Evidence synthesis for decision aid 'treatment choice in early Parkinson's Disease'

project: Shared Decision Making in Early Parkinson's Disease
date: November 2014

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Goal synthesis

Goal: To evaluate and combine best available evidence on the treatment of early Parkinson's Disease patients with Levodopa, pramipexole, ropinirole or rogitotine, to inform patients and clinicians about effect of treatment and adverse effects by means of a decision aid.

Methods: Systematic review if possible, in addition to high standard available reviews. If not possible, due to unavailability of higher order evidence, supplemented by qualitative reviewing and lower class evidence.

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1. Decision aid about treatment choice in early Parkinson's Disease

The Dutch multidisciplinary guideline on Parkinson's disease (PD) regards treatment of de novo Parkinson patients who are young and otherwise healthy with Levodopa or a Dopamine agonist (DA) equipotent. As Parkinson's Disease (PD) is yet incurable and progressive; symptom control is the main goal of treatment. The possibilities and choices in DP treatment are well known to neurologists, but not to patients. The guideline advices the treating physician to consider several characteristics in the decision, such as personal experience with the treatments, the patient's age and symptoms, and the patient's preferences. To be able to fully

consider the patient's preferences, the patient needs to be as informed as possible (and wanted) about the options and needs to be stimulated to balance these options and consider them in relation to the personal situation. Discussing all pros and cons with the patient requires a fair amount of time of the physician. Deciding for the patient might be considered unethical, possibly discourages adherence, and makes make no contribution to a truly informed and motivated patient. Therefore, a decision aid to support and inform the patient in the treatment decision is needed.

A decision aid is a structured tool which informs patients in plain language and understandable charts and figures about treatments options and their benefits and risks. Further, it stimulates patients to consider the information in relation to their own situation and to clearly formulate their preferences. In the next appointment with their physician patients can participate more actively in the treatment decision. Finally, the decision aid can be a trustworthy information source for patients to fall back on when they have questions regarding treatment, adverse effects or alternative options.

Obviously, the decision aid should offer balanced, trustworthy information, based on evidence based information. In the case of initial treatment for PD the evidence is less straightforward than it may seem. Especially on outcomes considered to be relevant by patients, such as influence on non-motor symptoms, chance to develop adverse effects (notably impulse control disorders, or other character changes) or influence on quality of life, information is lacking. RCT's only recently started including quality of life as a primary outcome measure and impulse control disorders are often not recognised or registered. Therefore, in this document the best available evidence on initial treatment of de novo, young Parkinson patients is assembled. It is the backbone of the decision aid.

2. Treatments studied

The decision aid concentrates on the use of levodopa and DAs that are available and used in the Netherlands for treatment for de novo PD patients. The Levodopa-formulas (Madopar® and Sinemet®) and non-ergot dopamine agonists pramipexole (Syfrol®), ropinirole (Requip®) and rotigotine (Neupro®) are included. Generic formulas for these therapies are also available in the Netherlands, but not explicitly included in the studies in this review. The decision aid discusses only levodopa and DAs, MAO-B inhibitors, like selegiline, rasagiline and amantadine are not included. MAO-B inhibitors are less often prescribed and are thought to be less effective. To keep the decision aid comprehensible for patients this option is not discussed. Nonetheless, MAO-B inhibitors are also available for this patient group.

3. Requirements for evidence and included studies

To be included in this evidence synthesis studies preferably provide high class evidence (RCT or meta-analysis of RCT's) about treatment with Levodopa and pramipexole, ropinirole or rotigotine, compared to placebo, for PD patients in the early phase of the disease, e.g. previously untreated. Since studies that meet all criteria are very scarce, lower levels of evidence studies are also included. Nonetheless, studies are required to compare treatment with Levodopa and/or one of the mentioned DAs to placebo . In the case of treatment of non-motor symptoms this requirement is loosened, since studies in this field are even more scarce. On this subject we therefore only refer to (systematic) reviews and consensus-based practice parameters that report recommendations based on a synthesis of best available evidence.

The most cited studies reviewing DAs and Levodopa are Antinoni(1) and Stowe(2). Stowe's tables with comparisons of DAs and Levodopa are very informative, but most of the included studies compare DAs that are not available or used (anymore) in the Netherlands (i.e. Cabergolide; Bromocriptine; Lisuride). Pergolide is available in the Netherlands, but clinicians are advised not to prescribe this ergot DA due to its relation with a increasing chance of valvular heart disease. The same holds for Antonini. Nonetheless, these are the most informative sources available.

References:

1. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet neurology. 2009;8:929-37.
2. Stowe R, Ives N, Clarke C, van Hilten JJ, Ferreira J, Hawker J, et al. Dopamine agonist therapy in early Parkinson ' s disease (Review). The Cochrane Library. 2009.

4. Effect of treatment on motor symptoms

Summary

The following table from Antonini et al. illustrates the average increase in the UPDRS motor scores for PD patients treated with ropinirole and pramipexole, compared to Levodopa(1). The effect size of Levodopa treatment is larger than that of the DAs. The duration of the trials is highly variable, making it impossible to compare treatments directly, but the decline in effect over time between seems larger for DAs (whould ropinirole and pramipexole have the same effect) than for Levodopa.

	Number on levodopa (agonist)	Duration (years)	ΔUPDRS part III score		Dyskinesia (% of patients)		Wearing-off (% of patients)	
			Levodopa	Agonist	Levodopa	Agonist	Levodopa	Agonist
Levodopa vs ropinrole[3]	89 (179)	5	−4·8±8·3	−0·8±10·1	45	20	34	23
Levodopa vs pramipexole[4]	151 (150)	2	−7·3±8·6	−3·4±8·6	30·7	9·9	38·0	23·8
Levodopa vs pergolide[6]	146 (148)	3	−2·8±7·8	2·8±9·8	26·0	8·2	43·8	30·6*

ΔUPDRS=change in unified Parkinson's disease rating scale. * Frequency of motor complications (fluctuations plus dyskinesia).

Table 2: **Results of the main trials of levodopa versus dopamine agonists in early Parkinson's disease**

From: Antonini et al. 2009;8:929-37,p.930(1).

In the next table from Baker et al. results from a meta-analysis on treatment with DAs in the early phase of PD are summarized. Analysis of the DAs versus Levodopa trials show that Levodopa is always more effective than DAs, both on the ADL as well as the motor scales of the UPDRS. On both scales a higher score represents worse functioning. For the relevant categories (non-ergot DAs only; pramipexole only; ropinirole only) the difference in effect ranges from 1.4 to 1.5 points for the ADL score, and 4.2 to 5.5 for the motor score. The article does not report on follow-up, so duration of treatment or disease is unknown.

Table 2
Results of subgroup and sensitivity analysis – efficacy (UPDRS)

	UPDRS ADL score		UPDRS motor score	
	Number of studies	Weighted mean difference (95% CI)	Number of studies	Weighted mean difference (95% CI)
DA versus placebo	6	−1.64 (−2.65 to −0.62)	10	−5.32 (−6.89 to −3.75)
Fixed effect	6	−0.91 (−1.22 to −0.60)	10	−4.64 (−5.24 to −4.05)
Fill and trim	8	−1.07 (−1.97 to −0.17)	9	−5.32 (−6.89 to −3.74)
Non-ergot DAs only	5	−1.67 (−2.83 to −0.51)	8	−5.69 (−7.54 to −3.85)
Ergot DAs only	1	−1.50 (−2.90 to −0.10)	2	−3.53 (−5.82 to −1.23)
Pramipexole only	3	−1.83 (−3.18 to −0.47)	4	−6.62 (−9.46 to −3.78)
Ropinirole only	0	N/A	2	−4.40 (−6.30 to −2.50)
DA versus levodopa	5	2.09 (1.26–2.92)	7	4.69 (3.76–5.61)
Fixed effect	5	2.02 (1.51–2.53)	7	4.69 (3.76–5.61)
Fill and trim	6	1.83 (0.98–2.69)	7	4.69 (3.76–5.61)
Excluding Jadad <3	4	1.83 (1.04–2.64)	6	4.76 (3.80–5.71)
Excluding open-label trials	4	1.83 (1.04–2.64)	6	4.54 (3.55–5.52)
Non-ergot DAs only	3	1.41 (0.77–2.05)	4	4.64 (3.39–5.89)
Ergot DAs only	2	3.05 (2.22–3.89)	3	4.75 (3.37–6.13)
Pramipexole only	2	1.40 (0.72–2.08)	2	4.17 (2.63–5.71)
Ropinirole only	1	1.50 (−0.30 to 3.30)	2	5.55 (3.41–7.68)

ADL = activities of daily living; CI = confidence interval; DA = dopamine agonists; N/A = not available; UPDRS = unified Parkinson's disease rating scale.

From: Baker et al. 2009;15:287–294,p.291(2).

Stowe et al.'s (3) Cochrane review does not present tables or graphs of the performance on motor symptoms of both treatments. Their conclusion is: "*(...) symptomatic control of Parkinson's disease was better with Levodopa than with agonists, but data were reported too inconsistently and incompletely to meta-analyse*." p.2 (3).

Decision Aid

Due to differences in follow-up and various types of DAs studied we are unable to draw stronger conclusions than the following: evidence indicates that Levodopa and DAs both have a positive influence on the motor symptoms of PD, although the effect of Levodopa is larger than that of any DA. The information for patients in the decision aid cannot be formulated more concrete.

