NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG35) – Parkinson's disease: National clinical guideline for diagnosis and management in primary and secondary care

Background information

Guideline issue date: 2004

3 year review: 2007

6 year review: 2010

National Collaborating Centre: NCGC

Review recommendation

- The guideline should be considered for an update, pending on the likely publication of the PD MED trial and PD SURG trial in 2012.

Factors influencing the decision

Literature search

1. From initial intelligence gathering and a high-level randomised control trial (RCT) search clinical areas were identified to inform the development of clinical questions for focused searches. Through this stage of the process 101 studies were identified relevant to the guideline scope. The identified studies were related to the following clinical areas within the guideline:
   - Diagnosis of Parkinson's disease (PD)
   - Symptomatic pharmacological management for early and late Parkinson's disease
   - Surgical interventions for people with Parkinson's disease

- Interventions for non motor features of Parkinson's disease: depression, psychotic symptoms, and occupational therapy.
- Interventions for non motor features of Parkinson's disease: dementia (four RCTs were identified for the effectiveness of memantine and six RCTs and one systematic review were identified for the clinical and cost effectiveness of rivastigmine in people with dementia and Parkinson's disease). This information would be included as part of the update review of CG42 Dementia: Supporting people with dementia and their carers in health and social care.
- Health economic analysis: MAO-B inhibitors, DBS and rivastigmine

2. Four clinical questions were developed based on the clinical areas above, qualitative feedback from other NICE departments and the views expressed by the Guideline Development Group, for more focused literature searches. They included:
   - Clinical and cost-effectiveness of transdermal dopamine patches in the treatment of people with functionally disabled early Parkinson's disease
   - Incidence/prevalence of impulse controlled disorder as an adverse event of the use of dopamine agonists in people with Parkinson's disease
   - Cost effectiveness of any deep brain stimulation procedure in the treatment of motor fluctuations and complications in people with Parkinson's disease
   - Clinical and cost effectiveness of MAO-B inhibitors as neuroprotective agents in reducing the progression rate of people with early Parkinson's disease

3. In total, 32 studies were identified through the focused searches. New evidence was identified in the following areas;
   - Interventions for non motor features of Parkinson's disease: depression (the use of antidepressants).

- Transdermal dopamine patches in the treatment of people with functionally disabled early Parkinson's disease.
- Management and monitoring of impulse controlled disorder as an adverse effect of the use of dopamine agonists in people with Parkinson's disease.
- MAO-B inhibitors as neuroprotective agents.

4. New evidence was identified which directly answered the research recommendations presented in the original guideline. A number of RCTs were identified that relate to:
   - The treatment of mild to moderate depression with specific antidepressants
   - The use of MAO-B inhibitors as neuroprotective agents
   - The use of memantine in treatment of dementia in people with Parkinson's disease (which would be addressed in the review of CG42 Dementia.

5. Several ongoing clinical trials (publication dates known) were identified focusing on:

   - Cost effectiveness of different classes of drugs used to treat Parkinson's disease (PD MED trial: estimated publication date is October 2011).
   - Cost effectiveness of surgery for Parkinson's Disease (PD SURG trial: estimated publication date is September 2011)
   - Deep brain stimulation (estimated publication date: between September 2011 and June 2014).
   - Use of levodopa as intestinal gel (estimated publication date: between June 2012 and June 2013).
   - Use of rasagiline, rotigotine as transdermal patches (estimated publication date: between August 2011 and June 2012).
   - Ropinirole for patients with Parkinson's disease. (estimated publication date is January 2012).

- Efficacy of continuous apomorphine infusion (estimated publication date is February 2011, but no results have been published till date).
- Effects of co-enzyme Q10 (estimated publication date is February 2012).
- Effect of donepezil in early dementia in patients with Parkinson's disease, effectiveness of surgery in Parkinson's disease patients (estimated publication date is April 2015).

Guideline Development Group and National Collaborating Centre perspective

6. A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Two responses were received with respondents highlighting that since publication of the guideline more literature has become available on:
   - The use of antidepressants.
   - Treatment of dementia in people with Parkinson's disease.
   - Cost effectiveness of DBS.
   - MAO-B inhibitors as neuroprotective agents,
   - Incidence and prevalence of impulse controlled disorders.
   - Use of transdermal patches of dopamine agonists.

   This feedback contributed towards the development of the clinical questions for the focused searches.

7. Ongoing research was cited by GDG members including:
   - The PD MED trial which is an HTA funded large randomised assessment of the relative cost-effectiveness of different classes of drugs for Parkinson's disease. PD MED and the UK PD SURG trial. It is a large randomised assessment of the relative cost-effectiveness of surgery for Parkinson's disease..
   - There is also ongoing research on newer agents available for PD which was not available when the last guideline was produced. This

includes intrajejunal levodopa infusion (Duodopa®), prolonged-release dopamine agonists and the rotigotine transdermal patch.

8. Two respondents agreed that there is sufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

Implementation and post publication feedback

9. In total 60 enquiries were received from post-publication feedback, most of which were routine. Key themes emerging from post-publication feedback included queries on implementation and audit of the guideline, the use of bananas and relationship to constipation, cost effectiveness model for deep brain stimulation, and a few queries on the recommendations within the guideline (how often to have physiotherapy, query on dopamine agonists, timescale for referral to specialist services and guidance on speech and language therapy for children).

10. No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

11. This feedback contributed towards the development of the clinical questions for the focused searches.

Relationship to other NICE guidance

12. NICE guidance related to CG35 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should be considered for an update, pending on the likely publication of the PD MED trial and PD SURG trial in 2012.

13. In total 19 stakeholders commented on the review proposal recommendation during the 2 week consultation period.

14. 18 stakeholders agreed with the review proposal recommendation that this guideline should be updated pending on the likely publication of the PD MED trial and PD SURG trial in 2012.

15. During consultation, additional areas from the original scope to consider in the update of the guideline were highlighted including:
    - A new technique for deep brain stimulation - pedunculopontine nucleus (PPN) should be considered separately from STN and GPi DBS.
    - The role for positron emission tomography (PET) to differentiate between vascular cause of the disease and Lewy body dementia in patients with possible “Parkinson’s plus” syndrome.
    - The use of I-123 Ioflupane should be used in patients where there is doubt over the diagnosis of Parkinson’s disease especially in those where differentiation from benign tremor is required and those patients on long term neuoleptics.
    - New best practice guideline on physiotherapy, speech and language therapy in Parkinson’s; occupational therapy; dietetics; and clinical psychology.
    - Evidence of the effectiveness of cognitive behavioural therapy (CBT) should be considered in patients with depression in Parkinson’s disease.

16. During consultation, stakeholders suggested new areas to consider that were not included in the original scope:
    - social care guidance, advice and support for carers, and end of life care

17. Individual stakeholder comments can be viewed in Appendix 2.

Anti-discrimination and equalities considerations

18. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope contains recommendations for diagnosis and treatment of adults with Parkinson's disease and parkinsonism.

Conclusion

19. From the evidence and intelligence identified through the process, it suggests that some areas of the guideline may need updating at this stage, particularly in relation to:
    - Interventions for non motor features of Parkinson's disease: depression (the use of antidepressants).
    - Transdermal dopamine patches in the treatment of people with functionally disabled early Parkinson's disease.
    - Management and monitoring of impulse controlled disorder as an adverse effect of the use of dopamine agonists in people with Parkinson's disease.
    - MAO-B inhibitors as neuroprotective agents.

20. The PD MED and PD SURG trial are likely to have a significant impact on the guideline. Therefore the guideline should be considered for an update when the results of these trials are published in 2012.

Relationship to quality standards and core library

21. This topic is not currently being considered for a quality standard.

22. This topic is currently being considered as one of the proposed core library topics.

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Centre for Clinical Practice
August 2011

Appendix 1

The following NICE guidance is related to CG35:

Guidance	Review date
CG21: Falls: The assessment and prevention of falls in older people. 2004	June 2011
CG 42: Dementia: management of dementia, including use of antipsychotic medication in older people. 2007	January 2012
CG23: Depression: management of depression in primary and secondary care. 2004	Replaced by CG 90: Depression in adults (update)
TA 19: Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease. 2001	Replaced by TA111 Alzheimer's disease donepezil, galantamine, rivastigmine (review) and memantine.
CG22: Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. 2004	Replaced by CG113: Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults.

