooled analysis of two RCTs in patients with MDD provided evidence to support the NICE CG90 recommendation for augmentation with antipsychotic medication with quetiapine[98].	**None identified**	**No evidence that could potentially impact the recommendations** **Sequencing treatments after initial inadequate response** A systematic review of the efficacy and safety of aripiprazole, olanzapine/fluoxetine combination, quetiapine, and risperidone[99] for the adjunctive treatment for treatment-resistant MDD in adults indicated all were effective on remission and on clinician-rated depression severity measures. However on measures of functioning and quality of life, these medications produced either no benefit or a very small benefit. A systematic review of antidepressant combination for MDD in incomplete responders identified 5 studies with combinations involving mianserin, mirtazapine and desipramine[100]. The review concluded that the practice of using a combination of antidepressants for major depression in incomplete responders is not warranted by the literature. A RCT comparing an early switch to a conventional strategy in patients with MDD to duloxetine found no differences in the primary end points[101].	None	**New evidence is consistent with guideline recommendations** NICE CG90 recommends the addition of an antipsychotic medication, such as quetiapine, in patients with an inadequate response to antidepressants. EU evidence supports this. The evidence found relating to switching treatments is in line with that presented in the guideline, as is the evidence on ECT, psychosocial therapies.

		One RCT indicated that combining pramipexole, and escitalopram for the treatment of MDD resistant depression was no more effective than either agent alone[102]. Whereas pooled data from 3 RCTs found that adjunctive aripiprazole in patients with MDD who showed minimal response to initial antidepressant therapy was clinically meaningful[97]. A RCT indicated that vortioxitene (unlicensed) was more effective than placebo in the prevention of relapse in patients with MDD[103] . **Adjunctive with psychosocial therapies** An RCT indicates that CBT as an adjunct to pharmacotherapy for primary care based patients is more effective that TAU for reducing symptoms of depression in individuals with resistant depression[104]. A small RCT (n=16) that compared MCBT with psycho-education for patients with major depression who did not achieve remission following antidepressant treatment indicated that MBCT was more effective than psyco-education[105]. **Adjunctive with Physical interventions** A patient-level meta-analysis of studies evaluating vagal nerve stimulation therapy for treatment-resistant depression indicated that the augmentation of treatment as usual		

		with vagal nerve stimulation was produced greater response and remission rates[106]. A RCT compared combined and monotherapy o**f** transcranial direct current stimulation (tDCS) with sertraline in individuals with MDD. The combined treatment showed more efficacy than either monotherapy which were comparable[107]. Whereas in another study tDCS was not effective as an augmentation treatment for resistant MDD[108].		

Q. In the treatment of depression, which patient characteristics predict response and relapse? For example, childhood trauma, age of onset, number of previous episodes, gender, and so on?

Evidence update	3 year review	4 year review	Other evidence	Comments
No relevant evidence identified	**No relevant evidence identified**	**No relevant evidence identified**	**None**	**No relevant evidence identified**

Q. In people whose depression has responded to treatment, what psychological and psychosocial strategies are effective in preventing relapse (including maintenance treatment)?
In people whose depression has responded to treatment, what strategies are effective in preventing relapse (including maintenance treatment)?

Evidence update	3 year review	4 year review	Other evidence	Comments
No evidence that could potentially impact the recommendations **Psychological interventions** Evidence demonstrating the value of psychological therapies to reduce relapses supports current guidance was identified.	**None identified**	**No evidence that could potentially impact the recommendations** **Psychological interventions** A systematic review by the HTA	GDG Feedback stated that a number of studies have provided more cautionary evidence about the role	**New evidence is consistent with guideline recommendations** Evidence appears to support current recommendations for continued therapy to prevent