References:

1. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet neurology. 2009;8:929-37.
2. Baker WL, Silver D, White M, Kluger J, Aberle J, Patel AA, et al. Dopamine Agonists in the treatment of early Parkinson's disease: A meta-analysis. Parkinsonism and Related Disorders. 2009;15:287–294.
3. Stowe R, Ives N, Clarke C, van Hilten JJ, Ferreira J, Hawker J, et al. Dopamine agonist therapy in early Parkinson ' s disease (Review). The Cochrane Library. 2009.

5. Effect on quality of life

Few studies report effect of treatment on quality of life (QoL) of PD patients in the early stage of the disease. Recently a RCT on the influence of initial treatment with Levodopa, a DA or MAOBI on patients self-rated QoL was published (1). Analysis revealed that patients on levodopa-sparing therapy consequently scored lower on QoL rating scales, although the difference is statistically insignificant. The difference revolved around 1.8 points on the PDQ-39 mobility scale between the two patient groups. This is below the minimum important clinical difference which was set at 6 points. Moreover, comparing DAs and MAOBI the difference was averagely 1.4 points on the same scale, favouring MAOBI.

Levodopa patients developed significantly more involuntary movements, but not more motor fluctuations. This difference was small but significant, with 36% of patients on levodopa therapy reporting dyskinesia after 7 years compared to 33% of patients on levodopa-sparing therapy. Comparing DA's and MAOBI rates of dyskinesia were comparable but significantly more patients on DAs developed motor complications. During the trail far more patients stopped their randomized treatment when receiving MAOBI (72% drop-out over 7 years) or DA (50% drop-out) compared to levodopa (7% drop-out). Overall the authors conclude that there is no compelling evidence to initiate PD treatment with levodopa-sparing therapy when it comes to QoL.

Decision aid

The decision aid does not report on influence of either treatment (levodopa or a DA) on QoL. This is because the differences between both options are too small to be regarded as clinical relevant. Information to patients would not differ between the treatments. On the supporting website the conclusion of the study is explained to patients, in understandable language.

References:

1. PD MED Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. The Lancet. 2014;384(9949):1196-1205.

6. Effect of treatment on non-motor symptoms

Summary

PD also expresses in non-motor symptoms (1-4). There is a wide range of non-motor symptoms associated with PD, of which only a minority has been studied specifically in PD patients. The symptoms are also present in the healthy population, but PD patients have a high chance to develop them and they are often more severe(1). Non-motor symptoms highly influence quality of life of both patients and carers(idem). Treatment of non-motor symptoms is often the same as that for 'normal patients'. Levodopa and DAs have a (suspected) influence on some non-motor symptoms.

Non-motor symptoms can be classified in the following groups of symptoms: neuropsychiatric (depression, attention deficit, dementia and others); sleep disorders (insomnia, RLS, somnolence and others); autonomic

symptoms (nocturia, orthostatic hypotension, erectile impotence and others); gastrointestinal symptoms (nausea, dribbling of salvia, constipation and others); sensory symptoms (pain, olfactory disturbance, visual dysfunction and others); and other symptoms (non-motor fluctuations, fatigue and others)(2). Some non-motor symptoms only present themselves during wearing-off and are thus likely to improve when wearing-off is improved or prevented(1-4). Adjusting dopaminergic therapy is therefore usually the first step.

Due to the wide range of symptoms and available treatments here we only summarize the –suspected– influence of DAs and Levodopa on the symptoms. Recently, some relevant treatment guidelines and reviews about treatment of non-motor symptoms in PD have been published. This selected sample is the base of this summary. Conclusions from these studies have not been rephrased, to prevent misinterpretation and drawing unintended conclusions. The representation of the findings is therefore diverse. For options other than Levodopa of DA's in the treatment of non-motor symptoms the references can be consulted.

Insomnia:
- Rotigotine patches can help to smooth disruptive symptoms such as restless legs syndrome (RLS) or night-time rigidity(1).
- Slow release of Levodopa and carbidopa Levodopa improves sleep quality(2).
- Pramipexole and Rotigotine result in significant improvement on the PD sleep scale(2).

Restless legs syndrome:
- Levodopa/carbidopa probably decreases RLS(4).
- Ropinirole and Pramipexole are approved for treating RLS in the general population in the US, but evidence in the case of PD patients is inconclusive(4).

Sleep dysfunction:
- Effect of dopaminergic treatment on sleep varies. "At low doses, these drugs promote slow-wave and REM sleep and induce somnolence (...), whereas, at high doses, they reduce slow-wave and REM sleep and induce wakefulness.". (2: p.48).

REM sleep behaviour disorder:
- Pramipexole in combination with Clonazepam improves symptom(1).
- Pramipexole (un-controlled study) and Levodopa (open-label study) both seem effective(2).

Depression:
- Pramipexole improves depressive symptoms(1;2;3); especially anhedonia(2).

Anxiety:
- Levodopa seems to improve symptom (n.s.)(2).

Apathy:
- DAs and Levodopa may induce apathy (in the 'on' state)(2).

Urinary bladder:
- Levodopa can both worsen and improve urgency and detrusor overactivity(2).

Nocturia:
- Rotigotine transdermal patch has a positive influence on nocturia(2).

Hypersexuality:
- Understudied, both DAs and Levodopa seem to attribute to the development of hypersexuality(2). Chances of developing a impulse control disorder (ICD), such as hypersexuality, a larger with a DA. For more information see section 6.3 on ICD's.

Pain:

- Levodopa seems to improve central pain perceptions(2).

Decision Aid

Due to the large variation of non-motor symptoms and the fragmented information on treatment we cannot draw firm conclusions for the decision aid. Patients need short and understandable information. Therefore, we decided to state: non-motor symptoms are little researched. There are indications that they improve with both Levodopa and DAs.

References:

1. Torodova A, Jenner P, Chaudhuri KR. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. Practical Neurology. 2014;0;1-13.
2. Chaudhuri KR,Schapira, AHV. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. The Lancet. 2009;8;464-74.
3. Connolly BS, Lang AE. Pharmacological Treatment of Parkinson Disease. A Review. Journal of the American Medical Association. 2014;311;1670-83.
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7. Adverse effects

The overall picture resulting from the comparison between DAs and LD is best illustrated in the following figure(1). There is a clear trade-off between motor-complications and other adverse effects for Levodopa vs DAs. It is this trade-off that should be clear to the patient.

Decision Aid

Although information on adverse effects (AEs) is important for patients, the decision aid should not scare the patient from using treatment or create information overload. On the other hand, we do not want to be incomplete or underestimate the chances of experiencing adverse effects. We therefore choose to present the chances for developing three AEs: nausea, dizziness and somnolence. We choose these three because they occur relatively often and differ between the two treatments. The decision aid further reports on chance on impulse control disorders (ICD), since this is considered a influential AE and on dyskinesia, as illustrative for the motor complications. The balance between these five is meant to represent the trade-off to patients, without scaring them.

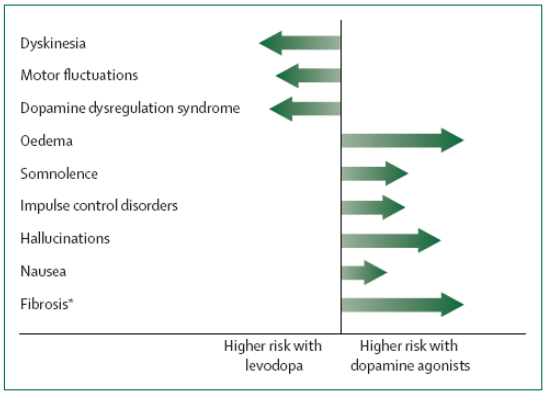

Figure: **Risk of motor complications and other adverse events with dopamine agonists versus levodopa**
The length of the arrows indicates the relative extent of risk. *Ergot agonists *vs* levodopa (see text).

References :

1. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet neurology. 2009;8:929-37.

7.1 Most common adverse effects

Summary

Before and during treatment patients request information on common adverse effects (AEs). Most informative, from the patients perspectives, are the absolute risks of developing these AEs. To determine these risks, we pooled the data from studies resulting from a systematic search (the search strategy is included in appendix A1). Statsdirect version 2.7.8 was used to pool the proportions of patients reporting the AEs (http://www.statsdirect.com/). Results from the random effects models are reported (1). This is mandatory since the included studies show large heterogeneity in outcome. Heterogeneity is expressed in the I^2. In these analyses the I^2 ranges from 60% to 98%. The most commonly used cut-off point for reporting random effects instead of fixed effects is 40%. Therefore, all reported proportions come from random effect models.

Included studies needed to concern de novo patients and monotherapy of Levodopa and/or one of the selected DAs (2-17). Not all studies reported on all side effects. Analysis revealed a large variety between studies in prevalence of AEs (heterogeinity) and study-duration. As the results show, risk of AEs, number of trials reporting on prevalence of the specific AE and robustness of evidence varies between AEs (results of the statistical analysis are included in appendix A.3). Some AEs have more heterogeneous outcomes than others. Due to data limitations we were unable to stratify or correct for probable relevant study- or patient-characteristics, such as individual dopamine agonist, study duration, dosage, patients' age, disease severity, etcetera. This is a limitation of the results. Reviews such as the Cochrane Review of 2009 (2) report on comparable problems.

The pooled results indicate the following absolute risks on commonly reported adverse effects in clinical trials with monotherapy for de novo Parkinson patients:

Table 7.1 Absolute risk on common adverse effects

	Levodopa	Dopamine Agonists (combined)
Nausea	0.28	0.30
Insomnia	0.12	0.12
Somnolence	0.09	0.27
Dizziness	0.15	0.17
Constipation	0.08	0.10
Oedema	0.10	0.15
Hallucinations	0.07	0.10
Headache	0.12	0.12

Another important side effect of dopaminergic treatment is the possibility to develop an impulse control disorders (ICDs). ICDs are traditionally underreported in RCTs. Therefore, we performed an additional, qualitative review of the literature on ICDs and Parkinson. The results of this review are presented in paragraph 6.3.