CG32: Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. 2006	June 2011
IPG 019: Deep brain stimulation for Parkinson's disease	No date given
IPG 65: Subthalamotomy for Parkinson's disease	No date given
Related NICE guidance in progress	
CG20: The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004	Expected publication date January 2012

Appendix 2

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CG35 Parkinson's Disease Consultation Comments Table

4-17 July 2011

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
Multiple System Atrophy Trust	Agree with proposal to update	Comments throughout this response are based on MSAT view that documentation should be reviewed in 2012 at the end of the PDMED trial when all information has been gathered; this would most certainly be important for people living with MSA.			Thank you very much for your comment.
Multiple System Atrophy Trust	Agree with proposal to update	Effects of co-enzyme Q10: latest reports are that there is no clinical evidence to say it improves symptoms or QOL. However, people with MSA tell MSAT they feel better when taking it, less tired. MSAT has continuing interest in this area.		Anectdotal evidence showing MSA patients feel less tired with Co-enzyme Q10	Thank you for your comment. However, the new evidence identified for the areas was considered insufficient and did not show any beneficial effect of co-enzyme Q10.
Multiple System Atrophy Trust	Agree with proposal to update	Use of rasagiline, rotigotine as transdermal patches. May be beneficial for people living with MSA, particularly when swallow impeded. May help MSA patients in hospital with infections that have worsened their			Thank you very much for your comment.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		swallow and unable to take usual medications.			
Multiple System Atrophy Trust	Agree with proposal to update	Ropinirole for Parkinson - Dopamine agonists are used in MSA for symptom control, more so in the younger person with varying effects. Often when Ldopa stops being effective a DA is tried, but many MSAT members take DAs as monotherapy.			Thank you very much for your comment.
Multiple System Atrophy Trust	Agree with proposal to update	An RCT compared the longterm clinical outcome of early versus delayed rasagiline treatment in early PD. The results showed that compared to delayed start, early initiation of rasagiline provided longterm clinical benefit, even in the face of other dopaminergic agents. This might reflect enduring benefits due to neuroprotection or effects on compensatory mechanisms in early PD. These studies show some potential effectiveness of using MAO-B inhibitors as neuroprotective agents.			Thank you very much for your comment.
Multiple System Atrophy Trust		Antipsychotic medication - RCTs showed quetiapine to be effective and well tolerated but small sample size does not allow any conclusive		There are times when MSA patients become confused or hallucinate so	Thank you very much for your comment.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		interpretation of results.		quetiapine can be used for short periods if problematic.	
Multiple System Atrophy Trust		An RCT assessed the effect of 3-month treatment of sertraline (50mg) or low-dose amitriptyline (25mg) on depression and QOL in patients with Parkinsons disease. Sertraline but not amitriptyline treatment determined a signficant benefit on QOL (PDQ-39 scale) and found no change in Unified Parkinsons Disease Rating Scale scores.			Thank you very much for your comment.
Multiple System Atrophy Trust		One RCT assessed the effect of fish oil supplementation in parkinsonian patients without depression. These results reveal that PD patients taking fish oil, with or without anti-depressants, presented improvement in depressive symptoms and indicate that the intake of omega-3 can be used with an antipdepressant effect or as adjuvant therapy with some other medication.		Depression can be a big issue for people living with MSA; most Trust members take anti-depressants. If they are also taking PD meds there are many contrain- indications with certain antidepressants, so ones used for PD will most likely be helpful in MSA too.	Thank you very much for your comment.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
Multiple System Atrophy Trust		DBS/apomorphine or duodopa are not treatments that are likely to be of benefit to people with MSA. They are invasive, not cost-effective and we have very little research of them within MSA		Whilst we do see impulse control disorders (gambling/ hypersexuality) in PD, they are much less common in "parkinson plus syndromes".	Thank you very much for your comment.
UK Clinical Pharmacy Association (UKCPA)	Agree	An update will be valuable when the major studies have reported as they may answer some currently unanswered questions and may help us to identify the ideal order of PD treatment.	none	No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope contains recommendations for diagnosis and treatment of adults with Parkinson's disease and parkinsonism.	Thank you very much for your comment.
UK Clinical Pharmacy Association (UKCPA)		**Clinical area 4: Interventions for non-motor features of Parkinson's Disease – Depression** The current recommendations states			Thank you very much for your comment.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		that; The management of depression in people with PD should be tailored to the individual, in particular, to their co-existing therapy & we think this is still true. • There is probably enough evidence to support the use of SSRI's preferred over the use of TCA's, although the doses used in comparative trials of TCAs were suboptimal			
UK Clinical Pharmacy Association (UKCPA)		**Clinical area 4: Interventions for non-motor features of Parkinson's Disease – Depression** • Would be reluctant to specify pramipexole as having a positive effect on PD patients mood due to higher incidence of other serious ADR's with pramipexole (e.g. gambling and hypersexuality) • Pramipexole is of significantly higher acquisition cost than alternative therapies & is used $2^{nd}/3^{rd}$ line in most localities			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
UK Clinical		**Clinical area 4: Interventions for**			Thank you very much for your

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
Pharmacy Association (UKCPA)		**non-motor features of Parkinson's Disease – Depression** • Effect of fish oil on PD depression needs further investigation before adding it to the guidelines			comment. This information will be passed on to the technical team when the guideline will be updated in the future.
UK Clinical Pharmacy Association (UKCPA)		**Clinical Area 1: Transdermal dopamine patches** Views differed widely from: • There may be sufficient evidence to add rotigotine patches as a possible treatment option in early Parkinson's Disease (sufficient evidence to suggest non-inferiority to alternative treatment options), and a useful option where there are swallowing difficulties. • Blacklisted (not prescribable) option in one Healthcare community • Therefore a consensus statement based on the literature would be a useful tool			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
Royal College of Nursing	Agree	There has been increasing interest in non-motor and particularly impulse control disorders in Parkinson's Disease, so it is not surprising that new evidence that may change current guidelines has been discovered. However, it seems sensible to wait for the publication of the two major trials mentioned before updating the current guideline.			Thank you very much for your comment.
Royal College of Nursing		Related NICE guidance in progress should also include Urinary Incontinence in Neurological Disorders, which is due for publication in 2012 also.			Thank you very much for your comment. It will be rechecked and amended as appropriate.
Department of Health		The Department of Health has no substantive comments to make regarding this consultation.			Thank you very much for your comment.
Walton Centre for Neurology and Neurosurgery NHS Trust	Agree	The study is mainly pharmacologically and surgically based. No comments on obtaining a correct diagnosis, or care other than with interventional agents mentioned in the new review.	Awaiting further Surgical interventional data in particular.		Thank you very much for your comment. However there was no new evidence identified on diagnosis which would currently change the recommendations in the guideline.
Lundbeck Ltd	Agree		STRIDE PD is not captured in literature search – Stocchi et al, Ann Neurol. 2010		Thank you very much for your comment. It was excluded as it was difficult to identify whether

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
			Jul;68(1):18-27. This is a very relevant study		it was a RCT or not from the abstract.
Lundbeck Ltd		Impulse controlled disorders would be better worded as impulse control disorders			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
Lundbeck Ltd		"People with functionally disabled early Parkinson's disease" – suggest change to "functionally disabled patients with early Parkinson's disease" or "people with functionally disabling early Parkinson's disease".			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
College of Occupational Therapists (COT)	Agree update now required.	In 2010 the *Occupational Therapy for people with Parkinson's; Best Practice Guidelines* were published by the COT in Partnership with Parkinson's UK. This document was developed from R.80 of the 2006 NICE Parkinson's Disease guideline. This 2010 publication provides evidence based, peer-reviewed and ratified guidance to enable Occupational Therapists to enact the R80 gpp and we recommend it should therefore be referenced in the NICE Parkinson's guideline to support practical implementation. Reference: NHS Evidence via the following link;			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		http://www.evidence.nhs.uk/search?q=Occupational+therapy+best+practice+Parkinson%E2%80%99s+disease			
British Psychological Society, The		This organisation responded and said they had no comments to make.			Thank you very much for your comment.
British Society for Stereotactic and Functional Neurosurgery & Society of British Neurological Surgeons	Agree	The evidence relating to DBS is correctly represented and we agree to the recommendation not to alter the current guidelines.	Regarding DBS, there is a new target – the pedunculopontine nucleus (PPN) that is used for on-freezing and falls and should be considered separately from STN and GPi DBS (there is a much lesser evidence base for this treatment)	None	Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
British Nuclear Medicine Society	Agree	**General** Firstly there appears confusion in the document provided by NICE between positron emission tomography (PET) and single photon emission computed tomography (SPET or SPECT). **PET**	There may be a role for PET in looking at associated changes in general brain metabolism in those patients with a possible “Parkinson’s plus” syndrome especially where there is an associated cognitive impairment where it may be possible to		Thank you very much for your comment. In the process of preparing this document, we do not order the full papers and just use the information from the abstracts. This information will be passed on to the technical team when the guideline will be updated in the

