National Institute for Health and Clinical Excellence

Clinical guideline: Depression in adults update

PRE-PUBLICATION CHECK FORM

No	Organisation	NICE	Section number in FULL guideline	Page number	ERROR REPORT	Response
1	Cambridgeshire and Peterborough NHS Foundation Trust	1	GDG Members	3	The affiliation given for XXXX should be given as "Cambridgeshire and Peterborough NHS Foundation Trust" rather than just "Cambridge". Please could this be amended- Thanks, XXXX	Thank you for your comment, this has now been corrected.
2	CPC Association of Counsellors in Primary Care	1	6.1	143-146	Generally it is not possible for our organisation to comment on the factual content since the statistical analysis of the research papers quoted is not within our scope. We will defer to NICE for this and are assured that this is of the highest quality. However the whole application of the guideline stands or falls on a particular research paradigm which is not applicable to the non manualisable therapies…. This could be said to be a fact which needs urgent re examination along the Popperian grounds that once a theory or a paradigm is limited in its use, it is redundant. So much excellent and up to date research is being ignored by NICE wrt the efficacy of the traditional psychological therapies because it is either a non RCT research study or a non specific depression study. This is not useful to the making of practice based recommendations nor to the pursuance of useful treatment for real people.	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
3	CPC Association of Counsellors in Primary Care	2		150-151	. You should not be worried that 'few factors consistently predict outcomes' Of course this is so. Unlike the assumptions in the guideline the traditional relational therapies do not aim to give access to an assumed "scientific" reality of what person should be like. Instead they take the patient's own reality seriously and their symptoms seriously too – this is the aim. No outcome can be predicted in advance and therefore no standard outcome exists to compare or measure against. . Therapy is an encounter	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.

					between two people and the real work is done by the patient…whether therapy takes place or not depends on entirely on the patient …..the guideline's sections 6- 8 is based again on a misunderstanding of the nature of therapy and also on a misunderstanding of the nature of depression. Depression is presented here as if it is an isolated problem or illness not as a state relating to the whole of the self. Much has already been written about this ,(we refer you to our original critique) and although changes have been made to this draft we are still in danger of ending up with a guideline that is of little real use to health professionals who need to know who and where to refer patients who have various levels of depression with various complexities and who need to know more about the range of psychological therapies, what they offer the patient, how long a treatment process may be needed and what this will require of the patient.	
4	CPC Association of Counsellors in Primary Care	3		256-257	Statements about limited evidence, under the sections on counselling and short term psychodynamic therapy, need to be related to the limits of the research paradigm (see above) otherwise they are likely to undermine health professional confidence in effective treatments such as these.	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
5	CPC Association of Counsellors in Primary Care	4		261	The research recommendations are once again based on an RCT model and an idea of generalisability and reproducibility for a psychodynamic approach ….it is encouraging that this research is recommended but this is not going to be answered within an RCT research model.	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
6	GlaxoSmithKline	1	Depression in adults (update) – Consultation Comments with NCC Responses	191	The following studies referenced in NCC response No 586 and also relied upon by NICE in NCC responses Nos 617,618,619 and 620 are incorrectly assigned as being RCTs (Randomised Controlled Trials). The studies do not meet any common RCT definition nor the description of an RCT in these guidelines: • Judge: This is not described by the authors as an RCT. There is a randomized placebo interruption phase with no randomization between control groups. • Bogetto: This is not described by the authors as an RCT. There is no blinding or randomization with respect to the allocation of SSRIs or the timing of the interruption. The reference to blinding concerns blinding to the previous assessments.	Thank you for your comment. We apologise for our inaccurate response to comment 586. The guideline actually states 'There have been prospective studies <u>including</u> RCTs which have examined the effect of discontinuation'. This implies that the cited studies are not necessarily all RCTs.