• 3 systematic reviews confirmed the effectiveness of MBCT in reducing the risk of relapse and support the NICE CG90 recommendation for use of MBCT in relapse prevention for patients at significant risk of relapse[109-111]. • A meta-analysis found that adjunctive treatment with IPT significantly reduced the recurrence rate compared with pharmacotherapy alone for relapse prevention[29]. The EU concluded this may be a consideration for future reviews of NICE CG90. **Medication for relapse prevention** Two meta-analyses (Glue et al. (2010) Kok et al. (2011)) showed that continued therapy with all drug classes reduced the risk of relapse compared with placebo[112,113]. **Electroconvulsive therapy (ECT)** An RCT provides some support for the recommendation of NICE CG90 that bilateral ECT is more effective than unilateral ECT[114]. **Transcranial magnetic stimulation** A systematic review by found evidence of moderate efficacy but there was no evidence (from 9 studies) for treatment effects lasting beyond 12 weeks[115]. A systematic review found that slow-frequency repetitive TMS had a moderate positive effect considered comparable to that of fast-frequency repetitive TMS[116].		found that there was inadequate evidence to determine the clinical effectiveness or cost-effectiveness of low-intensity interventions for the prevention of relapse or recurrence of depression[117]. An RCT indicated that MBCT in recurrent depressed patients in addition to treatment as usual was more effective at reducing post-treatment depressive symptoms than TAU[118]. Whereas another RCT found that MCBT was comparable to structured patient education in the treatment of recurrent depression in patients in remission from depression[119]. **Medication for relapse prevention** A Cochrane systematic review[120] on continuation and maintenance treatments for preventing relapse of depression in older people concluded continuing antidepressant medication for 12 months appears to be helpful. An RCT indicated that desvenlafaxine was effective	of MBCT in preventing recurrences/relapse than would be implied by the firm endorsement of MBCT in the current guideline (references not provided). They then stated that MBCT may not be as effective as previously thought other than in groups with particular features (E.g. unstable recovery, sexual abuse as a child). It is also **not** an option that many patients seem to want. No evidence in line with these statements has been found in the surveillance process.	relapse, although further research is needed to determine the optimal treatment regimen. NICE CG90 recommends individual CBT or MBCT as psychological interventions for relapse prevention in people who are at significant risk of relapse The evidence confirms the recommendation of NICE CG90 (to continue therapy for at least 2 years if at risk of relapse), although further research is needed to determine the optimal treatment regimen for relapse prevention. NICE CG90 notes that there are no major safety concerns with TMS used in severe depression, but recommends its use is restricted to research studies until optimal methods are determined. The recent evidence supports this view.

		compared to placebo in preventing relapse for a 6 month period in individuals with MDD who demonstrated a stable initial 20 week response to desvenlafaxine[121]. A RCT indicated that St John's wort was comparable to sertraline in preventing relapse in individuals with MDD[122]: **Transcranial magnetic stimulation** A meta-analysis of high-frequency repetitive TMS indicates that this approach accelerates and enhances the clinical response and remission to antidepressants in major depression compared to sham[123]. **ECT** An RCT indicated that in severe depression, high-dose ultra-brief right unilateral ECT appears to show matching acute antidepressant response to an equally high-dose brief pulse right unilateral ECT[124].		
13 Pharmacological and Psychological interventions for sub threshold depressive symptoms and persistent sub threshold depressive symptoms (dysthymia)				

Evidence update	3 year review	4 year review	Other Evidence	Comments
No evidence that could potentially impact the recommendations A systematic review and meta-analysis that included 6 RCTs of antidepressants (amitriptyline, fluoxetine, isocarboxazid and paroxetine) compared with placebo in patients with minor depression[125]. There was no significant difference between treatment arms in response to treatment or acceptability.	**None identified**	**None identified**	**None**	**New evidence is consistent with guideline recommendations** NICE CG90 does not recommend the routine use of antidepressants to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor, although they may be considered for some patients.

References for decision matrix

1. van der Feltz-Cornelis CM, Van Os TWDP, Van Marwijk HWJ et al. (2010) Effect of psychiatric consultation models in primary care. A systematic review and meta-analysis of randomized clinical trials. Journal of Psychosomatic Research 68 :(6) (pp 521-533).

2. Seekles W, Van SA, Beekman A et al. (7-7-2011) Stepped care treatment for depression and anxiety in primary care. A randomized controlled trial. Trials 12.

3. Oestergaard S and Moldrup C. (2011) Optimal duration of combined psychotherapy and pharmacotherapy for patients with moderate and severe depression: A meta-analysis. Journal of Affective Disorders 131 :(1-3) (pp 24-36).

4. Archer J, Bower P, Gilbody S et al. (2012) Collaborative care for depression and anxiety problems. Cochrane database of systematic reviews (Online) 10:2012.

5. Aragones E, Lluis PJ, Caballero A et al. (2012) Effectiveness of a multi-component programme for managing depression in primary care: A cluster randomized trial. The INDI project. Journal of Affective Disorders 142:15.