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		At present there is no clear role for role of PET techniques in patient presenting with suspected Parkinson's disease. Though methods such as F-18 DOPA hold some promise for imaging in the future it is unlikely to be less expensive than I-123 Ioflupane SEPCT and also requires a period of washout of anti-parkinsonian drugs before imaging which may limit its use in those patient's where stopping such drugs may be problematical. References Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, Vollmar S, Baudrexel S, Diederich NJ, Heiss WD, Hilker R. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo Neurology. 2010;74:885-92 Borghammer P, Chakravarty M, Jonsdottir KY, Sato N, Matsuda H, Ito K, Arahata Y, Kato T, Gjedde A. Cortical hypometabolism and hypoperfusion in Parkinson's disease	differentiate between a vascular cause and a Lewy body type dementia if MRI is unhelpful. PET remains however, a strong tool in research concerning the origins, natural history and interventions in Parkinson's disease.		future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		is extensive: probably even at early disease stages Brain Struct Funct. 2010;214:303-17 Bohnen NI, Koeppe RA, Minoshima S, Giordani B, Albin RL, Frey KA, Kuhl DE Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study J Nucl Med. 2011;52(:848-55.			
British Nuclear Medicine Society		SPECT. Single photon emission tomography has developed a mature clinical role in the diagnosis and monitoring of patients with Parkinson's disease. Multicentre phase III trials demonstrate that I-123 Ioflupane SPECT can differentiate between Parkinson's disease and benign tremor with an accuracy of about 94% on blinded reading of the scans. More recent work has suggested that Parkinson's disease is over diagnosed clinically and in a multi-centre trial it was shown that the false positive rate for clinical assessment was 56% compared with 3% for I-123 Ioflupane			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		SPECT. The technique has been widely adopted by a range of hospitals from large specialist University Hospitals to District General Hospitals. Once trained, staff, are able to produce and read scans with a high level of accuracy. Visual reading of the studies is just as accurate as the use of quantification techniques again demonstrating the robustness of the technique. Though the cost of the study can be high (about £800) work from Italy suggests it is cost effective in managing those patients in which there is doubt concerning benign tremor or Parkinson's disease The role of I-123 Ioflupane SPECT has continued to evolve beyond just simple comparison of benign tremor or Parkinson's disease to include assessment of those patients with tremor who have been on long term neuroleptic drugs where the use of I-123 Ioflupane SPECT can differentiate drug induced tremor and Parkinson's disease. A further role has been in the			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		diagnosis of Dementia of Lewy body type (DLB) where in a multicentre trial of over 300 patients the sensitivity of I-123 ioflupane imaging was 78% and specificity 91%.			
British Nuclear Medicine Society		References Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, Speelman JD, Horstink MH, Sips HJ, Dierckx RA, Versijpt J, Decoo D, Van Der Linden C, Hadley DM, Doder M, Lees AJ, Costa DC, Gacinovic S, Oertel WH, Pogarell O, Hoeffken H, Joseph K, Tatsch K, Schwarz J, Ries V. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group Mov Disord. 2000;15:503-10 Benamer HT, Oertel WH, Patterson J, Hadley DM, Pogarell O, Höffken H, Gerstner A, Grosset DG Prospective study of presynaptic dopaminergic imaging in patients with mild	**In summary;** I-123 Ioflupane imaging has become a mature technique and should be used in patients where there is doubt over the diagnosis of Parkinson's disease especially in those where differentiation from benign tremor is required and those patients on long term neuoleptics. An additional role has been shown in the identification of Parkinson plus syndromes in particular differentiating Lewy body dementia from other causes of cognitive impairment.		Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		parkinsonism and tremor disorders: part 1. Baseline and 3-month observations Mov Disord. 2003;18:977-84 Lorberboym M, Treves TA, Melamed E, Lampl Y, Hellmann M, Djaldetti R. [123I]-FP/CIT SPECT imaging for distinguishing drug-induced parkinsonism from Parkinson's disease. Mov Disord. 2006;21:510-4 Ottaviani S, Tinazzi M, Pasquin I, Nothdurfter W, Tomelleri G, Fincati E, Nordera G, Moretto G, Fiaschi A, Smania N, Giorgetti P, Antonini A. Comparative analysis of visual and semi-quantitative assessment of striatal [123I]FP-CIT-SPET binding in Parkinson's disease Neurol Sci. 2006;27:397-401 McKeith I, O'Brien J, Walker Z, Tatsch K, Booij J, Darcourt J, Padovani A, Giubbini R, Bonuccelli U, Volterrani D, Holmes C, Kemp P, Tabet N, Meyer I, Reininger C; DLB Study Group. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies:			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		a phase III, multicentre study Lancet Neurol. 2007; 6:305-13. Antonini A, Berto P, Lopatriello S, Tamma F, Annemans L, Chambers M. Cost-effectiveness of 123I-FP-CIT SPECT in the differential diagnosis of essential tremor and Parkinson's disease in Italy. Mov Disord. 2008;23:2202-9 Tinazzi M, Antonini A, Bovi T, Pasquin I, Steinmayr M, Moretto G, Fiaschi A, Ottaviani S. Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism J Neurol. 2009;256:910-5 Marshall VL, Reininger CB, Marquardt M, Patterson J, Hadley DM, Oertel WH, Benamer HT, Kemp P, Burn D, Tolosa E, Kulisevsky J, Cunha L, Costa D, Booij J, Tatsch K, Chaudhuri KR, Ulm G, Pogarell O, Höffken H, Gerstner A, Grosset DG. Parkinson's			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord. 2009;24:500-8			
Previous GDG member	Agree	Agree with plan to defer until PD MED results available			Thank you for your comment.
Previous GDG member	Agree		PD Dementia management should be included in the revised guideline - there are 2 RCTs published now for memantine in this indication and a RCT of donepezil should be published by the time a review is performed		Thank you for your comment. This information would be passed to the update review team looking at the review of CG42 Dementia: Supporting people with dementia and their carers in health and social care, as stated in the consultation document
Boehringer Ingelheim Ltd	1. background information: AGREE	We agree that sufficient new information has been published since the original guideline to warrant a review.	Will the reviewers consider the evidence from the following: Clinical Standards published by NHS Quality Improvement Scotland in October 2009 on	None	Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future but the technical team does not usually consider evidence from