					• Hindmarch: This is not described by the authors as an RCT. There is no randomization, especially with regard to the allocation to SSRI which is performed "under the usual clinical conditions". Some element of blinding is described with regard to the timing of placebo interruption. The interruption appears to happen at the same time. • Michelson: This is not described by the authors as an RCT. There is a randomized placebo substitution period, but the study is a comparison of SSRIs and there is no randomization to the choice of SSRI. • Rosenbaum: This is not described by the authors as an RCT. It is described as an open-label study with a randomized double-blind placebo-substitution period. The study is a comparison of SSRIs with no randomization between the SSRIs.	
7	GlaxoSmithKline	2	Full Guideline 11.10.1	391	The studies cited in this paragraph with the exception of one study, Baldwin et al, do not meet the definition of RCT. The reference to RCTs in this paragraph is therefore incorrect: "There have been prospective studies including RCTs which have examined the effect of discontinuation in people taking paroxetine compared with other antidepressants report an increase in discontinuation symptoms in those taking this drug compared with escitalopram (Baldwin et al., 2006), fluoxetine (Judge et al., 2002, Bogetto et al., 2002, Hindmarch et al., 2000, Michelson et al., 2000, Rosenbaum et al., 1998), sertraline (Hindmarch et al., 2000; Michelson et al., 2000), and citalopram (Hindmarch et al., 2000)."	Thank you for your comment. As noted above, this sentence reads 'There have been prospective studies including RCTs' which implies that the cited studies are not necessarily all RCTs.
8	David Healy	1	11.3	368-369	The surrounding sections are on the management of depression in the elderly etc. To be consistent this section should be on the management of depression in women and perhaps particularly women of child-bearing years if endocrine effects are the key issue. NICE leaves itself liable to a legal action under the Congenital Disabilities Act 1976 (see the 3rd comment below) if it does not mention at this point that antidepressants, and perhaps especially SSRIs, increase the risks of major birth defects, spontaneous abortion, primary pulmonary hypertension in the newborn as well as neonatal withdrawal syndrome, and that women of child bearing years should be informed of this and of the risks of	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.

					dependence on treatment prior to their starting treatment.	
9	David Healy	2	11.10	390-393	In this section, my impression is that no more than 20% of the literature cited, and possibly a lot less, has been written by the apparent authors. One of the most commonly cited authors in the section has recently featured in the media as having articles written for him by a pharmaceutical company. This is of relevance in that most of the literature cited is from the 1997-2002 period when "discontinuation syndromes" were at the centre of competing marketing efforts by Lilly, GlaxoSmithKline and other companies, and these companies were actively writing articles to appear under the names of friendly opinion leaders. In this section the quality of the evidence NICE cites is little better than the quality of the evidence that underpinned the first draft of the paediatric depression guideline. Linked to this issue of ghostwritten articles, there are notable conflicts of interest – not declared in the conflicts of interest section – that reach right into the construction of this guideline. This section essentially contains almost nothing that is evidence based and NICE appears to have conspicuously failed to consult the many user groups concerned with dependence on antidepressants, who would not agree with the contents of the guideline as it stands..	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
10	David Healy	3	11.10.7.1	393	Traditional definitions of physical dependence are such that the withdrawal problems that stem from antidepressants necessarily mean that antidepressants cause physical dependence. NICE seems to be offering a minority view on physical dependence. In any legal action, the meaning the patient attributes to the notion of physical dependence is likely to have primacy and in the case of women of child-bearing years telling them as the guidance advocates that they will not become physically dependent on treatment, when they may be unable to get off treatment and as a result may have	Thank you for your comment. There remains debate as to whether discontinuation symptoms alone, in the absence of tolerance and the desire to use drugs to prevent the effects of withdrawal, are sufficient to define physical dependence or dependency. To clarify our meaning we have amended recommendation 1.5.2.5 to read 'the fact that addiction does not occur with antidepressants'.