References:

1. DerSimonian R, Laird N. Meta-analysis in Clinical Trials. *Controlled Clinical Trials* 1986;7:177-188
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mild to moderate Parkinson's disease. The Pramipexole Study Group. Neurology. 1997;49(3):724-8.
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7.2 Motor-complications

Summary

Motor complications are a known long-term effect of dopaminergic therapy. The chance to develop them is higher for patients on Levodopa than for those using DAs. Predicting the chance of developing motor complications for the individual patient is impossible, although age of disease onset appears to be of influence at least in the case of Levodopa(1, 2). Whether the same holds for DAs is unclear.

Patients perceptions about motor complications such as dyskinesias can differ. Not all dyskinesias are equally severe, and sometimes patients do not even notice them. Overall, about 12% of all patients with dyskinesias end up with treatment resistant dyskinesias after 15 years of treatment, while 54% of patients do not regard their dyskniesias disabling(3). Another study revealed that 17% of levodopa treated PD patients need medication adjustment due to dyskinesias after 5 years of treatment, and 43% after 10 years of treatment(4). Thus, the severity of the symptom can vary greatly. Nonetheless, dyskinesias do lower patients' quality of life, independent of disease stage or motor fluctuations(5).

Information about the chance to develop dyskinesias is scarce, especially for DAs. After an extensive literature search and hand-searching the references of the reviews of Stowe and Antonini we found only two studies reporting the frequency of dyskinesias for both Levodopa and DA treated (pramipexole, ropinirole) patients. Combining these we find a 22% incidence of dyskinesia for patients on pramipexole of ropinirole (22 out of 100 patients) after 5 to 6 years, and a 51% chance for patients using Levodopa (51 out of 100 patients) (table 6.2). These results should be interpret with caution, since the evidence base is very small.

Table 7.2 Absolute risk to develop dyskinesias (best evidence)

		Duration (months)	DA-affected	DA-total	LD-affected	LD-total
CALM-PD(6)	Pramipexole	48	37	151	81	150
Int 056(7)	Ropinirole	60	36	177	40	88
			37/151	0,25	81/150	0,54
			36/177	0,20	40/88	0,45
	Total:		73/328	0,22	121/238	0,51

Decision Aid

Due to incomparability of evidence, the requirement of short and unambiguous statements and lack of space, the decision aid only states that the chance to develop motor complications in the long run is larger for levodopa than it is for dopamine agonists, while the chance of other AEs is larger with dopamine agonists than with levodopa.

Further, the decision aid reports on absolute risks of developing the some adverse effects. On motor complications dyskinesias were selected. This concern the risks of 51 out of 100 patients in the case of levodopa and 22 out of 100 patients in the case of dopamine agonist. Although the evidence for the presented figures is not that robust, it is the best available yet. Further, the figures presented in the decision aid are, of course, an indication for patients. Chances might be higher (or lower), since important characteristics such as age are not included in the equation. The figure should therefore be interpret cautiously.

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6. The Parkinson Study Group. Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease. A 4-Year Randomized Controlled Trial. Archives of Neurology. 2004;61:1044-53.
7. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's Disease who were treated with ropinirole or Levodopa. The New England journal of medicine. 2000;342:1484-91.

7.3 Impulse Control Disorders

Summary

The chance to develop an impulse control disorder (ICD) or punding during PD and after initiating treatment with either Levodopa or a dopamine agonist is relevant to both clinician and patient. Therefore, a literature review in Pubmed was performed. 16 out of 279 studies met the inclusion criteria. Search strategy and in- and exclusion criteria are reported in appendix A.2. The results of the studies are summarized in table 6.3. The studies are also shortly described.

The quality of the studies ranges from moderate to acceptable. RCT's are not available, most evidence comes from cohort studies and hardly any study differentiates among age groups. Due to the variety in study-population, disease phase and measurement instruments, no final/overall conclusions can be drawn. To our knowledge, no prospective study following a cohort of de novo PD patients is available. Therefore, no conclusions can be drawn regarding the chance to develop a ICD for a de novo PD patient after starting

treatment with a DA of LD. The following information relates to all PD-patients, without restrictions to disease stage or patient's age. Overall, the evidence is inconclusive, but in combination a trend is detectable from our review:

- Impulse control disorders are more common among PD patients than they are among the total population. This finding holds in a variety of countries.
- Percentages of patients suffering from ICD show large variation between studies. Measurement method, cut-off point and in- or exclusion of punding and other compulsive behaviours are influential.
- The distribution of patients over the different ICDs (pathological gambling, hypersexuality, binge eating and compulsive shopping) and punding varies. Hypersexuality and binge eating seem to be the most prevalent sorts of ICD, but evidence is unclear.
- A relation with (sort of) mediation is not always proven, but synthesis indicates a relation with treatment with dopamine agonists, higher doses of dopaminergic medication and, to a far lesser extent, use of Levodopa. It is suggested that DA's are more strongly related to ICDs and LD influences to punding more.
- Besides medication use, male gender, younger age of disease onset, longer disease duration and symptoms of depression are regularly found to be related to occurrence of an ICDs. Men have a larger chance of developing hypersexuality, women develop relatively more often binge eating or compulsive shopping. Development of pathological gambling seems not to be related to gender.

Decision aid

Since the evidence is often incomparable and unsuitable for meta-analysis, we base the figures presented in the decision aid on the most influential study on this subject, that of Weintraub et al. (2010). They find a prevalence of ICDs of 13.6% among all PD patients. Of patients on Levodopa-monotherapy 7.2% screened positively for an ICD and 14.0% of patients on DA-monotherapy. 17.7% of patients taking both LD and DA screened positively. Since this study is cross-sectional and the patient group is not restricted to early phase patients the absolute influence of medication-type is unclear. These figures should therefore be interpret with caution. Further, risk of ICD appears to be inherent to Parkinson's disease. Risk of developing an ICD cannot entirely be avoided, regardless of treatment choice.

Table 7.3 Summary of prevalence of ICD's in Parkinson patients

	Year, country	**N (PD)** **(%male)**	**Any ICD** **(%of all)**	**Pathological gambling [PG]**	**Hyper-sexuality [HS]**	**Binge eating [BE]**	**Compulsive shopping [SC]**	**Punding [PU]**	**Relation to medication**
Auyeung, Tsoi, Tang, et al.	2011 China	213 60%	15[1] 7.0%	13	8	1	1	N.S.	Higher DA dose (bromocriptine!) associated with ICD
Bastiaens, Dorfman, Christos, et al.	2013 USA	64 72%	18 39.1%	1	6	16	5	12[2]	Only DA-users studied
Fan, Ding, Ma, et al.	2009 China	312 62%	42[3] 13.5%	N.R.	N.R.	N.R.	N.R.	N.S.	Use of DA increases chance of ICD
Isaias, Siri, Cilia, et al.	2008 Italy	50 62%	14[4] 28%	3	5	N.S.	10	N.S.	Only DA-users studied
Joutsa, Martikainen, Vahlberg, et al.	2012 Finland	575 64%	192[5] 23.4%	48	124	64	55	87	No significant relation proven
Kenangil, Ozekmekci, Sohtaoglu, M., et al.	2010 Turkey	554 61%	33[6] 6.0%	4	14	9	8	19	Only DA-users studied
Lee, Kim, Kim, et al.	2010 South Korea	1167 43%	118 10.1%	15	33	40	29	49	High dose DA related to PG, HS and CS. High dose LD related to PU
Lim, Tan, Ngam, et al.	2011 Malaysia	200[7] 56%	47 23.5%	7	27	27	12	40[7]	No significant relation proven
Limotai, Oyama, Go, et al.	2012 USA	1040 ?	89 8.6%	N.R.	N.R.	N.R.	N.R.	12	Higher doses of LD/DA and LEDD associated with ICD's
Perez-Lloret, Rey, Fabre, et al.	2012 Brazil	203 62%	52 25.0%	5	20	28	13	N.S.	DA's associated with ICD's
Solla, Cannas, Floris, et	2011	349	35	11	14	10	4	12	Higher LEDD and use of DA's

	Year, country	N (PD) (%male)	Any ICD (%of all)	Pathological gambling [PG]	Hyper-sexuality [HS]	Binge eating [BE]	Compulsive shopping [SC]	Punding [PU]	Relation to medication
al.	Italy	53%	10.0%						associated with ICD's
Verbaan, van Rooden, Visser, et al.	2009 The Netherlands	353 64%	24[4] 6.8%	1	21	N.S.	3	N.S.	Not assessed per type of medication. Higher doses associated with C-behavior
Voon, Hassan, Zurowski, et al.	2006 Canada	297 69.0%	20[4] 6.7%	10	11	N.S.	2	N.S.	No significant relation proven
Weintraub, Koester, Potenza, et al.	2010 USA/Canada	3090 64.1%	420 13.6%	89	108	132	177	N.S.	DA-users significantly higher odd's ratio's for all ICD's than LD-users
Weintraub, Papay, Siderowf, et al.	2013 USA/Europe	168 71.4%	31[8] 18.5%	2	7	12	5	8	Not studied
Weintraub, Siderowf, Potenza, et al.	2006 USA	272 70.6%	11[4; 9] 4.0%	6	7	N.S.	1	N.S.	DA-use associated with development of ICD

N.R. = not reported in article but was included in study
N.S. = not included in study
[1] This includes present and past ICDs.
[2] Out of these 18 patients, no figures presented for total population.
[3] Of 42 patients who screened positive for an ICD, 12 declined the follow-up telephone interview. Of the remaining 30, 11 patients got confirmed as having an ICD.
[4] Binge eating and punding not assessed, so possible underestimation of prevalence of ICD's.
[5] Compulsive behavior, also including walkabout and hobbyism. 159 patients scored positively on an ICD.
[6] Also included: compulsive drug use (7 patients).
[7] Numbers obtained by combining patients and caregivers records (separate findings accessible in article). Further, punding also includes 'hobbyism' in this study.
[8] Also including 'walkabout' and 'hobbyism' as related behaviour symptoms.
[9] Only current ICD. ICD over the course of the disease results in 18 patients.