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
			Neurological Health Services. Available from: http://www.nhshealthquality.org/nhsqis/files/LongTermConditions_NeurologicalHealthServices_OCT09.pdf, last accessed 7 July 2011 Feedback we have received from around England suggests that neurology services find these standards helpful. Hauser RA and Auinger P Determination of minimally clinically important change in early and advanced Parkinson's disease Movement Disorders 2011;26(5):813-8 We consider this to be relevant to the translation of statistical and study information into clinical benefit for patients. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R and		other institutions. They undertake a systematic review and identify the available evidence.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
			Clarke C. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Movement Disorders 2010;25(15):2649-85. We consider this to be relevant to patient management Go CL, Rosales RL, Schmidt P et al. Generic versus branded pharmacotherapy in Parkinson's disease: does it matter? A review. Parkinsonism and related disorders 2011 doi:10.1016/j.parkreldis.2011.02.005 We consider this to be relevant to patient management		
Boehringer Ingelheim Ltd	2. Consideration of the	Please identify a) the date of the literature review for evidence b) the search strategy and c) the cut off date for inclusion of evidence			Thank you very much for your comment. The search strategies and the cut off dates can be found here.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	evidence: request for clarification	(inferred as March 2011 from the bibliography provided) The bibliography as published on the NICE website does not include publications from authors whose surname starts with letters later than P. See suggested list of additional publications in the next section.			
Boehringer Ingelheim Ltd	2. Consideration of the evidence AGREE	Evidence for symptomatic pharmacological management for early and late Parkinson's disease as listed in the bibliography has omitted the following publications and evidence presented at major international meetings: <u>General</u> Stowe R, Ives N, Clarke CE, van Hilten, Ferreira J, Hawker RJ, Shah L, Wheatley K, Gray R. Dopamine agonist therapy in early Parkinson's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006564. DOI: 10.1002/14651858.CD006564.pub2. Stowe R, Ives N, Clarke CE, Deane K,			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		van Hilten, Wheatley K, Gray R, Handley K, Furmston A. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson´ s disease patients with motor complications. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD007166. DOI: 10.1002/14651858.CD007166.pub2. <u>Pramipexole prolonged release in early Parkinson's disease</u> Rascol O et al. Efficacy, safety, and tolerability of overnight switching from immediate- to once daily extended-release pramipexole in early Parkinson's disease Movement Disorders 2010 Volume 25, Issue 14, Pages: 2326–2332 Poewe W et al. Sustained efficacy and tolerability of pramipexole extended-release in early Parkinson's disease Poster 370. Presented at The Movement Disorder Society's 14th Annual International Congress of Parkinson's Disease and Movement Disorders Buenos Aires, Argentina			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		June 13–17, 2010 [BI ref P10-07039] <u>Pramipexole in advanced Parkinson's disease</u> Schapira A et al. Efficacy and safety of once-daily (qd) pramipexole extended-release for advanced Parkinson's disease. Poster 2.276. Presented at XVIII WFN World Congress on Parkinson's disease and related disorders Miami Beach Florida 13-16 December 2009 [BI ref P10-00151] Schapira A et al. Decrease in off-time for extended- and for immediate-release pramipexole in advanced Parkinson's disease. SC203. Oral presentation at the 13th Congress of the European Federation of Neurological Societies (EFNS) September 12–15, 2009 Florence, Italy [BI ref P09-11547] Schapira AHV et al. Sustained Efficacy and Safety of Pramipexole Extended-Release in Advanced Parkinson's Disease: An Open-Label Trial. Poster P04.128 presented at 62nd Annual Meeting of the American Academy of			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		Neurology April 10–17, 2010 Toronto, ON, Canada [BI ref P10-05017] Schapira AHV et al. Overnight Conversion from Immediate-Release to Extended-Release Pramipexole for Adjunctive Treatment of Advanced Parkinson's Disease Poster PD4.003 presented at 62nd Annual Meeting of the American Academy of Neurology April 10–17, 2010 Toronto, ON, Canada [BI ref P10-05018] Schapira AHV et al. Sustained off-time decrease in patients using pramipexole extended-release as adjunctive treatment in advanced Parkinson's disease. Poster P1072 presented at the European Federation of Neurological Societies (EFNS) September 25-28 2010 Geneva Switzerland [BI ref P10-11375] <u>Patient convenience</u> Schapira AHV et al. Patient-reported convenience of once-daily versus three-times-daily dosing during long-term studies of pramipexole in early and advanced Parkinson's disease.			

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		Poster 410 Presented at The Movement Disorder Society's 15th Annual International Congress of Parkinson's Disease and Movement Disorders Toronto, ON, Canada June 5–9, 2011 [BI ref P11-07301] <u>Review articles</u> Antonini A, Calandrella D. Once-daily pramipexole for the treatment of early and advanced idiopathic Parkinson's disease: implications for patients. Neuropsychiatric Disease and Treatment 2011:7 297–302 Perez-Lloret S, Rascol O. Pramipexole extended-release (once-daily formulation) for the treatment of Parkinson's disease. Expert Opinion on Pharmacotherapy 2010;11(13):2221-30 Chwieduk CM, Curran MP. Pramipexole extended release in Parkinson's disease. CNS Drugs 2010;2494):327-36 Eisenreich W et al. Pramipexole extended release: A novel treatment			

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		option in Parkinson's disease. Parkinson's Disease 2010 Article ID 612619, 7 pages			
Boehringer Ingelheim Ltd	2. Consideration of the evidence AGREE	The consideration of Health economic analysis of MAO-B inhibitors cites Haycox et al drugs and Aging 2009 26 791-801. We draw the reviewers' attention to the following: Kovacs N et al. Cost Effectiveness of Rasagiline and Pramipexole as Treatment Strategies in Early Parkinson's Disease in the UK Setting: An Economic Markov Model Evaluation Drugs Aging 2011; 28 (2): 161-162			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
Boehringer Ingelheim Ltd	2. Consideration of the evidence AGREE	The Clinical and cost effectiveness of MAO-B inhibitors as neuroprotective agents in reducing the progression rate of people with early Parkinson's disease cites Olanow CW et al. NEJM 2009;361:1268-78. We draw the reviewers' attention to the following: Clarke CE et al. Should Treatment for Parkinson's Disease Start Immediately on			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		Diagnosis or Delayed until Functional Disability Develops? Movement Disorders 2011 DOI: 10.1002/mds.23519			
Boehringer Ingelheim Ltd	Table 1: Clinical area 2: Q: What is the effectiveness of MAO-B vs. Dopamine Agonists in the treatment of early Parkinson's disease? AGREE	As mentioned above, the consideration of Health Economic analysis of MAO-B inhibitors cites Haycox et al drugs and Aging 2009 26 791-801. We draw the reviewers' attention to the following: Kovacs N et al. Cost Effectiveness of Rasagiline and Pramipexole as Treatment Strategies in Early Parkinson's Disease in the UK Setting: An Economic Markov Model Evaluation Drugs Aging 2011; 28 (2): 161-162 Additionally, our in-house health economics specialist commented as follows on the Haycox paper: Key points 1. There is no evidence that statistically significant study results were appraised in a formal meta-			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		analysis/systematic review of rasagiline and pramipexole to provide the clinical inputs for the model. 2. There is no reassurance that the studies used for comparison (TEMPO, CALM-PD) are a comprehensive representation of the literature and it is possible therefore that there was selection bias in the choice of studies obtained from the literature. 3. The outcomes used in the model are not a comprehensive representation of outcomes important to patients with Parkinson's disease e.g. there is no consideration of non-motor symptoms such as depression in the model. ***Commentary*** The key points arise from a number of concerns with the model design, the data sources used and the conclusions of this study.			

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		Table Issues with model design and data sources/model inputs **Issue** / **Study desig** Age of clinical publications used / Details of literature provided, but list of include none later th September 2008 Choice of clinical data sources / TEMPO (6 year dat CALM-PD (4 year d Clinical disease duration (average) / Rasagiline patients months; pramipexol ±17 months Assumption of stable disease? / Assumption that pra dose does not chan years in the base ca dose used for sensi Patient withdrawal rates / Not documented in Choice of pramipexole dose used in model / DDD (potentially su pramipexole dose) Choice of model / Model transition allo			

Stakeholder	Agree with proposal to update?	Comments			Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		transition to end point – addition of levodopa	rasagiline patients to switch to or to have pramipexole added and then levodopa added; pramipexole patients switched directly to added levodopa	irrespective of data inputs			
		Choice of end point – emergence of levodopa-induced complications	Chosen as a proxy for emergence of dyskinesia (within 2 years of levodopa therapy)[2]; assumption that dyskinesia is linked to disability and impaired QOL	Evidence suggests that for patients, QOL is more closely associated with presence of non motor symptoms[3,4,]			
		Costs associated with addition of levodopa	Chosen because studies estimate that direct medical costs for patients with dyskinesias are double or treble those for patients without dyskinesias[5,6,7]	Costs derived from Swedish, Canadian or French studies, cited in Haycox et al may not be applicable in UK Costs quoted are from 1999 to 2006 – what would they be at 2010 levels?			
		Time to endpoint – addition of levodopa	Clinical study data allows patients in the pramipexole study to take supplementary levodopa after 10 weeks, whereas patients in the rasagiline study could take levodopa only after the first 6 months.	Data inputs favour rasagiline; not comparing like with like			
		Calculation of utilities[8]	Model assumes identical utilities for rasagiline or pramipexole monotherapy; assessment by VAS[8]	No consideration of impact of non-motor symptoms			

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Calculation of utilities[8]	Fluctuations used as a marker for the emergence of dyskinesia	May create artificial shortening of time to dyskinesia
Assumption of patient adherence	Model assumes all patients take every dose each day at prescribed time	Variable patient adherence would be appropriate to include in sensitivity analysis
Choice of transition probabilities of pramipexole cycles (pramipexole to levodopa)	Probability at 0.15 pramipexole to levodopa for each cycle compared to variable probability of switching for rasagiline to dopamine agonist or rasagiline to levodopa	Model design favours rasagiline, irrespective of data inputs
Choice of drug costs	based on NHS wholesaler purchase price	It would be more appropriate to use NHS's Net Ingredient Cost (NIC) or Drug Tariff reimbursement figure
Choice of variables in sensitivity analysis (1)	Pramipexole dose only	It is likely that other factors would have an impact on sensitivity analysis e.g. NHS price change through PPRS, patient adherence, patient withdrawal etc
Choice of variables in sensitivity analysis (2)	Pramipexole dose only	Lower pramipexole dose chosen in sensitivity analysis may be sub-therapeutic
Choice of values for clinical outcomes	Values of clinical outcomes for pramipexole assumed to be identical for all doses used in sensitivity analysis	Unlikely that clinical outcomes would be identical for different pramipexole doses over a 5 year period