					a child borne with major birth defects would leave NICE specifically liable under the Congenital Disabilities Act (1976).	We have also inserted a section in the full guideline section 11.10 to discuss addiction, physical dependence and discontinuation symptoms.
11	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	1	10.7.1	313	Guidelines read "…..One is licensed primarily for depression, and the other for stress urinary incontinence." We propose this is changed to read "Cymbalta is licensed for major depressive disorder (MDD), generalised anxiety disorder (GAD) and diabetic peripheral neuropathic pain (DPNP) whilst Yentreve is licensed for Stress urinary incontinence (SUI)"	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
12	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	2	10.7.1	315 & 322	Guidelines read "Two trials specifically examined depression-related pain using the self-report BPI scale. There was an average reduction of three-quarters of a point (on an 11-point Likert scale) for the 'average pain in last 24 hours' item." "…….and there does not seem to be an important reduction in pain associated with depression in those trials which reported this measure (WMD = -0.74 (-1.13 to -0.34) that is, ¾ of a point difference between the groups)" We refer to the above comments and believe that there has been a major omission; the study by Brecht et al (2007) referred to above shows pain response rates of 60% & 44% for duloxetine and placebo respectively (which translate to an NNT of 6 which is clinically relevant).	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
13	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	3	10.13.1.3	358	Guidelines read "The increased likelihood of the person stopping treatment because of side effects (and the consequent need to increase the dose gradually) with venlafaxine, duloxetine and TCAs. " Please note that there is no need to increase the dose of duloxetine (The Cymbalta SPC recommends a start and maintenance dose of 60mg in the treatment of MDD) we would suggest this is reworded to read "The increased likelihood of the person stopping treatment because of side effects; and with venlafaxine and TCAs the consequent need to increase the dose gradually"	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
14	Eli Lilly and Company Limited /Boehringer	4	11.2	364	The full guideline states that 'There is no difference in the efficacy of the various antidepressants for which studies	Thank you for your comment. However, your comment relates to an issue other

	Ingelheim Ltd				have been undertaken in older adults' (based on a Cochrane meta-analysis of 15 studies by Wilson et al in 2001) and concludes that 'the evidence relating to the treatment of elderly patients was not updated as there are few new data'. However since the Cochrane review in 2001, 22 studies have been published on antidepressant treatment in the elderly (list attached below). An update of the Cochrane review in 2006 (Mottram, Wilson and Strobl, 2006) has been published which now reports differences: 'The review suggests that classical TCAs are associated with a higher withdrawal rate due to side effect experience'. In addition, a meta-analysis by Nelson et al (2008) suggests that the OR for response and remission with duloxetine is among the highest of all antidepressants (OR of 2.39 for response and 2.03 for remission at 8 weeks). Whilst paroxetine showed similar high ORs, these may have been driven by a longer study duration. The meta-analysis also reported that discontinuation rates for duloxetine were not different from placebo. A retrospective pooled data analysis (Nelson et al 2005) for patients aged 55 and older supports these findings. The estimated probability of remission was significantly higher in duloxetine treated patients than placebo patients (44.1% versus 16.1%, p=0.033).	than a factual error. Therefore we cannot respond to it.
15	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	5	12.1.16.2	433	In section 12.1.3 the GDG comment that RCTs investigating switching techniques are difficult to interpret due to selection bias, and go on to highlight that open label studies have provided meaningful results in the past in this area. Lilly provided open label evidence to support the use of duloxetine in patients who have not responded to their initial treatment. Perahia et al (2008) investigated switching strategy of direct versus tapered switch to duloxetine in patients who were SSRI partial or non-responders. The GDG appeared to only review this trial in light of the switching technique assessed (as evidenced by their response). While the study did not include a control group, secondary efficacy endpoints showed response rates of over 50% and remission rates of more than 35% in both	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.

					duloxetine arms from start to endpoint. These represent clinically meaningful results in a patient group which is usually difficult to treat. Switching to duloxetine was also associated with clinically significant improvements in pain measures in a group of patients that had significant levels of pain at baseline (mean scores of >30mm on all 6 VAS pain scales). A recent meta-analysis comparing within- versus across-class switches in patients who fail to respond to a SSRI, found that there was a statistically significant advantage in remission rates when switching patients to a non-SSRI rather than an SSRI antidepressant (Papakostas et al, 2008). To date there is no contradictory trials refuting the evidence found in the Perahia study; furthermore since reference is made to venlafaxine as a treatment option in non/poor responders to SSRIs, we would urge NICE to reconsider the inclusion of the following our original comment highlighted in the consultation phase: 12.1.16.2 When switching to another antidepressant, be aware that the evidence for the relative advantage of switching either within or between classes is weak. Consider switching to: • initially a different SSRI or a better tolerated newer-generation antidepressant • subsequently an antidepressant of a different pharmacological class that may be less well tolerated (for example venlafaxine, a TCA or an MAOI) **<u>or to duloxetine</u>**.	
16	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	7			<u>Refs</u> • Brecht S et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: A randomized controlled trials Journal of Clinical Psychiatry 2007; 68: 1707-1716 • Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly (Cochrane Review). In Cochrane Library, 2006 Issue 1. Oxford: Update Software.	