6. Fortney JC, Pyne JM, Mouden SB et al. (1-4-2013) Practice-based versus telemedicine-based collaborative care for depression in rural federally qualified health centers: a pragmatic randomized comparative effectiveness trial. American Journal of Psychiatry 170:414-425.

7. Cooper LA, Ghods Dinoso BK, Ford DE et al. (2013) Comparative effectiveness of standard versus patient-centered collaborative care interventions for depression among African Americans in primary care settings: The BRIDGE study. Health Services Research 48:February.

8. Gensichen J, Petersen JJ, Von KM et al. (2013) Cost-effectiveness of depression case management in small practices. British Journal of Psychiatry 202:June.

9. Hunkeler EM, Hargreaves WA, Fireman B et al. (2012) A web-delivered care management and patient self-management program for recurrent depression: A randomized trial. Psychiatric Services 63:01.

10. Apil SRA, Hoencamp E, Judith Haffmans PM et al. (2012) A stepped care relapse prevention program for depression in older people: A randomized controlled trial. International Journal of Geriatric Psychiatry 27:June.

11. Cuijpers P, Donker T, Johansson R et al. (2011) Self-guided psychological treatment for depressive symptoms: A meta-analysis. PLoS ONE 6 :(6).

12. Van't Hof E, Cuijpers P, Waheed W et al. (2011) Psychological treatments for depression and anxiety disorders in Low- and middle- income countries: a meta-analysis. African Journal of Psychiatry 14:200-207.

13. Morgan AJ, Jorm AF, and Mackinnon AJ. (2013) Self-Help for Depression via E-mail: A Randomised Controlled Trial of Effects on Depression and Self-Help Behaviour. PLoS ONE 8:e66537.

14. Cuijpers P, Donker T, Van SA et al. (2010) Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. [Review]. Psychological medicine 40:1943-1957.

15. Williams C, Wilson P, Morrison J et al. (2013) Guided Self-Help Cognitive Behavioural Therapy for Depression in Primary Care: A Randomised Controlled Trial. PLoS ONE 8:e52735.

16. Johansson R, Sjoberg E, Sjogren M et al. (2012) Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. PloS one 7:e36905.

17. So M, Yamaguchi S, Hashimoto S et al. (2013) Is computerised CBT really helpful for adult depression?-A meta-analytic re-evaluation of CCBT for adult depression in terms of clinical implementation and methodological validity. BMC Psychiatry 13.

18. Krishna M, Honagodu A, Rajendra R et al. (2013) A systematic review and meta-analysis of group psychotherapy for sub-clinical depression in older adults. International Journal of Geriatric Psychiatry 28:881-888.

19. Watts S, Mackenzie A, Thomas C et al. (2013) CBT for depression: A pilot RCT comparing mobile phone vs. computer. BMC Psychiatry 13.

20. Pfeiffer PN, Heisler M, Piette JD et al. (2011) Efficacy of peer support interventions for depression: A meta-analysis. General Hospital Psychiatry 33 :(1) (pp 29-36).

21. Driessen E, Cuijpers P, Hollon SD et al. (2010) Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. Journal of Consulting and Clinical Psychology 78 :(5) (pp 668-680).

22. Krogh J, Nordentoft M, Sterne JAC et al. (2011) The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Psychiatry 72 :(4) (pp 529-538).

23. Lindwall M, Larsman P, and Hagger MS. (2011) The reciprocal relationship between physical activity and depression in older European adults: A prospective cross-lagged panel design using SHARE data. [References]. Health Psychology 30:453-462.

24. Bridle C, Spanjers K, Patel S et al. (2012) Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. British Journal of Psychiatry 201:180-185.

25. Chi I, Jordan-Marsh M, Guo M et al. (2013) Tai chi and reduction of depressive symptoms for older adults: A meta-analysis of randomized trials. Geriatrics and Gerontology International 13:January.

26. Rimer J, Dwan K, Lawlor DA et al. (2012) Exercise for depression. [Update of Cochrane Database Syst Rev. 2009;(3):CD004366; PMID: 19588354]. Cochrane Database of Systematic Reviews 7:CD004366.

27. Robertson R, Robertson A, Jepson R et al. (2012) Walking for depression or depressive symptoms: A systematic review and meta-analysis. Mental Health and Physical Activity 5:66-75.

28. Cuijpers P, Clignet F, van MB et al. (2011) Psychological treatment of depression in inpatients: A systematic review and meta-analysis. Clinical Psychology Review 31 :(3) (pp 353-360).