Included studies

The literature search resulted in 16 included articles. In table 6.3 the results of the studies are summarized. Each included study is described shortly, followed by a summary of the conclusions.

- Auyeung, M., Tsoi, T. H., Tang, W. K., et al. (2011). "- Impulse control disorders in Chinese Parkinson's disease patients: the effect of ergot derived dopamine agonist." Parkinsonism Relat Disord **17**(8): 635-637.

213 Chinese (Hong Kong) PD patients were screened for past and present ICD's, using both the Questionnaires for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), and the selection criterion for hedonistic homeostatic dysregulation. 15 patients were diagnosed with an ICD, 11 active and 4 prior. 13 had PG, 8 HS, 1 BE and 1 CS. 8 patients had >1 ICD. Of the 213 patients, 97 were on LD monotherapy and 105 used LD and ergot DA Bromocriptine. Only one ICD-patients was on LD monotherapy. In logistic regression younger age at onset of PD, history of anxiety or depression and higher dose of DA exposure are related to developing an ICD.

- Bastiaens, J., Dorfman, B. J., Christos, P.J. et al. (2013). "- Prospective cohort study of impulse control disorders in Parkinson's disease." Mov Disord **28**(3): 327-333.

64 DA-using patients (18 female) were followed up to a maximum of 150 months (partly retrospectively) to determine if and when they would develop ICD's and/or punding. ICD's were assessed in a semi structured interview with patients and available caregivers. 18 patients developed an ICD (9 female): 16 cases of BE (7 female), 6 cases of HS (1 female), 5 cases of CS (3 female) and 1 female patient developed PG. 8/18 patients had two ICD's, 1/18 had three. 12/18 had concomitant punding. The median time to ICD onset was 23 months (range: 3-120 months) after starting DA treatment and 1-19 years (median 5.5 years) after PD onset. All patients used DA's, higher doses were associated with development of more serious ICD('s).

- Fan, W., Ding, H.,Ma, HJ., et al. (2009). "- Impulse control disorders in Parkinson's disease in a Chinese population." Neurosci Lett **465**(1): 6-9.

Questionnaires were mailed out to 400 PD patients and their spouses. The questionnaires included the South Oaks Gambling Screen SOGS, the Lejoyeux's Compulsive Shopping questionnaire, and a specially designed hypersexuality questionnaire. There were items to detect binge eating, drug addiction, dopamine dysregulation syndrome, and internet addiction based on DSM-IV definitions. 312 patient-questionnaires and 132 spouse-questionnaires were returned. 42 patients screened positively for a ICD (13.5%), but 12 declined the follow-up telephone interview. Of the remaining 30 patients, 11 got diagnosed with an ICD. In logistic regression use of DA's and daily alcohol consumption were independent risk factors for ICD behaviour.

- Isaias, I.U., Siri, C., Cilia, R. et al. (2008). "- The relationship between impulsivity and impulse control disorders in Parkinson's disease." Mov Disord **23**(3): 411-415.

50 PD patients were compared to 100 healthy controls. All patients used DA+LD, only two were on DA monotherapy. 14 patients and 20 controls scored positively for an ICD, as determined with the Minnesota Impulsive Disorders Interview (MIDI) and the SOGS. This difference was not significant. Besides the ICD's hyperseksuality, PG and CS, also intermittent explosive disorder was distinguished (found in 3 patients). Binge eating was not studied. 5 patients had multiple ICD's. Younger age was significantly related to ICD's, male gender was only significant for patients. People with ICD(s) scored higher on impulsivity and depression, both among patients and healthy controls.

- Joutsa, J. Martikainen, K., Vahlberg, T., et al. (2012). "- Impulse control disorders and depression in Finnish patients with Parkinson's disease." Parkinsonism Relat Disord **18**(2): 155-160.

A questionnaire was sent to a 1000 members of the Finnish Parkinson association and returned by 605 patients (575 usable questionnaires). The questionnaire included screening for ICD's with QUIP: five questions for each ICD (gambling, sexual behavior, shopping, and eating), and additional questions of other compulsive behaviors (hobbyism, punding, walkabout, and compulsive medication use). Problem gambling was also screened for using the South Oaks Gambling Screen (SOGS). 159 patients scored positively for a ICD (69 had multiple), 192 patients scored positively for compulsive behavior (including ICDs, punding, walkabout and hobbyism). Male gender, younger age, younger PD onset and depressive symptoms were significantly related to compulsive behavior.

- Kenangil, G., Ozekmekci, S., Sohtaoglu, M., et al. (2010). "- Compulsive behaviors in patients with Parkinson's disease." Neurologist **16**(3): 192-195.

Of 554 patients from a movement disorder clinic in Istanbul University hospital, 33 (27 males) scored positively for an ICD. Presence of ICD was determined with an interview with direct questions regarding ICD's, based on DSM-IV. All ICD-patients used a DA, 22 also used LD. 19 patients were diagnosed with punding; 14 with HS; 9 with BE; 8 with CS; 7 with compulsive drug abuse and 4 with increasing demand for gambling.

- Lee, J-Y., Kim, J-M., Kim J.W., et al. (2010). "- Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease." Parkinsonism Relat Disord **16**(3): 202-207.

1167 South Korean PD patients were interviewed (modified version of the Minnesota Impulsive Disorders Interview (MIDI)) and screened for ICD's. ICD's were present in 10.1% of the patients (PU: 4.2%; BE: 3.4%; HS: 2.8%; CS: 2.5%; PG:1.3%). Of 69 ICD patients (excluding punding) 4 patients had 3 ICDs, and 18 had 2 ICDs. Of 49 patients with punding 12 also had one of more ICD. 93.7% of the patients used LD, 72.8% (also) used an DA. Number of patients taking monotherapy of either are not provided. Higher doses of DA had significant Odds ratio's for ICDs PG, CS and HS. Higher doses LD had a significantly higher odds ratio for punding. Binge eating was not influenced by either DA or LD dose.

- Lim, S-Y.,Tan, Z.K., Ngam, P.I., et al. (2011). "- Impulsive-compulsive behaviors are common in Asian Parkinson's disease patients: assessment using the QUIP." Parkinsonism Relat Disord **17**(10): 761-764.

200 patients-caregiver dyads were interviewed (using the QUIP) to determine ICDs and compulsive behavior in patients. 190 caregivers and 195 patients completed the questionnaire. Agreement between both reporters was moderate, occurring in 149 pairs. ICDs occurred in 47 patients (30 according to patients), with 27 cases of BE (17), 26 of HS (16), 12 of CS (7) and 7 of PG (5). Male gender and longer PD duration were positively associated with impulsive-compulsive behavior.

- Limotai, N., Oyama, G., Go, C., et al. (2012). "- Addiction-like manifestations and Parkinson's disease: a large single center 9-year experience." Int J Neurosci **122**(3): 145-153.

For this study the charts of 1040 patients from the University of Florida Center for Movement Disorders & Neurorestoration were screened for ICD's, dopamine dysregulation syndrome (DDS), and the dopamine agonist withdrawal syndrome (DAWS). The maximal follow-up period was from July 2002 until March 2010. Of 1040 patients, 25 met the criteria for DAWS, 14 for DDS and 89 for ICD's. Combinations were very common. 70 of 89 ICD patients used a DA. ICD's were significantly related to higher doses of LD, DA and LEDD. There are significant associations with ICD's and age, age at onset and sex.

- Perez-Lloret, S., Rey, M. V., Fabre, N., et al. (2012). "- Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with Parkinson disease." Clin Neuropharmacol **35**(6): 261-265.

The study includes 203 PD patients and 52 poststroke controls. Screening for ICD's was performed with the short version of the QUIP (QUIP-s). 52 PD patients screened positive for ICD's, 5% of these patients had multiple ICD's. BE (28) was most common, followed by HS (20), CS (13) and PG (5). Younger age, MAO-B exposure and DA exposure were associated with the presence of ICD symptoms in logistic regression. Comparing DA's the Odds ratio of Bromocriptine and ICD was highest with 6.05 (1.34Y27.30), followed by ropinirole, 6.02 (2.04Y17.75); pramipexole, 5.82 (1.81Y18.73); apomorphine, 1.87 (0.64Y5.50); and piribedil, 2.18 (0.56Y8.53).

- Solla, P., Cannas, A., Floris, G. L., et al. (2011). "- Behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease patients with and without motor complications." Prog Neuropsychopharmacol Biol Psychiatry **35**(4): 1009-1013.

349 PD patients and their caregivers (if available) were interviewed about ICD's, DDS, neuropsychiatric disorders, dementia and motor complications. The questionnaire for ICD's was based on recently proposed criteria on pathological gambling (American Psychiatric Association, 2000), hypersexuality (Voon et al., 2006), compulsive shopping (McElroy et al., 1994), binge eating (Nirenberg and Waters, 2006) and punding (Evans et al., 2004). ICD's were detected in 52 patients (PG: 11; HS: 14; BE: 10; CS: 4) and punding in 12. All patients, except those with CS, were taking significantly higher doses of LEDD and used DA's more frequently. Males had larger risk on HS, females had a larger chance on depression and anxiety. ICD's were significantly more frequent in patients with motor complications. Dyskinesias and ICD's were also related.