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		References to support statements in table: 1. Parkinson Study Group CALM Cohort Investigators. Long-term Effect of Initiating Pramipexole vs. Levodopa in Early Parkinson Disease. Arch Neurol. 2009;66(5):563-570 2. Bezard E, Brotchie JM, Gross C. Pathophysiology of levodopa-induced dyskinesia: potential for new therapies. Nature Reviews Neuroscience 2001;577-88 3. Schrag A, Jahanshahi M, Quinn N What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;69:308-12 4. Global Parkinson's disease survey steering committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord 2002;17:60-7 5. Pechevis M, Clarke CE, Vieregge P et al. Effects of			

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		dyskinesias in Parkinson's disease on quality of life and health related costs: a prospective European study. Eur J Neurol 2005 12(12):956-63 6. Maurel F, Lilliu H, Le Pen C Social and economic cost of L-dopa induced dyskinesias in patients with Parkinson's disease. Rev Neurol (Paris) 2001;157(5):507-14 7. Le Pen C, Wait S, Moutard-Martin F et al. Cost of illness and disease severity in a cohort of French patients with Parkinson's disease. Pharmacoeconomics 1999;16(1):59-69 8. Palmer CS, Schmier JK, Snyder E et al. Patient preferences and utilities for 'off time' outcomes in the treatment of Parkinson's disease. Quality of Life Research 2000 9: 819-27 ***Issues with study conclusions***			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		The uncertainties and assumptions in the clinical data sources and model design, together with the age of the clinical and cost data used in this model should be sufficient to cast doubts on the conclusion that rasagiline is more cost-effective than pramipexole over 5 years in the treatment of early Parkinson's disease. ***Key message*** The results of this study alone are insufficient for a healthcare professional to use as the basis for a prescribing decision. Any perceived cost-effectiveness may not be realised in clinical practice.			
Boehringer Ingelheim Ltd	Table 1: Clinical Area 4: Interventions for non motor features of	Evidence for this update is from Barone P et al Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010; 9: 573–80, cited incorrectly in the bibliography as 'Bxarone' [ref ID94]			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	Parkinson's disease – depression AGREE	Additional evidence on impact of pramipexole on mood and motivational symptoms in Parkinson's disease is from Leentjens AF et al. Clin Ther 2009;3189-98 [ref ID284]			
Boehringer Ingelheim Ltd	Table 2: clinical area 2: incidence / prevalence of impulse control disorder as an adverse event of the use of dopamine agonists in patients with Parkinson's disease AGREE	Evidence is cited for the incidence of ICDs with dopamine agonists. We would refer the reviewers to: Weintraub D et al. Impulse Control Disorders in Parkinson Disease: A Cross-Sectional Study of 3090 Patients. Arch Neurol. 2010;67(5):589-595			Thank you very much for your comment but this paper is already included in the evidence.

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Boehringer Ingelheim Ltd	Table 2: clinical area 4: clinical and cost-effectiveness of MAO-B inhibitors as neuroprotective agents vs placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease DISAGREE	Neuroprotection, delay in disease progression, disease modification or delay in clinical progression is considered an area of emerging clinical and scientific opinion. The issue has not been resolved in favour of one generally accepted viewpoint and is the subject of opinion articles in leading specialist neurology publications, as well as in more general clinical publications. Of note, the European Medicines Evaluation Agency (EMEA, now the European medicines Agency, EMA) guideline on clinical investigation of drugs in PD [CPMP/EWP/563/95 Rev.1; EMEA London, 24 July 2008] requires both the demonstration of a significant delay in clinical disease progression and the demonstration of an effect on the underlying pathophysiology of the disease by e.g. biochemical markers or neuroimaging measures. Therefore in order to make a claim for disease modification, two criteria must be met: firstly, a demonstrated delay in clinical measures of disease progression; secondly, a quantifiable effect on the			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

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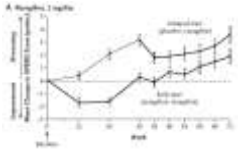
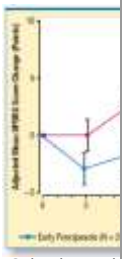
		underlying pathophysiological process which correlates to a meaningful and persistent change in clinical function. The ADAGIO study design does not address or meet the requirements of the EMEA guideline. As seen in the figure below, deterioration in UPDRS score was seen in patients treated with 1mg rasagiline (the licensed dose) over the study period in the ADAGIO study, unlike patients treated over a similar timeframe with pramipexole in the PROUD study.			

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		Comparison between A and PROUD  Olanow W et al. N Engl J Med 2009;361:1268-78.  Schapira et al. Presented at t Congress on P and Related D Miami Beach, 13–16, 2009 Boehringer Ingelheim considers therefore that no definitive statement can be made about the neuroprotective effect of MAO-B inhibitors or indeed any other pharmacological treatment for PD.			

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Boehringer Ingelheim Ltd	Relationship to other NICE guidance: DISAGREE	We consider that the reviewers may wish to consider the following related guidance: Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, Benson J, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, Steel J (2009). Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.			Thank you very much for your comment. The lists of related NICE guideline were extracted from what was available in the guideline.
Royal College of General Practitioners	Disagree	General. In view of new information coming through in 2012 from clinical trials it might be suitable to wait until these trials are published			Thank you very much for your comment.
Medtronic Ltd	Agree	Medtronic support the recommendation that the guideline should be considered for an update, subject to the publication of the PD MED trial and PD SURG trial in 2012.			Thank you very much for your comment.
Abbott	Agree on need to	Abbott considers that it would be important to review the clinical			Thank you very much for your comment. However, there

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	update in a timely manner	effectiveness and cost effectiveness of co-careldopa intestinal gel (Duopoda) in a timely manner as this was not included in previous NICE guidance as it was not licensed in 2004. However, it has been licensed for a number of years now and is an important therapy option for patients in advanced Parkinson's Disease which has not been reviewed by NICE. Approximately 2,200 patients globally are treated with Duodopa as of May 2011. As such Abbott considers it would be helpful for NICE to release guidance which reviews the clinical effectiveness and cost effectiveness of this drug, to minimise variation in patients' access to this therapy. Given that the PD Med and PD SURG trials are due to be published in 2012 Abbott hopes that the review of this guideline can be initiated now, perhaps with additional searches specific to these therapeutic areas being updated after these publications have taken place, to ensure the reviewed guideline would be available in a timely manner.			wasn't any evidence identified for intestinal gel (Duaodopa). This information will be passed on to the technical team when the guideline will be updated in the future.
GlaxoSmithKline UK	Agree	**Overall comment**			Thank you very much for your comment.

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		There is adequate new evidence to justify the update of the current clinical guideline to ensure it remains relevant to patients and their families and carers, clinicians, health service managers and commissioners.			
GlaxoSmithKline UK	Agree	**Review and inclusion of licensed treatments for Parkinson's disease not included in the previous guideline.** Whilst not included in the review of dopamine agonists (pages 8-11), but discussed on page 49, new agents including prolonged release dopamine agonists are licensed and used in the management of PD. Evidence on all prolonged release formulations should be reviewed as a monotherapy, adjunct therapy and as a levodopa sparing agent. Additionally this evidence should be reviewed in the context of how and when dopamine agonists should be prescribed compared with immediate release dopamine agonist			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		preparations. Stocchi, F (2011) PREPARED: Comparison of prolonged and immediate release ropinirole in advanced Parkinson's disease. Movement Disorders, 26, (7): 1259 – 1265. Tompson,D.J. and Vearer, D. (2007) Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson's disease. Journal of Clinical Therapeutics, 29:2654–2666.			
GlaxoSmithKline UK	Agree	**Review and inclusion of licensed treatments for Parkinson's disease not included in the previous guideline.** The "real world" PD Med trial as referred to on page 48 should provide a naturalistic view the effectiveness (health related quality of life) of treatments currently received by patients.			Thank you very much for your comment.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
GlaxoSmithKline UK	Agree	**Interventions for non-motor features of Parkinson's disease – Depression (page 26).** Consideration of the effects of other drugs on depressive symptoms should be given. There is additional evidence not captured by the initial searches in the consultation document. Depression data (Beck Depression Inventory-II) was also collected as a secondary end point in a double-blind, placebo-controlled, 24-week study where PD patients were randomised to ropinirole prolonged release or placebo. Pahwa, R. et al. (2007) Ropinirole 24-hour prolonged release randomized, controlled study in advanced Parkinson disease. Neurology, 68:1108–1115.			Thank you very much for your comment. This paper is already included in the evidence.
GlaxoSmithKline UK	Agree	**Management and monitoring of impulse controlled disorder as an adverse effect of the use of dopamine agonists in people with Parkinson's disease.**			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		Should the evidence allow, the guidelines should be updated to provide appropriate and supportive education to both PD patients and clinicians. The evidence to assess the role of dopamine agonists in impulse control disorders in PD patients should be compared with evidence for the presence of impulse control disorders in PD patients on levodopa alone.			
GlaxoSmithKline UK	Agree	**Clinical and cost-effectiveness of MAOB-inhibitors as neuroprotective agents versus placebo or levodopa (page 44).** In reviewing the evidence for neuroprotection, the application in clinical practice should be outlined clearly i.e. whether the role of MAOB inhibitors should be as a neuroprotective agent or as a levodopa sparing agent.			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
GlaxoSmithKline UK	Agree		Regular access to specialist nursing care and palliative		Thank you very much for your comment. They are already