29. Cuijpers P, Geraedts AS, Van OP et al. (2011) Interpersonal psychotherapy for depression: A meta-analysis. American Journal of Psychiatry 168 :(6) (pp 581-592).

30. Hegerl U, Hautzinger M, Mergl R et al. (2010) Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. International Journal of Neuropsychopharmacology 13:31-44.

31. Krishna M, Jauhari A, Lepping P et al. (2011) Is group psychotherapy effective in older adults with depression? A systematic review. International Journal of Geriatric Psychiatry.26 (4) (pp 331-340), 2011.Date of Publication: April 2011. 331-340.

32. Kojima R, Fujisawa D, Tajima M et al. (2010) Efficacy of cognitive behavioral therapy training using brief e-mail sessions in the workplace: a controlled clinical trial. Industrial Health 48:495-502.

33. Godfrin KA and van HC. (2010) The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: A randomized controlled study.[Erratum appears in Behav Res Ther. 2011 Feb;49(2):144]. Behaviour Research & Therapy 48:738-746.

34. Geschwind N, Peeters F, Drukker M et al. (2011) Mindfulness training increases momentary positive emotions and reward experience in adults vulnerable to depression: A randomized controlled trial. [References]. Journal of Consulting and Clinical Psychology 79:618-628.

35. Clarke G, Kelleher C, Hornbrook M et al. (2009) Randomized effectiveness trial of an Internet, pure self-help, cognitive behavioral intervention for depressive symptoms in young adults. [References]. Cognitive Behaviour Therapy 38:222-234.

36. Bohlmeijer ET, Fledderus M, Rokx TAJJ et al. (2011) Efficacy of an early intervention based on acceptance and commitment therapy for adults with depressive symptomatology: Evaluation in a randomized controlled trial. [References]. Behaviour Research and Therapy 49:62-67.

37. Samad Z, Brealey S, and Gilbody S. (2011) The effectiveness of behavioural therapy for the treatment of depression in older adults: A meta-analysis. International Journal of Geriatric Psychiatry.26 (12) (pp 1211-1220), 2011.Date of Publication: December 2011. 1211-1220.

38. Arean PA, Raue P, Mackin RS et al. (2010) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. [References]. The American Journal of Psychiatry 167:1391-1398.

39. Cape J, Whittington C, Buszewicz M et al. (2010) Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. [Review] [86 refs]. BMC Medicine 8:38.

40. Cuijpers P, van Straten A, Bohlmeijer E et al. (2010) The effects of psychotherapy for adult depression are overestimated: A meta-analysis of study quality and effect size. [References]. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences 40:211-223.

41. Cuijpers P, Dekker J, Hollon SD et al. (2009) Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. Journal of Clinical Psychiatry 70:1219-1229.

42. Barth J, Munder T, Gerger H et al. (2013) Comparative Efficacy of Seven Psychotherapeutic Interventions for Patients with Depression: A Network Meta-Analysis. PLoS Medicine 10:e1001454.

43. Cuijpers P, Berking M, Andersson G et al. (2013) A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Canadian Journal of Psychiatry 58:July.

44. Mohr DC, Ho J, Duffecy J et al. (2012) Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: A randomized trial. JAMA - Journal of the American Medical Association 307:30.

45. Gould RL, Coulson MC, and Howard RJ. (2012) Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. Journal of the American Geriatrics Society 60:1817-1830.

46. Casanas R, Catalan R, del Val JL et al. (2012) Effectiveness of a psycho-educational group program for major depression in primary care: A randomized controlled trial. BMC Psychiatry 12.

47. Cuijpers P, Hollon SD, Van SA et al. (2013) Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open 3:e002542.

48. Nieuwsma JA, Trivedi RB, McDuffie J et al. (2012) Brief psychotherapy for depression: A systematic review and meta-analysis. International Journal of Psychiatry in Medicine 43:01.

49. Gartlehner G, Hanse R, Morgan L et al. (2011) Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder. Annals of Internal Medicine 155:772-785.

50. Ali MK and Lam RW. (2011) Comparative efficacy of escitalopram in the treatment of major depressive disorder. Neuropsychiatric Disease and Treatment 7 :(1) (pp 39-49).

51. Eyding D, Lelgemann M, Grouven U et al. (16-10-2010) Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 341 :(7777) (pp 816).

52. Schueler Y-B, Koesters M, Wieseler B et al. (2011) A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. Acta Psychiatrica Scandinavica 123 :(4) (pp 247-265).