- Verbaan, D., van Rooden, S. M., Visser, M., et al. (2009). "- Psychotic and compulsive symptoms in

Parkinson's disease." Mov Disord **24**(5): 738-744.

353 PD patients were interviewed with a 'semi-structured interview-based scale of seven items (hallucinations, illusions, paranoid ideation, altered dream phenomena, confusion, sexual preoccupation, and compulsive behavior (shopping or gambling)) called SCOPA-PC. All items, except for those about compulsive behaviour, were based on the Parkinson Psychosis Rating Scale. The compulsive behaviour-items are based on the DSM-IV-criteria. Depending on the cut-off the number of patients reporting compulsive behaviour (including sexual preoccupation) was 68 (number of patients with a score of ≥1) or 24 (score ≥2). Only sexual preoccupation (36 vs. 21); Compulsive shopping (26 vs. 3) and compulsive gambling (7 vs. 1) were assessed. The 24 patients (scoring ≥2) were significantly more often men, had younger disease onset, had higher daily dosed of LD and/of DA and had more motor fluctuations.

- Voon, V., Hassan, K., Zurowski, M., et al. (2006). "- Prevalence of repetitive and reward-seeking behaviors in Parkinson disease." Neurology **67**(7): 1254-1257.

396 PD patients were approached to fill-in a short questionnaire including items about ICD behaviour. 297 completed the questionnaire. Patients who scored positive on the ICD-items were approached for an appointment with a psychiatrist. 55 patients scored positively, of which 30 were eligible, willing and available to be psychiatrically assessed. HS lifetime prevalence was 2.4%, 1.3% of patients had subsyndromal HS. Current prevalence of CS was 0.7%. PG prevalence was 3,4% (as previously reported in another study). All compulsive behaviours were more frequent on DA's than LD, but this was not statistically tested.

- Weintraub, D., Koester, J., Potenza, M.N., et al. (2010). "- Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients." Arch Neurol **67**(5): 589-595.

3090 PD patients of 33 movement disorder centres in the USA and 13 in Canada were assessed by trained research staff for the presence of symptoms of ICD's (PG, HS, BE and CS). The semi-structured diagnostic instruments were based on the Massachusetts Gambling Screen, the MIDI and the DSM-IV. 98.1% of all patients used LD and/or a DA. 66.0% used at least one DA and 86.8% was taking LD. At least 1 active ICD was detected in 13.6% of all patients, with 28.7% of ICD-patients having 2 or more ICDs. PG was present in 5.0%; HS in 3.5%; CS in 5.7% and BE in 4.3% of all patients. ICD were more common in patients treated with DAs (17.1% had a ICD) than in patient not treated with DAs (6.9%). This difference was significant for all ICDs. An ICD was present in 17.7% of patients taking both a dopamine agonist and Levodopa, 14.0% taking a dopamine agonist without Levodopa, and 7.2% taking Levodopa without a dopamine agonist. Age younger than 65; being unmarried, living in the USA, current smoking, family history of gambling problems, treatment with DA, treatment with LD increase the risks (odd's ratio) of developing a ICD significantly.

- Weintraub, D., Papay, K., Siderowf, A., et al. (2013). "- Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study." Neurology **80**(2): 176-180.

168 PD patients and 143 healthy controls were screened for ICDs with the QUIP. Besides PG, HS, BE, CS and punding also wandering and hobbyism are included in the QUIP. 18.5% of patients and 20.3% of healthy controls scored positively for impulse control or related behavioural symptoms. The differences between patients and controls were not significant, with the exception of hobbyism which was more common among controls. The diagnosis of PD did not predict ICD behaviour in logistic regression analysis.

- Weintraub, D., Siderowf, A., Potenza, M.N. et al. (2006). "- Association of dopamine agonist use with impulse control disorders in Parkinson disease." Arch Neurol **63**(7): 969-973.

PD patients at 1 of 2 movement disorders centres (the University of Pennsylvania/the Philadelphia Veterans Affairs Medical Center) were screened for PG, HS or CS with a modified MIDI-interview. Due to the veteran population men were overrepresented in the sample. Patients were asked after current and past symptoms related to the ICDs. To verify accuracy, patients charts were checked over the course of their disease. Also, information about dose and sort of medication was collected. 273 patients completed the screening process, 18 patients screened positive for an ICD during their disease, 11 patients had a current ICD. Current and previous percentages were: PG 6% and 7%; HS 7% and 7%; CS 1% and 4%. All patients with ICD used an DA. Younger age, longer disease duration, history of ICD symptoms prior to PD and use of DA or amantadine were associated with active ICD. Higher dose of LEDD was borderline insignificant.

8. Omissions in literature and subsequently in the decision aid

As indicated throughout this document, scientific evidence in the treatment of de novo PD actually is rather thin. There are several relevant factors from the perspective of patients, that could not be addressed in this synthesis. Future research should include these. For the decision aid, the most important factors on which

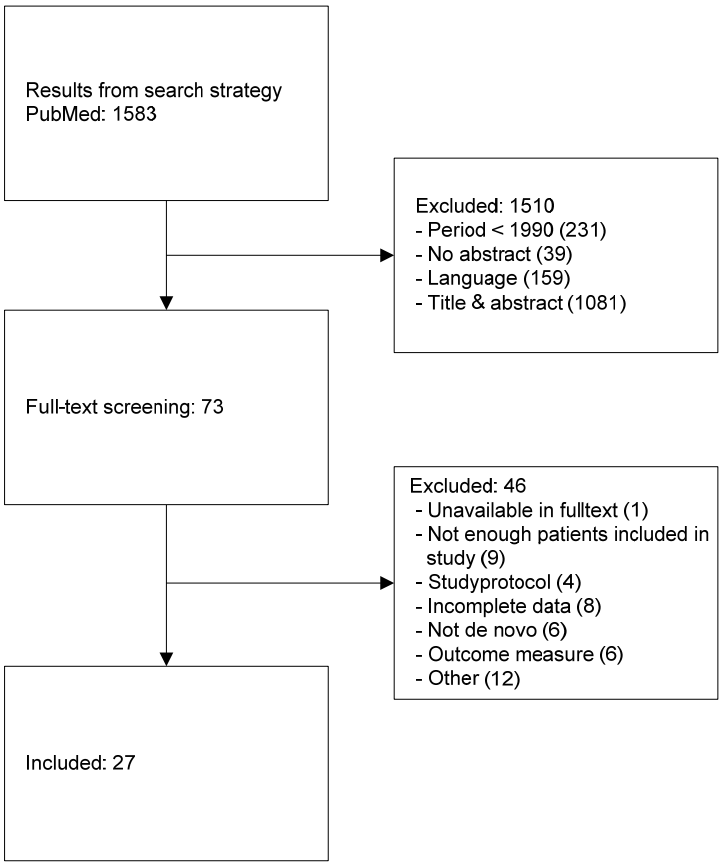
comparative data is lacking are:

- Research is often unclear about the differences in effect of treatment for different age groups. As the decision aid (in accordance with the Dutch guideline) compares treatment with Levodopa and DAs only for patients younger than 65, the evidence should concentrate on this age group. This is impossible.
- Patients often request for information relevant for their type of PD. They are conscious that tremor-dominant PD might require other treatment than rigidity-dominant PD. Evidence on which type of PD responses best to which type of treatment was not to be found, which forced us not to report on this subject in the decision aid.

Appendix

A.1 Search strategy in Pubmed (august 2013):

Parkinson's disease [MESH] and (Levodopa [MESH] OR "Dopamine Agonists" [Pharmacological Action] OR Ropinirol OR Pramipexol OR Rotigotine))) AND (early[tiab] OR initial[tiab] OR start[tiab] OR de novo [tiab] OR drug naive [tiab] OR mild [tiab] OR agonist-naive [tiab] OR monotherapy [tiab] OR new user [tiab])))) NOT Deep brain stimulation [title])) NOT Restless legs syndrome [title] Filters: Humans



A.2 Search strategy and in-/exclusion criteria 'Impulse control disorders'

Search strategy:

Search	Add to builder	Query	Items found	Time
#3	Add	Search **(((Parkinson's disease [mesh]) AND (impulse control disorders [tiab] OR pathological gambling [tiab] OR hypersexuality [tiab] OR binge eating [tiab] OR compulsive shopping [tiab] OR punding [tiab] OR compulsive behavior [tiab]))) NOT (Deep brain stimulation [tiab] OR subthalamic stimulation [tiab])**	279	04:20:37
#2	Add	Search **(Parkinson's disease [mesh]) AND (impulse control disorders [tiab] OR pathological gambling [tiab] OR hypersexuality [tiab] OR binge eating [tiab] OR compulsive shopping [tiab] OR punding [tiab] OR compulsive behavior [tiab])**	315	04:17:15
#1	Add	Search **Parkinson's disease [mesh]**	44689	04:16:48