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
			care were identified as key priorities for implementation of CG 35 (NICE, 2006) however do not appear to have been included in the consultation document. Both are two key areas for the delivery of effective management of a long term neurological condition. New evidence or case studies supporting these services should be reviewed, e.g. Ryton, B. and Liddle, B.J.(2009) Implementing NICE clinical guidelines on Parkinson's disease. Clinical Medicine, 9:5: 436–40. Axelrod, L. et al. (2010) Workloads of Parkinson's specialist nurses: implications for implementing national service guidelines in England. Journal of Clinical Nursing, 19: 3575–3580.		recommended in the guideline and no new evidence was identified that would change the current recommendations.

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GlaxoSmithKline UK	Agree	**Changing environment over the next 2-3 years** Page 48 reports the recent price reduction for prolonged release ropinirole. There are likely cost savings available in the appropriate patient population. There should be consideration of the appropriate use of generics that should consider two scenarios i) treatment initiation and ii) treatment switching. Whilst active ingredients are identical, preparations can differ and therefore appropriate consideration would act to ensure the benefit to the patient is not adversely affected but where appropriate potential savings to the NHS can be realised.			Thank you very much for your comment. The PD MED trial considers the cost effectiveness of the pharmacologic options for the treatment of patients with Parkinson's disease.
GlaxoSmithKline UK	Agree	**Average NHS costs for stage III-IV patients** On page 49, one of the themes of enquiries post publication of the previous guideline was around understanding the costs for stage III-IV			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		patients and the impact this may have on resultant incremental cost-effectiveness analysis. This does not appear to have been included in the initial searches but should be incorporated in any future updates of the guideline. Recent studies have attempted to disaggregate costs by stage of disease. Findley, L.J. et al (2011) The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset. Journal of Medical Economics, 14: 1: 130–139. Further, resource utilisation is also being captured within the PD Med trial (direct medical costs and institutional care).			
British Association for Psychopharmacology		This organisation responded and said they had no comments to make.			Thank you very much for your comment.

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Parkinson's UK	We agree that the guideline needs updating. We also agree with the four area identified for updating in the review consultation document. However, there are several further areas that need to be encompassed in this review in	**<u>Areas not included in the review consultation document</u>** There are a number of recommendations within the existing published Parkinson's guideline that have not been mentioned in the review consultation document. These include, communicating with people with Parkinson's disease and their carers (R1-7); specialist nurses (R77). We recommend that all of these recommendation are included in the updated version of the guideline as they are still very relevant to delivering quality cost effective care for people with Parkinsons's.	We agree that the guideline needs updating. We also agree with the four area identified for updating in the review consultation document. However, there are several further areas that need to be encompassed in this review in addition to those proposed in the Parkinson's review consultation document. These include: ♦ Extending the scope of the Parkinson's guideline to include social care, carers and end of life issues ♦ New best practice guideline on physiotherapy in Parkinson's ♦ Dutch guidelines on Speech and Language Therapy ♦ New best practice guidelines on occupational therapy		Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	addition to those proposed in the Parkinson's review consultation document. These include: ♦ Extending the scope of the Parkinson's guideline to include social care,		♦ New best practice guidelines on dietetics ♦ New best practice guidelines on clinical psychology ♦ Drug therapy for Parkinson's disease dementia ♦ Parkinson's audit		

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	carers and end of life issues ♦ New best practice guideline on physiotherapy in Parkinson's ♦ Dutch guidelines on Speech and Language				

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	Therapy ♦ New best practice guidelines on occupational therapy ♦ New best practice guidelines on dietetics ♦ New best practice guidelines				

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
	♦ on clinical psychology ♦ Drug therapy for Parkinson's disease dementia ♦ Parkinson's audit				
Parkinson's UK		**Psychological therapies and interventions** Consideration should be given to the evidence included in the briefing paper 'Psychological services for people with Parkinson's disease' (PDF, 157KB) This was produced by the British			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		Psychological Society in February 2009. In particular this should include: ♦ Cognitive behavioural therapy (see below) ♦ Neuropsychological assessment ♦ Neuropsychological rehabilitation			
Parkinson's UK		**Cognitive behavioural therapy** Evidence of the effectiveness of cognitive behavioural therapy (CBT) should be considered Psychotherapy for primary depression and anxiety disorders is a widely accepted treatment option (National Institute for Health and Clinical Excellence, 2007). In particular, cognitive-behavioural therapy (CBT) for the treatment of depression in older adults (Laidlaw et al., 2008) as been proven to be an effective evidence-based treatment (Arean & Cook, 2002). Preliminary studies into the potential effectiveness of cognitive behavioural therapy for depression in PD have suggested that this intervention can be			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

Stakeholder	Agree with proposal to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Reply to Stakeholder comments
		of significant benefit to some people with the condition (Dobkin et al., 2007). Treatment packages have been developed (Dobkin et al., 2006), and many clinical psychologists working with older adult populations in the UK will use cognitive behavioural and other psychotherapeutic models to inform effective psychological interventions for their clients who have PD. Cole and Vaughan (2005), in their review of the feasibility of using a cognitive behavioural therapy for depression in PD, highlight the evidence in support of CBT for depression in older adults who have chronic illnesses other than PD. Although there are challenges associated with adapting psychotherapy for these populations, there is considerable evidence for the effectiveness of psychological treatment (Cole & Vaughan, 2005). Psychological interventions other than CBT, for example, cognitive-analytic therapy (Hepple & Sutton, 2004) may also have considerable potential for application with people who have mood disorders associated with PD. Clinical psychologists and			

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		neuropsychologists are ideally placed to assess people for their suitability for psychotherapy and to supervise or undertake these psychological interventions. *Extract from 'Psychological services for people with Parkinson's disease'*			
Parkinson's UK		**Occupational therapy** Consideration should be given to the evidence published in the best practice guidance Occupational therapy for people with Parkinson's - produced by The British Association and College of Occupational Therapists in partnership with Parkinson's UK. In particular this should include: • Intrinsic cueing techniques (Farely and Koshland 2005; Maitra 2007; Tamir et al 2007) ♦ Extrinsic cueing techniques (Neiuwboer et al 2007; Lim et al 2005a, 2005b ; Rochester et al 2005 ;Hackney et al 2007) ♦ Optimizing activities (KNGF 2006;			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

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		Mak and Hui-Chan 2008; ♦ Vocational rehabilitation (Sweetland et al 2007) ♦ Exercise and activity based interventions (Crissle and Newhouse 2006; Dibble et al 2009; Fisher et al 2008; Hackney et al 2007; Hackney and Earhart 2009)			
Parkinson's UK		**Dietetics** Consideration should be given to the evidence published in Best Practice guideline for dietitians on the management of Parkinson's. British Dietetic Association in partnership with Parkinson's UK (2010) http://www.parkinsons.org.uk/advice/publications/professionals/dietitians_best_practice_guide.aspx			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
Parkinson's UK		**Physiotherapy** Consideration should be given to the evidence published in Quick reference cards (UK) and Guidance Notes for physiotherapists working with people			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

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		with Parkinson's disease (2009) **http://www.parkinsons.org.uk/advice/publications/professionals/quick_reference_cards.aspx**			
Parkinson's UK		**<u>Parkinson's disease dementia</u>** **<u>Memantine</u>** Two studies have shown that the use of memantine to manage the symptoms or PDD and DLB is worthy of consideration. The first study (Johansson 2011) concluded "that the findings inform clinical practice that any possible memantine-associated benefits might be rapidly lost after drug withdrawal. The magnitude of deterioration suggests a symptomatic rather than a disease-modifying effect of the drug. Open-label results should merely be considered inspiration for future trials." The second study (Emre 2010) interpreted that "memantine seems to improve global clinical status and behavioural symptoms of patients with			Thank you very much. In the consultation document the following was stated: Interventions for non motor features of Parkinson's disease: dementia (four RCTs were identified for the effectiveness of memantine and six RCTs and one review were identified for the clinical and cost effectiveness of rivastigmine in people with dementia and Parkinson's disease). This information would be passed to the update review team looking at the review of CG42 Dementia: Supporting people with dementia and their carers in health and social care.