53. Komossa K, Depping AM, Gaudchau A et al. (2010) Second-generation antipsychotics for major depressive disorder and dysthymia. Komossa.Katja., Depping.Anna.M., Gaudchau.Andrea., Kissling.Werner., Leucht.Stefan.Second generation.antipsychotics.for major.depressive.disorder.and dysthymia.Cochrane Database of Systematic Reviews: Reviews 2010 Issue.12 John Wiley & Sons., Ltd Chiche .

54. Arroll B, Elley CR, Fishman T et al. (2009) Antidepressants versus placebo for depression in primary care. [Review] [66 refs]. Cochrane Database of Systematic Reviews CD007954.

55. Fournier JC, DeRubeis RJ, Hollon SD et al. (6-1-2010) Antidepressant drug effects and depression severity: a patient-level meta-analysis. [Review] [30 refs]. JAMA 303:47-53.

56. Fang Y, Yuan C, Xu Y et al. (2011) A pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or thyroid hormone in adult Chinese patients with treatment-resistant major depression. [References]. Journal of Clinical Psychopharmacology 31:638-642.

57. Kasper S, Baldwin DS, Larsson LS et al. (2009) Superiority of escitalopram to paroxetine in the treatment of depression. European Neuropsychopharmacology 19:229-237.

58. Kendrick T, Chatwin J, Dowrick C et al. (15-1-2009) Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. Health technology assessment (Winchester, England) 13:iii-iiv.

59. Martinez JM, Katon W, Greist JH et al. (2012) A pragmatic 12-week, randomized trial of duloxetine versus generic selective serotonin-reuptake inhibitors in the treatment of adult outpatients in a moderate-to-severe depressive episode. International Clinical Psychopharmacology.27 (1) (pp 17-26), 2012.Date of Publication: January 2012. 17-26.

60. Demyttenaere K, Corruble E, Hale A et al. (2013) A pooled analysis of six month comparative efficacy and tolerability in four randomized clinical trials: agomelatine versus escitalopram, fluoxetine, and sertraline. CNS spectrums 18:Jun.

61. Kasper S, Corruble E, Hale A et al. (2013) Antidepressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control. International Clinical Psychopharmacology 28:12-19.

62. Asnis GM, Bose A, Gommoll CP et al. (2013) Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: A phase 3, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 74:March.

63. Maneeton N, Maneeton B, Srisurapanont M et al. (2012) Quetiapine monotherapy in acute phase for major depressive disorder: A meta-analysis of randomized, placebo-controlled trials. BMC Psychiatry 12.

64. Sheehan DV, Locklear J, Svedsater H et al. (2012) Long-term functioning and sleep quality in patients with major depressive disorder treated with extended-release quetiapine fumarate. International Clinical Psychopharmacology 27:September.

65. Katona C, Hansen T, and Olsen CK. (2012) A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. International Clinical Psychopharmacology 27:215-223.

66. Alvarez E, Perez V, Dragheim M et al. (2012) A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. International Journal of Neuropsychopharmacology 15:June.

67. Baldwin DS, Loft H, and Dragheim M. (2012) A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). European Neuropsychopharmacology 22:July.

68. Jain R, Mahableshwarkar AR, Jacobsen PL et al. (2013) A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5A mg vortioxetine in adults with major depressive disorder. International Journal of Neuropsychopharmacology 16:March.

69. Mahableshwarkar AR, Jacobsen PL, and Chen Y. (2013) A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Current Medical Research and Opinion 29:March.

70. Learned S, Graff O, Roychowdhury S et al. (2012) Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder: Two randomized, placebo- and active-controlled clinical trials. Journal of Psychopharmacology 26:May.

71. Papakostas GI, Vitolo OV, IsHak WW et al. (2012) A 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder. Journal of Clinical Psychiatry 73:December.

72. Liebowitz MR, Tourian KA, Hwang E et al. (2013) A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry 13.

73. Papakostas GI, Culpepper L, Fayyad RS et al. (19-7-2013) Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol.

74. Leucht C, Huhn M, and Leucht S. (2012) Amitriptyline versus placebo for major depressive disorder. Cochrane database of systematic reviews (Online) 12:2012.

75. Hellerstein DJ, Stewart JW, McGrath PJ et al. (2012) A randomized controlled trial of duloxetine versus placebo in the treatment of nonmajor chronic depression. Journal of Clinical Psychiatry 73:July.