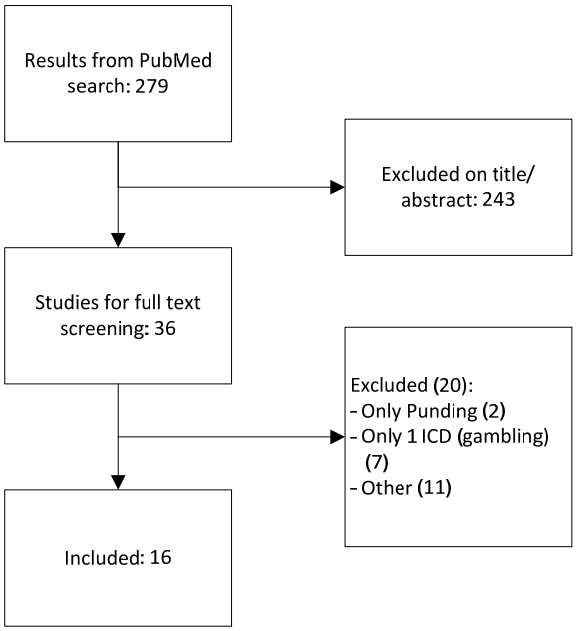
07-11-2013

In- and exclusioncriteria:
Inclusion:

- Idiopathic Parkinson disease;
- Treatment with non-ergot dopamine agonist, available in the Netherlands (Ropinirol (Requip®), Pramipexol (Sifrol®), Rotigotine (Neupro®));
- Treatment with Levodopa (Levodopa-carbidopa,(Sinemet®), Levodopa-benserazide (Madopar®);
- Outcome measure: prevalence of ICDs (pathological gambling, hyper sexuality, binge eating, compulsive shopping, etc.) or punding;
- Design: experimental, cohort studies, case-control studies (?),

Exclusion:

- Non-idiopathic PD (notably: Restless leg syndrome, Lewy-body dementia, parkinsonisms, Multiple System Atrophy (MSA), Progressive Supranucleair Paralysis (PSP));
- Advanced therapies (DBS, Duodopa, Levodopa-infusion; Apomorphine injections);
- Adjunct therapies/combination therapies;
- Severe cognitive impairment;
- Studies after genetic markers or biological factors;
- Studies after dopamine deregulation syndrome or decision-making;
- Ergot dopamine agonists (Bromocriptine, Cabergoline, Lisuride, Pergolide, Piribedil, alpha-droergotamine, CQA206-291, alpha DHEC);
- Mao-B inhibitors (Selegiline (Eldepryl®), Rasasgiline (Azilect®)) or Amantadine (Symmetrel®), advanced medical therapies (Entacapone, Stalevo), Anticholinergica.
- Design: Uncontrolled (experimental), non-systematic review, case reports, opinion pieces, practice guidelines, descriptive review;
- Published before 1990;
- Published in other languages than Dutch or English;
- Unavailable for all university libraries in the Netherlands.



A.3 Results of analyses of adverse effects (pooled data from meta-analyses)

This chapter presents the outcomes of meta-analyses for the following adverse effects:

A.3.1a	Constipation Dopamine agonists	p. 19
A.3.1b	Constipation Levodopa	p. 22
A.3.2a	Dizziness Dopamine agonists	p. 25
A.3.2b	Dizziness Levodopa	p. 28
A.3.3a	Oedema Dopamine agonists	p. 31
A.3.3b	Oedema Levodopa	p. 33
A.3.4a	Somnolence Dopamine agonists	p. 35
A.3.4b	Somnolence Levodopa	p. 38
A.3.5a	Insomnia Dopamine agonists	p. 41
A.3.5b	Insomnia Levodopa	p. 44
A.3.6a	Nausea Dopamine agonists	p. 46
A.3.6b	Nausea Levodopa	p. 49
A.3.7a	Hallucination Dopamine agonists	p. 52
A.3.7b	Hallucinations Levodopa	p. 55
A.3.8a	Headache Dopamine agonists	p. 57
A.3.8b	Headache Levodopa	p. 60

A.3.1a Constipation Dopamine agonists

Stratum	Responding	Total	Source
1	29	163	USA-B
2	23	213	USA/C
3	12	116	USA R
4	7	215	rotigotine patch (2007)
5	9	228	rotigotine patch (2007)
6	13	202	Singer 2007
7	11	181	Watts 2007
8	7	140	Stocchi 2008
9	7	149	Stocchi 2008
10	13	106	Hauser 2010
11	16	103	Hauser 2010
12	32	223	Poewe 2011
13	25	213	Poewe 2011
14	31	151	CALM-PD
15	17	179	Int 056

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.17791411	0.12250809	0.24541525	6.31497882	6.66554968	USA-B
2	0.10798122	0.06969335	0.15761075	8.24027724	6.98064198	USA/C
3	0.10344828	0.05460675	0.17373177	4.50519831	6.18551352	USA R
4	0.03255814	0.01318836	0.06592892	8.31728918	6.99067823	rotigotine patch (2007)
5	0.03947368	0.01820615	0.07360836	8.81786677	7.05226624	rotigotine patch (2007)
6	0.06435644	0.03470904	0.10753726	7.81671159	6.92248069	Singer 2007
7	0.06077348	0.0307252	0.10613717	7.00808625	6.7953876	Watts 2007
8	0.05	0.02033613	0.10030493	5.42934155	6.46191299	Stocchi 2008
9	0.04697987	0.01909426	0.09439941	5.77589526	6.54749101	Stocchi 2008
10	0.12264151	0.06694589	0.20058711	4.12013862	6.04357696	Hauser 2010

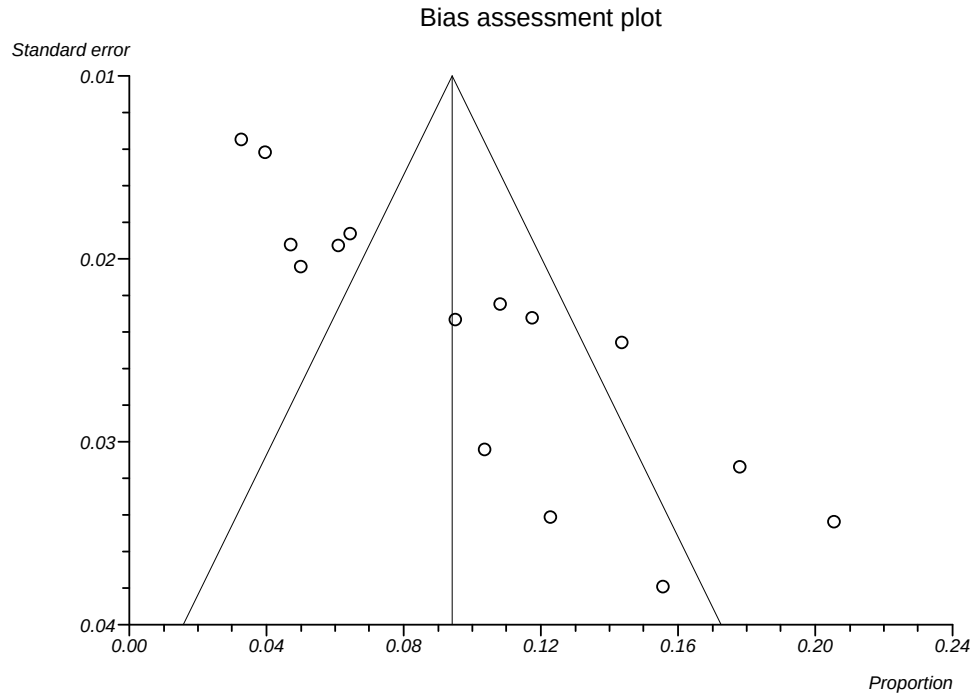
11	0.15533981	0.09147724	0.23997103	4.00462072	5.99713229	Hauser 2010
12	0.14349776	0.10026811	0.19649672	8.62533693	7.02929834	Poewe 2011
13	0.11737089	0.07741443	0.16837208	8.24027724	6.98064198	Poewe 2011
14	0.20529801	0.14395655	0.27856565	5.8529072	6.56541465	CALM-PD
15	0.09497207	0.05630278	0.14770305	6.93107432	6.78201385	Int 056

Fixed effects (inverse variance)
Pooled proportion = 0.09406997 (95% CI = 0.08314538 to 0.10559494)

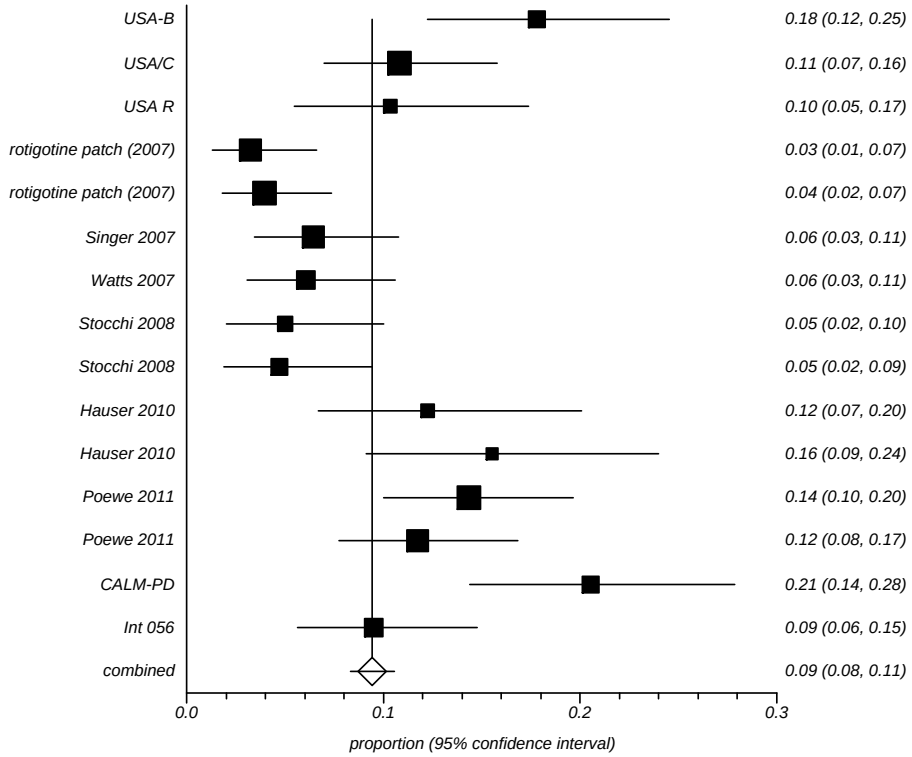
Non-combinability of studies
Cochran Q = 75.46542252 (df = 14) P < 0.0001
Moment-based estimate of between studies variance = 0.02546483
I^2 (inconsistency) = 81.4% (95% CI = 69.5% to 87.3%)