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		mild to moderate DLB, and might be an option for treatment of these patients". **Donepezil** A RCT into the use of donepezil in PDD is under review in Movement Disorders Journal. It is hoped this will be published later this year.			
Parkinson's UK		**Parkinson's disease audit** Parkinson's UK, supported by the appropriate professional societies and colleges, have developed an audit tool based on the NICE Parkinson's guideline and National Service Framework for long-term neurological conditions. This has been piloted and has been accredited by HQIP as the appropriate audit for Parkinson's clinical services. The 2010 report is available at http://www.parkinsons.org.uk/pdf/Parkinsons_Audit_2010_report.pdf. The current tool includes modules for the assessment of newly diagnosed			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

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		patients, existing patients, physiotherapy, occupational therapy and speech & language therapy. There is also a module to allow for an audit of general service provision in accordance with the existing guidelines. The use of this accredited audit tool should be highlighted by NICE.			
Parkinson's UK		**New Parkinson's epidemiological data** Parkinson's UK will publish a new epidemiological study in 2011 which will completely update prevalence and incidence figures for Parkinson's disease in the UK. This new evidence should be used in any health economic calculation in the review of the Parkinson's guideline.			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
Parkinson's UK		**References** Arean, P.A. & Cook, B.L. (2002). Psychotherapy and combined psychotherapy/ pharmacotherapy for late life depression. *Biol Psychiatry, 52*, 293–303. Armitage (2009) Parkinson's Disease:			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.

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		Relatives' perceptions of the effectiveness of care in residential institutions, and the coherence of these perceptions with the content of care plans. Bradford Institute for Health research A Argon & J Kings (2010) Occupational therapy for people with Parkinson's Best practice guidelines. College of Accupational Therapists in partnership with Parkinsons' UK S Bernard, F Aspinal, K Gridley, G Parker (2010) Integrated Services for People with Long-term Neurological Conditions: Evaluation of the Impact of the National Service Framework. *Social Policy Research Unit, University of York* Cole, K. & Vaughan, F.L. (2005). The feasibility of using cognitive behaviour therapy for depression associated with Parkinson's disease: A literature review. *Parkinsonism Relat Disord, 11*, 269–276. Crizzle AM, Newhouse IJ (2006) Is physical exercise beneficial for			

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		persons with Parkinson's disease? *Clinical Journal of Sport Medicine, 16(5),* 422–425. Dibble LE, Addison O, Papa E (2009) The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *Journal of Neurological Physical Therapy, 33(1),* 14–26. Dobkin, R.D., Allen, L.A. & Menza, M. (2006). A cognitive behavioural treatment package for depression in Parkinson's disease. *Psychosomatics, 47*, 259–263. Dobkin, R.D., Allen, L.A. & Menza, M. (2007). Cognitive behavioural therapy for depression in Parkinson's disease: A pilot study. *Mov Disord, 22*, 946–952. M Emre, M Tsolaki, U Bonuccelli.(2010) Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial *Lancet Neurol 2010; 9: 969–77*			

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		Farley BG, Koshland GF (2005) Training BIG to move faster: the application of the speed- amplitude relation as a rehabilitation strategy for people with Parkinson's disease. *Experimental Brain Research,167(3),* 462–467. Fisher BE, Wu AD, Salem GJ, Song J, Lin C- H, Yip J, Cen S, Gordon J, Jakowec M, Petzinger G (2008) The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Archives of Physical Medicine and Rehabilitation, 89(7),* 1221–1229. K Green (2010) Bet Practice guideline for dietitians on the management of Parkinson's. British Dietetic Association in association with Parkinson' sUK Hackney ME, Earhart GM (2009) Effects of dance on movement control in Parkinson's disease: a comparison of Argentine tango and American			

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		ballroom. *Journal of Rehabilitation Medicine, 41(6),* 475–481. Hackney ME, Kantorovich S, Levin R, Earhart GM (2007) Effects of tango on functional mobility in Parkinson's disease: a preliminary study. *Journal of Neurologic Physical Therapy, 31(4),* 173–179. Hepple, J. & Sutton, L. (Eds.) (2004). *Cognitive Analytic Therapy and later life: A new perspective on old age.* New York: Brunner-Routledge. C. Johansson, C. Ballard, O. Hansson, S. Palmqvist, L. Minthon, D. Aarsland and E. Londos (2011) Efficacy of memantine in PDD and DLB: an extension study including washout and open-label treatment *Int J Geriatr Psychiatry 2011; 26: 206–213.* KNGF (Royal Dutch Society for Physical Therapy) (2006) *KNGF guidelines for physical therapy in patients with Parkinson's disease.* Amersfoort: Royal Dutch Society for			

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		Physical Therapy. Available at: *https://www.cebp.nl/vault_public/cms/?ID=47* Accessed on 13.02.10. Laidlaw, K., Davidson, K., Toner, H., Jackson, G., Clark, S., Law, J., Howley, M., Bowie, G., Connery, H. & Cross, S. (2008). A randomised controlled trial of cognitive behaviour therapy vs. treatment as usual in the treatment of mild to moderate late life depression. *Int J Geriatr Psychiatry, 23*, 843–850. Lim LIIK, Van Wegen EEH, De Goede CJT, Jones D, Rochester L, Hetherington V, Nieuwboer AM, Willems A, Kwakkel G (2005a) Measuring gait and gait- related activities in Parkinson's patients' own home environment: a reliability, responsiveness and feasibility study. *Parkinsonism and Related Disorders, 11(1),* 19–24. Lim LIIK, Van Wegen EEH, De Goede CJT, Deutekom M, Nieuwboer AM, Willems AM, Jones D, Rochester L, Kwakkel G (2005b) Effects of external			

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		rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. *Clinical Rehabilitation, 19(7),* 695–713. Maitra KK (2007) Enhancement of reaching performance via self- speech in people with Parkinson's disease. *Clinical Rehabilitation, 21(5),* 418–424. V MacNeill & C Jenkinson (2008) Respite care needs and experiences of patients with Parkinson's disease and teri carers. Poster presentation Dept Public Health University of Oxford Mak MKY, Hui- Chan CWY (2008) Cued task- specific training is better than exercise in improving sit- to-stand in patients with Parkinson's disease: a randomised controlled trial. *Movement Disorders, 23(4),* 501–509. Nieuwboer A, Kwakkel G, Rochester L, Jones D, Van Wegen E, Willems AM, Chavret F, Hetherington V, Baker K, Lim I (2007) Cueing training in the home improves gait- related mobility in Parkinson's disease: the RESCUE trial. *Journal of Neurology,*			

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		Neurosurgery and Psychiatry, 78(2), 134–140. Psychological services for people with Parkinson's disease (2009) The British Psychological Society and Parkinsons Disease Society Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems AM, Kwakkel G, Van Wegen E (2005) The effect of external rhythmical cues (auditory and visual) on walking during a functional task in homes of people with Parkinson's disease. *Archives of Physical Medicine and Rehabilitation, 86(5),* 999–1006. KP Roland, ME Jenkins & AM Johnson (2010) An exploration of the burden experience by spousal caregivers of individuals with Parkinson's disease. Mov Disord. 2010 Jan 30;25(2):189- 93.			

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		Sweetland J, Riazi A, Cano SJ, Playford ED (2007) Vocational rehabilitation services for people with multiple sclerosis: what patients want from clinicians and employers. *Multiple Sclerosis, 13(9),* 1183–1189. Tamir R, Dickstein R, Huberman M (2007) Integration of motor imagery and physical practice in group treatment Wermuth, L. & Bech, P. (2006). Depression in Parkinson's disease – a review. *Acta Neurol Scand, 114*, 360.			
UCB Pharma Ltd		'Consideration of the evidence: non motor symptoms and importance of depression (chapter 2) UCB would ask that the definition of non motor symptoms is expanded to consider: early morning akinesia, sleep disturbances and pain			Thank you very much for your comment.
UCB Pharma Ltd		High level RCT search (Chapter 2) UCB identified several high quality RCTs on the use of transdermal DA			Thank you very much for your comment.