76. Magni LR, Purgato M, Gastaldon C et al. (2013) Fluoxetine versus other types of pharmacotherapy for depression. SO: Cochrane Database of Systematic Reviews .

77. Kamijima K, Hashimoto S, Nagayoshi E et al. (2013) Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression. Neuropsychiatric Disease and Treatment 9:24.

78. Coleman KA, Xavier VY, Palmer TL et al. (2012) An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator. CNS Spectr. 17:131-141.

79. Quah-Smith I, Smith C, Crawford JD et al. (2013) Laser acupuncture for depression: A randomised double blind controlled trial using low intensity laser intervention. Journal of Affective Disorders 148:June.

80. Wollmer MA, De BC, Kalak N et al. (2012) Facing depression with botulinum toxin: A randomized controlled trial. Journal of Psychiatric Research 46:May.

81. Khoraminya N, Tehrani-Doost M, Jazayeri S et al. (2013) Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Australian and New Zealand Journal of Psychiatry 47:March.

82. Lyoo IK, Yoon S, Kim T-S et al. (2012) A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. American Journal of Psychiatry 169:01.

83. Sepanjnia K, Modabbernia A, Ashrafi M et al. (2012) Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: Randomized double-blind placebo-controlled trial. Neuropsychopharmacology 37:August.

84. Khajavi D, Farokhnia M, Modabbernia A et al. (2012) Oral scopolamine augmentation in moderate to severe major depressive disorder: A randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 73:November.

85. Garlow SJ, Dunlop BW, Ninan PT et al. (2012) The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. Journal of Psychiatric Research 46:November.

86. Kasper S, Ebert B, Larsen K et al. (2012) Combining escitalopram with gaboxadol provides no additional benefit in the treatment of patients with severe major depressive disorder. International Journal of Neuropsychopharmacology 15:July.

87. Qu S-S, Huang Y, Zhang Z-J et al. (2013) A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. Journal of Psychiatric Research 47:June.

88. Martiny K, Refsgaard E, Lund V et al. (2012) A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. Journal of Clinical Psychiatry 73:September.

89. Chalder M, Wiles NJ, Campbell J et al. (2012) Facilitated physical activity as a treatment for depressed adults: Randomised controlled trial. BMJ (Online) 344:e2758.

90. Pfaff JJ, Alfonso H, Newton RU et al. (6-7-2013) ACTIVEDEP: a randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. Br J Sports Med .

91. Danielsson L, Noras AM, Waern M et al. (22-3-2013) Exercise in the treatment of major depression: A systematic review grading the quality of evidence. Physiother Theory Pract .

92. Alexopoulos GS, Raue PJ, Kiosses DN et al. (2011) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. Archives of General Psychiatry 68:33-41.

93. Blasey CM, DeBattista C, Roe R et al. (2009) A multisite trial of mifepristone for the treatment of psychotic depression: a site-by-treatment interaction.[Erratum appears in Contemp Clin Trials. 2010 Jan;31(1):134], [Erratum appears in Contemp Clin Trials. 2009 Sep;30(5):497]. Contemporary Clinical Trials 30:284-288.

94. Kok RM, Nolen WA, and Heeren TJ. (2012) Efficacy of treatment in older depressed patients: A systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. Journal of Affective Disorders 141:103-115.

95. Farahani A and Correll CU. (2012) Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. Journal of Clinical Psychiatry 73:April.

96. Garlow SJ, Kinkead B, Thase ME et al. (2013) Fluoxetine increases suicide ideation less than placebo during treatment of adults with minor depressive disorder. Journal of Psychiatric Research 47:September.

97. Nelson JC, Thase ME, Bellocchio EE et al. (2012) Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. International Clinical Psychopharmacology 27:May.

98. Bauer M, El-Khalili N, Datto C et al. (2010) A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. [Review]. Journal of Affective Disorders 127:19-30.

99. Spielmans GI, Berman MI, Linardatos E et al. (2013) Adjunctive Atypical Antipsychotic Treatment for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes. PLoS Medicine 10:e1001403.

100. Rocha FL, Fuzikawa C, Riera R et al. (2013) Antidepressant combination for major depression in incomplete responders-A systematic review. Journal of Affective Disorders 144:1-6.

101. Romera I, Perez V, Menchon JM et al. (2012) Early switch strategy in patients with major depressive disorder: A double-blind, randomized study. Journal of Clinical Psychopharmacology 32:August.