Random effects (DerSimonian-Laird)
Pooled proportion = 0.09724788 (95% CI = 0.07227372 to 0.12547478)

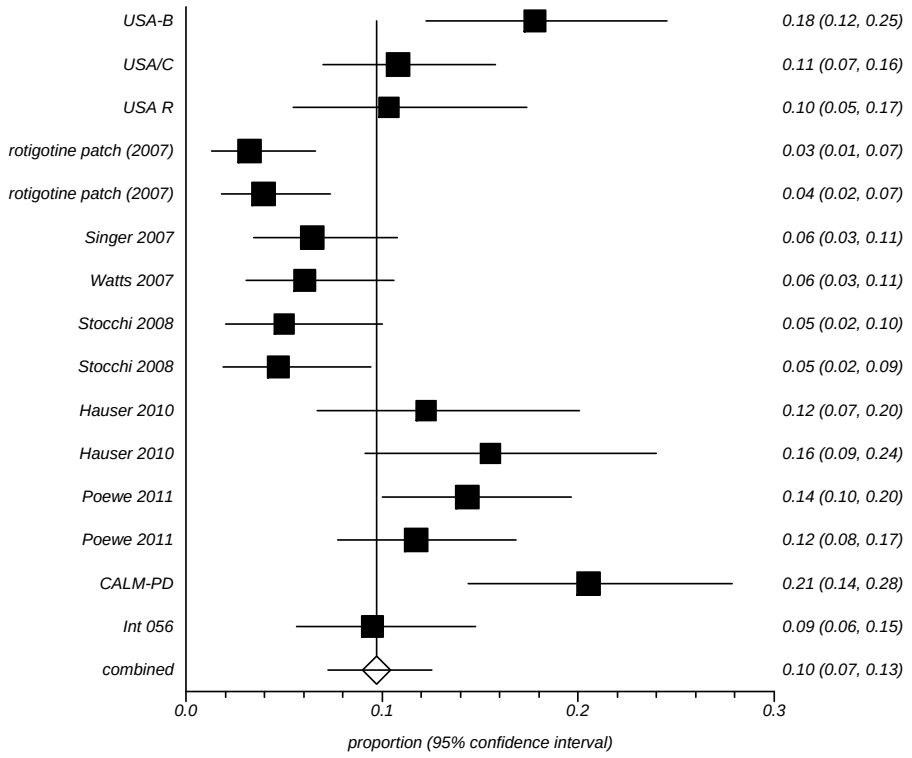
Bias indicators
Begg-Mazumdar: Kendall's tau = 0.6952381 P = 0.0001
Egger: bias = 6.38382741 (95% CI = 4.45522973 to 8.31242509) P < 0.0001
Harbord: bias = 5.28782158 (92.5% CI = -4.02474898 to 14.60039214) P = 0.2917



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.1b Constipation Levodopa

Stratum	Responding	Total	
1	19	150	CALM-PD
2	11	89	Int 056
3	4	92	ELLDOPA
4	7	88	ELLDOPA
5	3	91	ELLDOPA
6	10	215	Hauser 2009

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.12666667	0.07801453	0.19072061	20.65663475	18.39851905	CALM-PD
2	0.12359551	0.06334346	0.21039404	12.3119015	15.27080812	Int 056
3	0.04347826	0.01197159	0.10759345	12.72229822	15.48095694	ELLDOPA
4	0.07954545	0.03258001	0.15704871	12.1751026	15.19894364	ELLDOPA
5	0.03296703	0.00685089	0.09333243	12.58549932	15.41179747	ELLDOPA
6	0.04651163	0.02252639	0.08387117	29.54856361	20.23897478	Hauser 2009

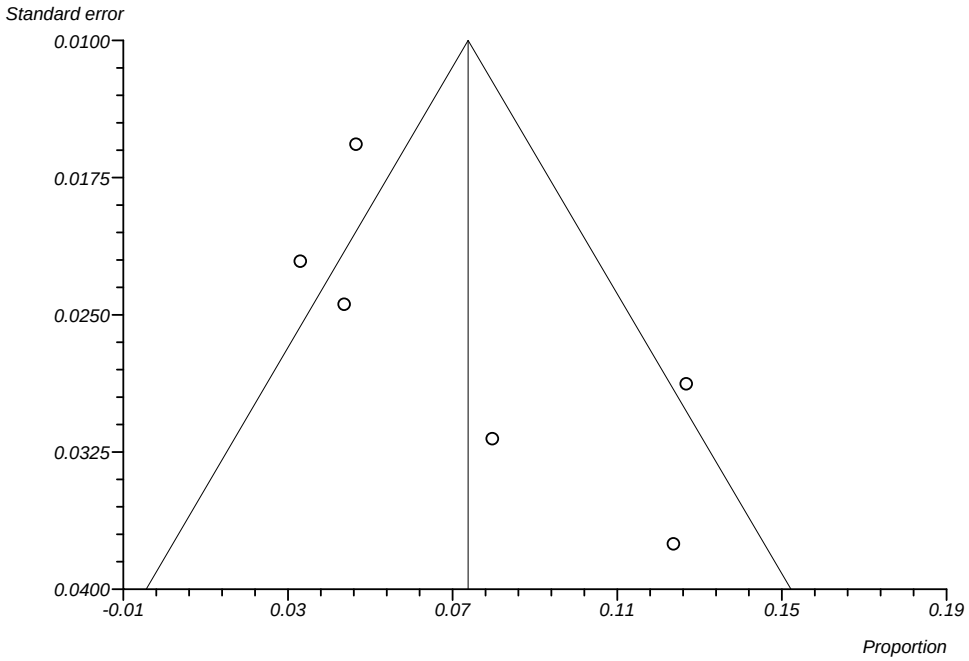
Fixed effects (inverse variance)
Pooled proportion = 0.07386845 (95% CI = 0.0560435 to 0.09393178)

Non-combinability of studies
Cochran Q = 14.03273544 (df = 5) P = 0.0154
Moment-based estimate of between studies variance = 0.0152927
I^2 (inconsistency) = 64.4% (95% CI = 0% to 83.2%)

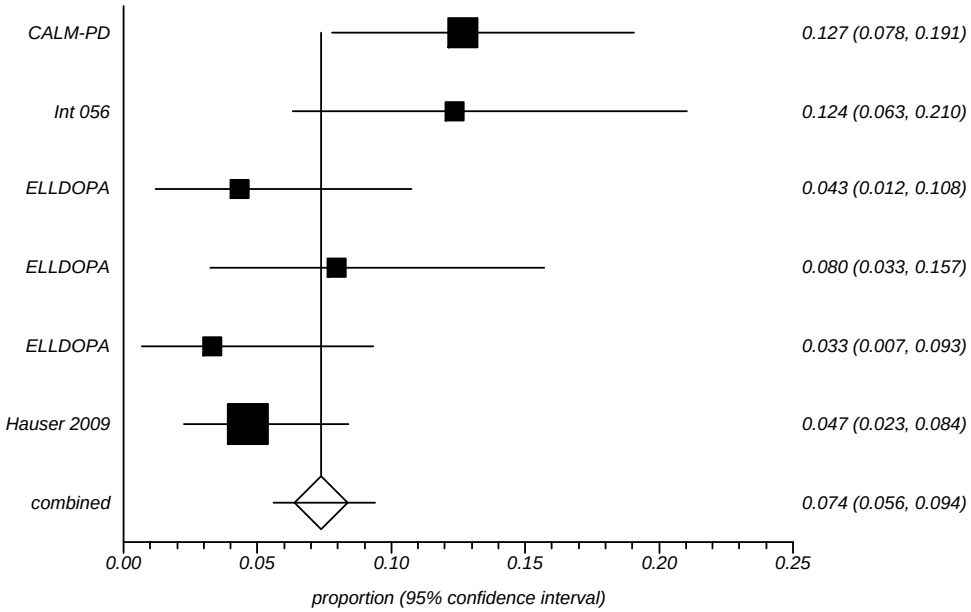
Random effects (DerSimonian-Laird)
Pooled proportion = 0.0751125 (95% CI = 0.04568047 to 0.11111715)