					• Nelson JC, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Kennedy JS. Duloxetine for the treatment of major depressive disorder in older patients. Am J Geriatr Psychiatry 2005; 13(3): 227-35 • Nelson JC et al. Efficacy of second generation antidepressants in late-life depression: A meta-analysis of the evidence. American Journal of Geriatric Psychiatry 2008; 16: 558-567 • Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol Psychiatry 2008; 63(7): 699-704. • Perahia DGS et al. Switching to Duloxetine From Selective Serotonin Reuptake Inhibitor Antidepressants: A Multicenter trial Comparing 2 Switching Techniques. Journal of Clinical Psychiatry 2008; 69: 95-105 • Wilson, K., Mottram, P., Sivanranthan, A., et al. Antidepressant versus placebo for depressed elderly (Cochrane Review). In Cochrane Library, 2001 Issue 2. Oxford: Update Software.	
17	Eli Lilly and Company Limited /Boehringer Ingelheim Ltd	8			22 elderly studies published since Cochrane review by Wilson in 2001: 1. Allard P, Gram L, Timdahl K, et al. Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: A double-blind, randomised 6-month comparative trial with citalopram. Int J Geriatr Psychiatry. 2004;19:1123–1130. 2. Bose A, Li D, Gandhi C. Escitalopram in the acute treatment of depressed patients aged 60 years or older. Am J Geriatr Psychiatry. 2008 Jan;16(1):14-20. 3. de Vasconcelos Cunha UG, Lopes Rocha F, Avila de Melo R, et al. A placebo-controlled double-blind randomized study of venlafaxine in the treatment of depression in dementia. Dement Geriatr Cogn Disord. 2007;24:36–41. 4. Dombrovski AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves healthrelated quality of life: A randomized, controlled trial of paroxetine and interpersonal psychotherapy. J Am Geriatr Soc. 2007;55:1325– 1332.	

5. Gastó C, Navarro V, Marcos T, et al. Single-blind comparison of venlafaxine and nortriptyline in elderly major depression. J Clin Pyschopharmacol.2003;23:21–26.
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8. Kasper S, de Swart H, Friis Andersen H. Escitalopram in the treatment of depressed elderly patients. Am J Geriatr Psychiatry. 2005;13:884–891.
9. Kok RM, Nolen WA, Heeren TJ. Venlafaxine versus nortriptyline in the treatment of elderly depressed inpatients: a randomised, double-blind, controlled trial. Int J Geriatr Psychiatry. 2007 Dec;22(12):1247-54.
10. Oslin DW, Ten Have TR, Streim JE, et al. Probing the safety of medications in the frail elderly: Evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry. 2003;64:875–882.
11. Rapaport MH, Lydiard RB, Pitts CD, Schaefer D, Bartolic EI, Iyengar M, Carfagno M, Lipschitz A. Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial. J Clin Psychiatry. 2009 Jan;70(1):46-57. Epub 2008 Oct 7.
12. Rapaport MH, Schneider LS, Dunner DL, et al. Efficacy of controlled release paroxetine in the treatment of late-life depression. J Clin Psychiatry. 2003;64:1065–1074.
13. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, Rotz BT, Mohs RC. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry. 2007 Jun;164(6):900-9.