102. Franco-Chaves JA, Mateus CF, Luckenbaugh DA et al. (2013) Combining a dopamine agonist and selective serotonin reuptake inhibitor for the treatment of depression: A double-blind, randomized pilot study. Journal of Affective Disorders 149:July.

103. Boulenger J-P, Loft H, and Florea I. (2012) A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. Journal of Psychopharmacology 26:November.

104. Wiles N, Thomas L, Abel A et al. (2013) Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: Results of the CoBalT randomised controlled trial. The Lancet 381:February.

105. Chiesa A, Mandelli L, and Serretti A. (2012) Mindfulness-based cognitive therapy versus psycho-education for patients with major depression who did not achieve remission following antidepressant treatment: A preliminary analysis. Journal of Alternative and Complementary Medicine 18:01.

106. Berry SM, Broglio K, Bunker M et al. (2013) A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Medical Devices: Evidence and Research 6:28.

107. Brunoni AR, Valiengo L, Baccaro A et al. (2013) The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 70:383-391.

108. Palm U, Schiller C, Fintescu Z et al. (2012) Transcranial direct current stimulation in treatment resistant depression: A randomized double-blind, placebo-controlled study. Brain Stimulation 5:July.

109. Chiesa A and Serretti A. (30-5-2011) Mindfulness based cognitive therapy for psychiatric disorders: A systematic review and meta-analysis. Psychiatry Research 187 :(3) (pp 441-453).

110. Piet J and Hougaard E. (2011) The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis. Clinical Psychology Review 31 :(6) (pp 1032-1040).

111. Guidi J, Fava GA, Fava M et al. (2011) Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. Psychological medicine 41 :(2) (pp 321-331).

112. Glue P, Donovan MR, Kolluri S et al. (2010) Meta-analysis of relapse prevention antidepressant trials in depressive disorders. Australian and New Zealand Journal of Psychiatry 44 :(8) (pp 697-705).

113. Kok RM, Heeren TJ, and Nolen WA. (2011) Continuing treatment of depression in the elderly: A systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. American Journal of Geriatric Psychiatry 19 :(3) (pp 249-255).

114. Kellner CH, Knapp R, Husain MM et al. (2010) Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. The British journal of psychiatry : the journal of mental science 196:226-234.

115. Allan CL, Herrmann LL, and Ebmeier KP. (2011) Transcranial magnetic stimulation in the management of mood disorders. Neuropsychobiology 64 :(3) (pp 163-169).

116. Schutter DJ. (2010) Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. [Review]. Psychological medicine 40:1789-1795.

117. Rodgers M, Asaria M, Walker S et al. (2012) The clinical effectiveness and cost-effectiveness of low-intensity psychological interventions for the secondary prevention of relapse after depression: a systematic review. Health technology assessment (Winchester, England) 16:May.

118. van Aalderen JR, Donders AR, Giommi F et al. (2012) The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. Psychological medicine 42:989-1001.

119. Stangier U, Hilling C, Heidenreich T et al. (2013) Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: A multicenter prospective randomized controlled trial. The American Journal of Psychiatry 170:624-632.

120. Wilkinson P and Izmeth Z. (2012) Continuation and maintenance treatments for depression in older people. Cochrane Database of Systematic Reviews 11:CD006727.

121. Rosenthal JZ, Boyer P, Vialet C et al. (2013) Efficacy and safety of desvenlafaxine 50 mg/d for prevention of relapse in major depressive disorder: A randomized controlled trial. Journal of Clinical Psychiatry 74:February.

122. Sarris J, Fava M, Schweitzer I et al. (2012) St John's wort (Hypericum perforatum) versus sertraline and placebo in major depressive disorder: continuation data from a 26-week RCT. Pharmacopsychiatry 45:Nov.

123. Berlim MT, Van Den Eynde F, and Daskalakis ZJ. (2013) High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: A meta-analysis of randomized, double-blind, and sham-controlled trials. Journal of Clinical Psychiatry 74:February.

124. Mayur P, Byth K, and Harris A. (2013) Acute antidepressant effects of right unilateral ultra-brief ECT: A double-blind randomised controlled trial. Journal of Affective Disorders 149:July.

125. Barbui C, Cipriani A, Patel V et al. (2011) Efficacy of antidepressants and benzodiazepines in minor depression: Systematic review and meta-analysis. British Journal of Psychiatry 198 :(1) (pp 11-16).