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		patches that have been overlooked by the NICE guidelines review team (details will be forwarded) that should be considered			
UCB Pharma Ltd		Clinical and cost effectiveness of dopamine patches in early PD (chapter 2) UCB welcomes the evaluation of the patch delivery but asks that any review also considers that benefits of patch delivery that go beyond motor symptoms - so areas like kinetics of delivery and treatment times			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will be updated in the future.
UCB Pharma Ltd		Use of DA is an effective treatment option for wearing off phenomenon (clinical area 2) UCB would ask for a wider literature review and meta-analysis to look at the benefits of DA patch delivery in patients with wearing off phenomenon			Thank you very much for your comment.
UCB Pharma Ltd		Effectiveness of antidepressants compared to DA treatment in Parkinson's (clinical area 4) UCB has evidence for the benefits of rotigotine transdermal patch in terms of improvement of depression scores and we ask that this information is			Thank you very much for your comment.

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		considered in line with pramipexole			
UCB Pharma Ltd		Clinical and cost effectiveness of dopamine patches in early PD (Clinical area 1(Q1)) The guidelines group has included evidence on the constant delivery benefit with rotigotine patch and also the control of early morning impairment. We ask that these significant benefits are reflected in the cost effectiveness review of the dopamine patch			Thank you very much for your comment.
UCB Pharma Ltd		Listing of reference from Prescribe international in the evidence table (Anon, Prescribe International, 17:60) (References, appendix 1) UCB would ask that the systematic review ensures that the correct weight is given to the evidence standards as outlined in previous NICE methods guides. UCB is surprised to find inclusion of an anonymous review on rotigotine			Thank you very much for your comment.
UCB Pharma Ltd		REFERENCES • LeWitt P.A. et al. Advanced Parkinson disease treated with			Thank you very much for your comment. This information will be passed on to the technical team when the guideline will

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		rotigotine transdermal system. Neurology 2007; 68: 1262 – 1267 (not included) • Parkinson Study Group A Controlled Trial of Rotigotine Monotherapy in Early Parkinson's Disease Arch Neurol. 2003;60:1721-1728 (a useful extra reference) • Poewe W.H. et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007; 6: 513–20 (included but not referenced) • Trenkwalder C. et al. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study (RECOVER). Movement Disorders 2011; 26(1): 90-99 (not included) • Watts R.L. et al. Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson Disease. Neurology 2007; 68: 272 – 276 (included as per the Jankovic			be updated in the future.

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		paper but this is also a useful reference) • Schnitzler et al. High compliance with rotigotine transdermal patch in the treatment of idiopathic Parkinson's disease. Parkinsonism and Related Disorders 16 (2010) 513-516 (a useful reference for compliance of the transdermal patch) • Stowe et al. Meta-Analysis of the Comparative Efficacy and Safety of Adjuvant Treatment to Levodopa in Later Parkinson's Disease Movement Disorders 2011;26(4):587-598 (this is a very recent and comprehensive review including rotigotine in advanced PD			

These organisations were approached but did not respond:

Abbott Laboratories Limited
Adults Strategy and Commissioning Unit
Age Concern Cymru
Airedale NHS Foundation Trust
Alliance Pharmaceuticals Ltd

Alzheimers Society
Anglesey Local Health Board
Association for Continence Advice
Association of British Health-Care Industries
Association of British Neurologists
Association of Dance Movement Psychotherapy UK
Association of Professional Music Therapists
Association of the British Pharmaceuticals Industry (ABPI)
Barchester Healthcare
Barnsley PCT
Barts and The London NHS Trust
Bayer Healthcare PLC
Birmingham Clinical Trials Unit
BMJ
Brain and Spine Foundation
Bristol-Myers Squibb Pharmaceuticals Ltd
Britannia Pharmaceuticals Limited
British Association for Psychopharmacology
British Association of Art Therapists
British Association of Neuroscience Nurses
British Dietetic Association
British Geriatrics Society
British Geriatrics Society-Special Interest Group in Diabetes
British Medical Association (BMA)
British National Formulary (BNF)
British Neuropsychiatry Association
British Society of Rehabilitation Medicine
BUPA
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Care Quality Commission (CQC)
Central Area of North Wales NHS Trust
Chartered Society of Physiotherapy (CSP)
Cheltenham & Tewkesbury Primary Care Trust
Chephalon Ltd
CHESs Research Centre
Cochrane Movement Disorders Group

College of Mental Health Pharmacy
Community District Nurses Association
Community Psychiatric Nurses' Association
Connecting for Health
Co-operative Pharmacy Association
Cornwall & Isles of Scilly PCT
Cornwall Acute Trust
Cure Parkinsons Trust, The
Cyberonics S.A & N.V.
David Lewis Centre, The
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Dudley Beacon & Castle Primary Care Trust
Eisai Ltd
Eli Lilly and Company Ltd
Faculty of Public Health
Fremantle Hospital
Gateshead PCT
GE Healthcare
Gedling Primary Care Trust
George Eilot Hosptal Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Greater Peterborough PCT
Guys and St Thomas NHS Foundation Trust
Hampshire Partnership NHS Foundation Trust
Healthcare Improvement Scotland
Healthcare Quality Improvement Partnership
Help the Aged
Help the Hospices
Herefordshire Primary Care Trust
Hertfordshire Partnership NHS Trust
Independent Healthcare Advisory Services
Institute of Sport and Recreation Management
James Parkinson Centre
Lewy Body Society, The
Liverpool PCT

Maidstone and Tunbridge Wells NHS Trust
Mansfield District PCT
Medicines and Healthcare Products Regulatory Agency (MHRA)
Medtronic International Trading Sarl
Medway NHS Foundation Trust
Mental Health Nurses Association
Mid Staffordshire General Hospitals NHS Trust
Ministry of Defence (MoD)
Napp Pharmaceuticals
National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
National Council for Palliative Care
National Patient Safety Agency (NPSA)
National Schizophrenia Fellowship (Rethink)
National Treatment Agency for Substance Misuse
National Tremor Foundation
NETSCC, Health Technology Assessment
Neurological Alliance
Newcastle PCT
Newcastle, North Tyneside & Northumberland Mental Health Trust
NHS Direct
NHS Plus
Niger Delta University
Norfolk Suffolk and Cambridgeshire Local Specialised Commissioning Group
Norgine Ltd
North Essex Mental Health Trust
North Staffordshire Combined Healthcare NHS Trust
Nottingham University Hospitals NHS Trust
Novartis Pharmaceuticals UK Ltd
Nutricia Ltd (UK)
Orion Pharma (UK) Ltd
Orphan Europe (UK) Ltd
Outer North East London Community Services
Oxleas and Queen Elizabeth NHS Trust
Parkinsons Disease Information Network
Parkinson's Disease Society
PERIGON Healthcare Ltd

Peterborough & Stamford NHS Hospitals Trust
Pfizer Limited
Pierpoint
Pilgrims Hospices in East Kent
Plymouth PCT
Primary Care Neurology Society
Princess Alexandra Hospital NHS Trust
Progressive Supranuclear Palsy [PSP Europe] Association
Public Health Wales
Qbtech Ltd
Relatives and Residents Association
Roche Products Limited
Rotherham NHS Foundation Trust
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians London
Royal College of Psychiatrists
Royal College of Psychiatrists in Wales
Royal College of Speech and Language Therapists
Royal College of Surgeons of England
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine
Royal West Sussex Trust
Sanctuary Care
Schwarz Pharma
Scottish Intercollegiate Guidelines Network (SIGN)
Selby & York PCT
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sherwood Forest Hospitals NHS Trust
Social Care Institute for Excellence (SCIE)

Society of British Neurological Surgeons
South Birmingham Primary Care Trust
South Staffordshire PCT
Staffordshire Moorlands PCT
Stockport PCT
Sue Ryder Care
Tameside and Glossop Acute Trust
Teva Pharmaceuticals Ltd
Teva UK Limited
Trafford Primary Care Trusts
UK Specialised Services Public Health Network
United Kingdom Council for Psychotherapy
University College London Hospitals (UCLH) Acute Trust
Valeant Pharmaceuticals
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Wessex Neurological Centre
West Midlands Ambulance Service NHS Trust
Wirral Hospital Acute Trust
York Teaching Hospital NHS Foundation Trust