					14. Raskin J, Wiltse CG, Dinkel JJ, et al. Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. J Clin Pyschopharmacol. 2008;28:32–38. (based on same study as Raskin et al 2007) 15. Roose SP, Sackeim HA, Krishnan KR, et al, for the Old-Old Depression Study Group. Antidepressant pharmacotherapy in the treatment of depression in the very old: A randomized, placebo-controlled trial. Am J Psychiatry. 2004;161:2050–2059. 16. Rosenberg C, Lauritzen L, Brix J, et al. Citalopram versus amitriptyline in elderly depressed patients with or without mild cognitive dysfunction: A Danish multicentre trial in general practice. Psychopharmacol Bull. 2007; 40:63–73. 17. Rossini D, Serretti A, Franchini L, et al. Sertraline versus fluvoxamine in the treatment of elderly patients with major depression: A doubleblind, randomized trial. J Clin Psychopharmacol. 2005;25:471–475. 18. Schatzberg A, Roose S. A doubleblind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry. 2006;14: 361–370. 19. Schneider LS, Nelson JC, Clary CM, et al, for the Sertraline Elderly Depression Study Group. An 8-week multicenter, parallel-group, doubleblind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry. 2003;160:1277–1285. 20. Sheikh JI, Cassidy EL, Doraiswamy PM, et al. Efficacy, safety, and tolerability of sertraline in patients with late-life depression and comorbid medical illness [published correction appears in J Am Geriatr Soc 2004;52:1228]. J Am Geriatr Soc. 2004;52:86–92. 21. Wehmeier PM, Kluge M, Maras A, et al. Fluoxetine versus trimipramine in the treatment of depression in geriatric patients. Pharmacopsychiatry. 2005;38:13–16. 22. Wilson KC, Mottram PG, Ashworth L, Abou-Saleh MT. Older community residents with depression: Long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. Br J Psychiatry.	

					2003;182:492–497.	
18	Lundbeck Ltd.	1	10.11.2	351	*Escitalopram Average Daily Dosage of 20 mg should be corrected to 10mg in Table 82 and the Unit Cost amended accordingly (this error is a transcript of an error already in Cipriani et al.)* The daily dose range for escitalopram has been directly derived from Cipriani et al. 2009. It should be noted that 10-30 mg/day was wrongly defined as the daily dose range in the Cipriani et al publication. However, in the recent Cochrane review of escitalopram by Cipriani et al. which reviewed all available study information for escitalopram, no studies were performed with a dosage above 20 mg/day. [Cipriani et al. Escitalopram versus other antidepressive agents for depression (Review); Cochrane Review, The Cochrane Library, 2009, Issue 3]. In 21 out of 22 studies the dosage of escitalopram was within the therapeutic dosage range (10 to 20 mg/day). In one study (SCT-MD-35) the escitalopram dosage was set at 4 mg/day (fixed dose). Eleven trials used a fixed- and the remaining eleven a flexible dosage regimen. The use of a fixed- or a flexible-dose regimen was consistent among comparisons within the review for the majority of included trials. However, in three out of 22 studies one of the two compounds used a fixed-dose while the other used a flexible-dose design (Burke 2002; Khan 2007; Ventura 2007). *Therefore the correct dose range should be 4-20 mg instead of 10-30 mg.* The recommended licensed dose range for escitalopram in the UK is 5mg to 20mg (Escitalopram Summary of Product Characteristics).	Thank you. The average daily dosage of escitalopam has been corrected to 10mg and the economic analysis amended accordingly.
19	Lundbeck Ltd.	2	10.11.4 & 5	353-356	By correcting the dose range and average daily dose error as detailed above, this changes the cost analyses in section 10.11.4 & 5. It is not clear from the Full Guideline how the cost effectiveness results have been obtained and it would be helpful to include more information on these calculations. However, we believe that the cost analyses need to be corrected to include a lower average daily dose of either 10	Thank you. The average daily dose has been changed to 10mg per day.

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>or 15mg for escitalopram, and that the cost-effectiveness calculations also need to be corrected accordingly, as follows:

Table 1: Antidepressant and monitoring cost for escitalopram by dose used (10, 15 and 20 mg/day)<table><tr><th></th><th>Moderate</th><th></th><th>Severe</th><th></th></tr><tr><th></th><th>Initial</th><th>Maintenance</th><th>Initial</th><th>Maintenance</th></tr><tr><td>Esc 20 mg</td><td>163</td><td>272</td><td>304</td><td>413</td></tr><tr><td>Esc 15 mg</td><td>152</td><td>239</td><td>293</td><td>380</td></tr><tr><td>Esc 10 mg</td><td>140</td><td>205</td><td>281</td><td>346</td></tr></table></td><td></td></tr>
<tr><td>20</td><td>Lundbeck Ltd.</td><td>3</td><td>10.5.3</td><td>305</td><td>Text under table 69 should state ‘Compared with individual SSRIs, there were no statistically significant differences on efficacy outcomes other than compared with citalopram, where escitalopram was more effective with a small effect size’.</td><td>Thank you, we have corrected to: there were no clinically important differences.</td></tr>
<tr><td>21</td><td>Lundbeck Ltd.</td><td>4</td><td>10.5.4</td><td>306</td><td>Text under table 70 should state ‘There were no statistically significant differences between escitalopram and duloxetine, venlafaxine or buproprion on efficacy measures, although all effect sizes favoured escitalopram’.</td><td>Thank you, we have corrected to: there were no clinically important differences.</td></tr>
<tr><td>22</td><td>Lundbeck Ltd.</td><td>5</td><td>10.7.1</td><td>321</td><td>Two tables labelled as Table 74 in this section.</td><td>Thank you this has been amended.</td></tr>
<tr><td>23</td><td>Lundbeck Ltd.</td><td>6</td><td>10.9.5</td><td>344</td><td>Table 77 missing in table numbering sequence.</td><td>Thank you this has been amended</td></tr>
<tr><td>24</td><td>Lundbeck Ltd.</td><td>7</td><td>10.11.2</td><td>347</td><td>Text reference to economic decision tree schematic refers to figure 10. Schematic labelled as figure 11.</td><td>Thank you this has been amended</td></tr>
<tr><td>25</td><td>Lundbeck Ltd.</td><td>8</td><td>10.11.2</td><td>346, 350, 351</td><td>Reference to antidepressant model stated as in section 6.3. This should be section 8.9.</td><td>Thank you this has been amended</td></tr>
<tr><td>26</td><td>ULTRASIS</td><td>1</td><td>All Sections</td><td>All pages</td><td>The footer describes the document as ‘ Depression in adults with a chronic physical health problem’</td><td>Thank you, this has been corrected.</td></tr>
<tr><td>27</td><td>ULTRASIS</td><td>2</td><td>7.1.1</td><td>P156</td><td>In the light of the guidelines conclusion on page 164 (about which, for the record, we beg to differ on) that all CCBT products are similarly effective, then it has to be accepted that all products would perform similarly when analysed against an NHS TAU comparator in primary care. However as this analysis has only been performed using the Beating the Blues data it is suggestive, as presented, that this is a peculiarity of Beating the Blues. This is further emphasised</td><td>Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.</td></tr>
</table>

					by the manner of the presentation of this analysis throughout the review, (see further comments below). Given your conclusions in the guideline this is illogical and erroneous. Please correct. If your conclusions are, in fact, meant to be 'all products are clinically effective but not necessarily the same' then you need to do a similar analysis on each one	
28	ULTRASIS	3	7.1.1	P156	'In this study, we calculated that only 61% of the population met diagnosis for either subthreshold depression or depression.' i)How was this calculated? Data provided by the authors of the RCT indicates that 217 of the 274 participants (ie 79%) were above the BDI cut-off of 14 and above) and all the participants were above a cut-off of 10 (I believe that this is consistent with minor/subthreshold depression). I imagine you also took into account the anxiety disorders – but please check your figure. ii) It is factually inconsistent to provide this calculation for Beating the Blues and not for other individual programs (although I acknowledge that you state overall 53% met full diagnostic criteria) iii) Please check for consistency with the statement about Beating the Blues above with the statement re ' caseness on a recognised scale' 'in our comment 4 below	Thank you, we have now corrected this to: In this study, we calculated that only 39% of the population met criteria for MDD. (i) This was calculated based on the data given to us by the author. (ii) Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it. (iii) Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.
29	ULTRASIS	4	7.1.2	P159	.'..... while the remainder had no formal diagnosis, although were above threshold for caseness on a recognised scale.' It is unclear whether you are referring to true depression caseness (ie DSM IV or equivalent criteria) here or are including subthreshold depression. If the former then I doubt the accuracy of this statement, given that the Spek study excluded ' caseness'? Please check.	Thank you, we have amended this to: The patients in the trials included in this review were drawn predominantly from groups in the mild-to-moderate range of depressive symptoms (mean baseline BDI scores between 18 and 25). Approximately half (53%) met diagnostic criteria while the remainder had no formal diagnosis.
30	ULTRASIS	5	7.1.1	P158 Table 20	In your response to our previous comments (Comment 309) you accept that the Andersson and Christensen studies are sufficiently different in their controls such that they should be	Thank you, we have corrected this by including a separate analysis in Table 21.

					analysed separately - and not subsequently meaned. Your response was ' we have now revised the section and analysed the studies separately'. In fact this does not seem to have been done as they are meaned in the table and in Appendix 19. Please check	
31	ULTRASIS	6	7.1.2	P159	Last paragraph is incorrect. The SMD quoted of -0.02 is **not** statistically significant. Surely you meant to include data against the non-active control here? I may be wrong but I think you have included data for the active control .Please check	Thank you, we have corrected it.
32	ULTRASIS	7	7.1.2	P 159 and P160	The effect size descriptors are not consistent; -0.02 is described as small, -0.40 as medium , and -0.56 as small/medium.	Thank you, we have corrected it to: -0.02 very small; -0.40 small/medium; -0.56 medium.
33	ULTRASIS	8	Appendix 19b	P 2	Depression self report measures at end-point. See Comment 5 above. Christensen and Andersson are sufficiently different in their controls such that they cannot be meaned	Thank you, we have corrected this by including a separate analysis in Table 21.
34	ULTRASIS	9	Appendix 19b	P4 and P5	'Depressed sample only analysis at endpoint and follow-up'. Whilst recognising the merit of providing an analysis of the results from true depression caseness only, the fact remains that this is not the case for most of the data sets included in the Forest plots entitled ' Depressed Sample only'. These Forest plots are a mixture of an analysis of true caseness (Beating the Blues), possible caseness (ie above threshold for caseness on a recognised scale), and sub-threshold depression (Spek study). The tables are therefore factually inconsistent, and the comparisons implicit within the mode of presentation can only lead to false conclusions. For a more fitting and correct presentation there are a number of alternatives:- i) analyse the data on true diagnosed cases of depression for all studies or ii) assuming that true caseness data is not available, use data from the Beating the Blues study that is above a recognised threshold on the recognised scales used. I'm sure that this could be made available on request. A third alternative is simply to present the Beating the Blues data whilst acknowledging, (given your conclusions that the products are all clinically effective,) that this may represent the performance of all products in this setting and against this comparator. If as you suggest in your response to our original comments that a 2% per week remission rate is appropriate then one might expect to see similar effects	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.

					There is no reason why you should not present data for both the second and third alternatives.	
35	ULTRASIS	10	7.1 and 19b	All pages	The data analyses and presentations are inconsistent between the CCBT programmes, and in particular between Beating the Blues and free programmes which you overtly recommend. Interested parties will , no doubt, use these analyses to make judgements about which programme to use and it is important, therefore that analysis and presentation are consistent. This inconsistency is not simply a matter of ' judgement' and thus I feel it appropriate to raise again. To enumerate:- 1) ' Calculations' assessing the percentage of data above a caseness threshold were done specifically for Beating the Blues but not for other products (although I acknowledge that you state 53% of the total population met full diagnostic criteria) 2) Your responses to my original comments indicate that the GDG felt that a sub-analysis of a depression only sample was appropriate. Yet such an analysis has only been performed for Beating the Blues (and not on data representing the 53% above). 3) From your responses it is evident that the BtB data on depression caseness highly informed your conclusions about the uncertainty of recommending one product over another – but you have not compared like with like. 4) Analyses of depression caseness are presented in tables (labelled depression only) where likely caseness is also included. Given the low overall level of true caseness this presentation is innaccurate Failure to provide consistent analysis and presentation provides misinformation to parties interested in comparative performance.	Thank you for your comment. However, your comment relates to an issue other than a factual error. Therefore we cannot respond to it.

					5) Your response to our original comment 306 indicates that you were concerned not to include participants with a primary diagnosis of an anxiety disorder in the sub-threshold depression population of Beating the Blues. Given that participants with a specific anxiety disorder were identified in identification of the study sample then this concern was inappropriate. Moreover, this concern has not been addressed in your presentation of other data sets where the risk that the populations may include primary diagnoses of an anxiety disorder have not been evaluated.	

Stakeholder organisations that confirmed they did not have comments to make:

- Department of Health
- National Hospital for Neurology & Neurosurgery (NHNN)
- Association of British Neurologists