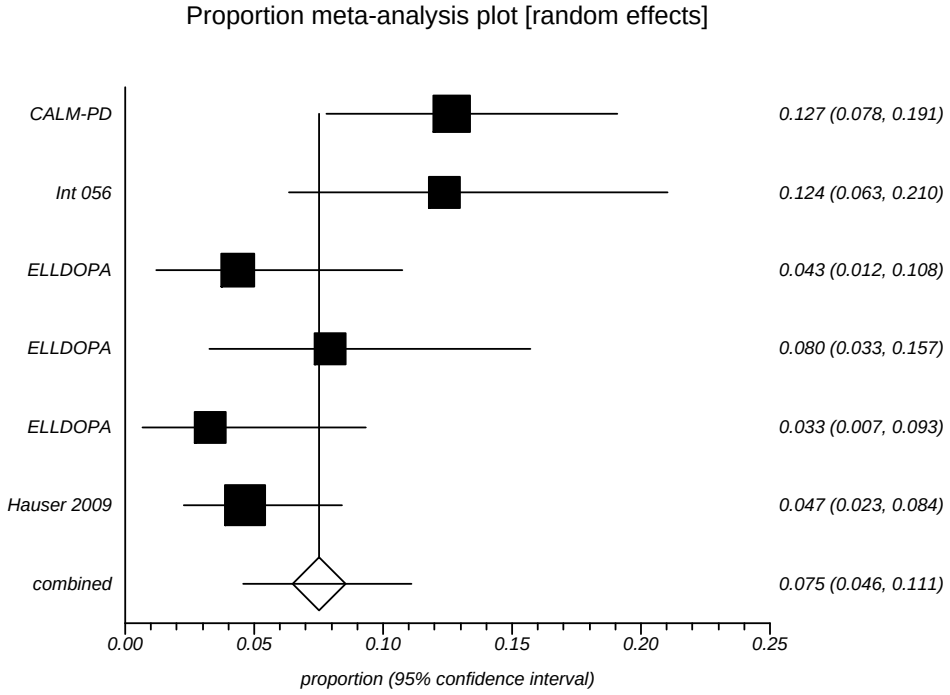
Bias indicators
Begg-Mazumdar: Kendall's tau = 0.6 P = 0.1361 (low power)
Egger: bias = 3.48875407 (95% CI = -1.10282234 to 8.08033049) P = 0.1025
Harbord: bias = 0.89487457 (92.5% CI = -9.52016036 to 11.3099095) P = 0.8472

Bias assessment plot



Proportion meta-analysis plot [fixed effects]




Proportion meta-analysis plot [random effects]
CALM-PD
Int 056
ELLDOPA
ELLDOPA
ELLDOPA
Hauser 2009
combined
0.127 (0.078, 0.191)
0.124 (0.063, 0.210)
0.043 (0.012, 0.108)
0.080 (0.033, 0.157)
0.033 (0.007, 0.093)
0.047 (0.023, 0.084)
0.075 (0.046, 0.111)
0.00
0.05
0.10
0.15
0.20
0.25
proportion (95% confidence interval)

A.3.2a Dizziness Dopamine agonists

Stratum	Responding	Total	
1	12	28	USA-A
2	39	213	USA/C
3	14	41	Int R
4	42	116	USA R
5	14	215	rotigotine patch (2007)
6	17	228	rotigotine patch (2007)
7	43	202	Singer 2007
8	34	181	Watts 2007
9	9	140	Stocchi 2008
10	9	149	Stocchi 2008
11	26	223	Poewe 2011
12	25	213	Poewe 2011
13	39	151	CALM-PD
14	36	179	Int 056

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.42857143	0.24462394	0.62820637	1.26471871	5.04092008	USA-A
2	0.18309859	0.13355979	0.24168912	9.33275185	7.55333502	USA/C
3	0.34146341	0.20083411	0.50594747	1.83166158	5.72242471	Int R
4	0.36206897	0.27488696	0.45647842	5.10248583	7.09384568	USA R
5	0.06511628	0.03605387	0.10684135	9.41997383	7.55880312	rotigotine patch (2007)
6	0.0745614	0.04403266	0.11669728	9.9869167	7.59218855	rotigotine patch (2007)
7	0.21287129	0.15854692	0.27582673	8.85303096	7.52149242	Singer 2007
8	0.1878453	0.13373544	0.25247602	7.93720017	7.45098217	Watts 2007
9	0.06428571	0.02981431	0.11852576	6.14914959	7.25968544	Stocchi 2008
10	0.06040268	0.02798908	0.11156485	6.5416485	7.30966939	Stocchi 2008
11	0.11659193	0.07759231	0.16615272	9.76886175	7.57977225	Poewe 2011
12	0.11737089	0.07741443	0.16837208	9.33275185	7.55333502	Poewe 2011
13	0.25827815	0.19055408	0.33573966	6.62887048	7.32005878	CALM-PD
14	0.20111732	0.14501404	0.26739422	7.84997819	7.44348738	Int 056

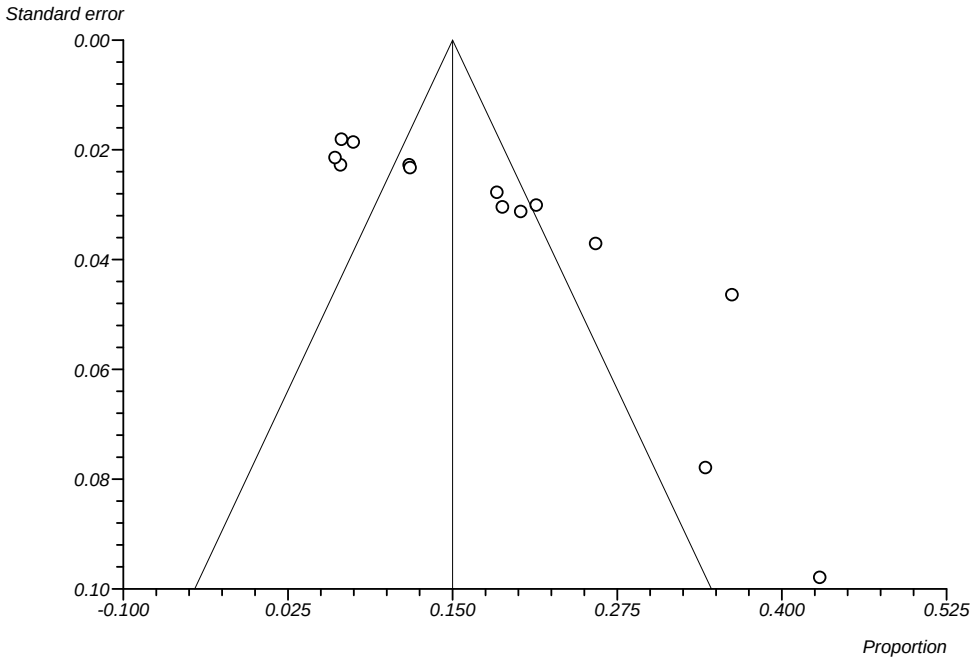
Fixed effects (inverse variance)
Pooled proportion = 0.1503005 (95% CI = 0.13597034 to 0.16521643)

Non-combinability of studies
Cochran Q = 129.10598141 (df = 13) P < 0.0001
Moment-based estimate of between studies variance = 0.05513774
I^2 (inconsistency) = 89.9% (95% CI = 85.3% to 92.6%)

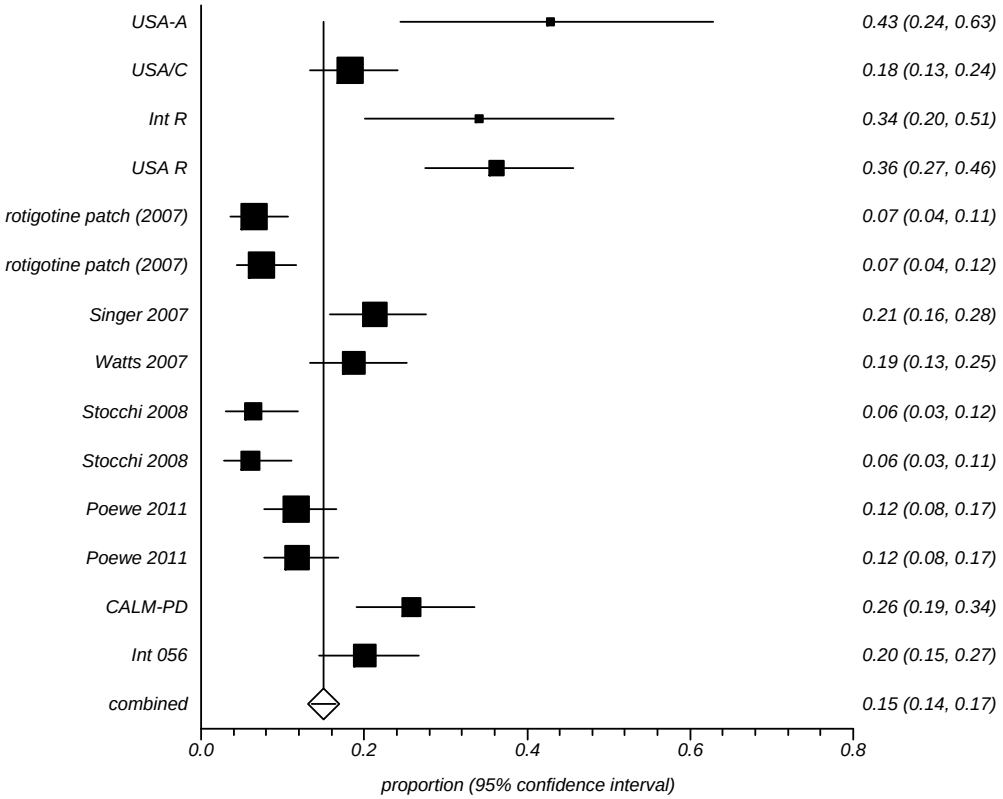
Random effects (DerSimonian-Laird)
Pooled proportion = 0.17159272 (95% CI = 0.12491366 to 0.2239629)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.78021978 P < 0.0001
Egger: bias = 6.99026456 (95% CI = 4.4602352 to 9.52029392) P < 0.0001
Harbord: bias = 7.7942359 (92.5% CI = 1.53711005 to 14.05136176) P = 0.0318

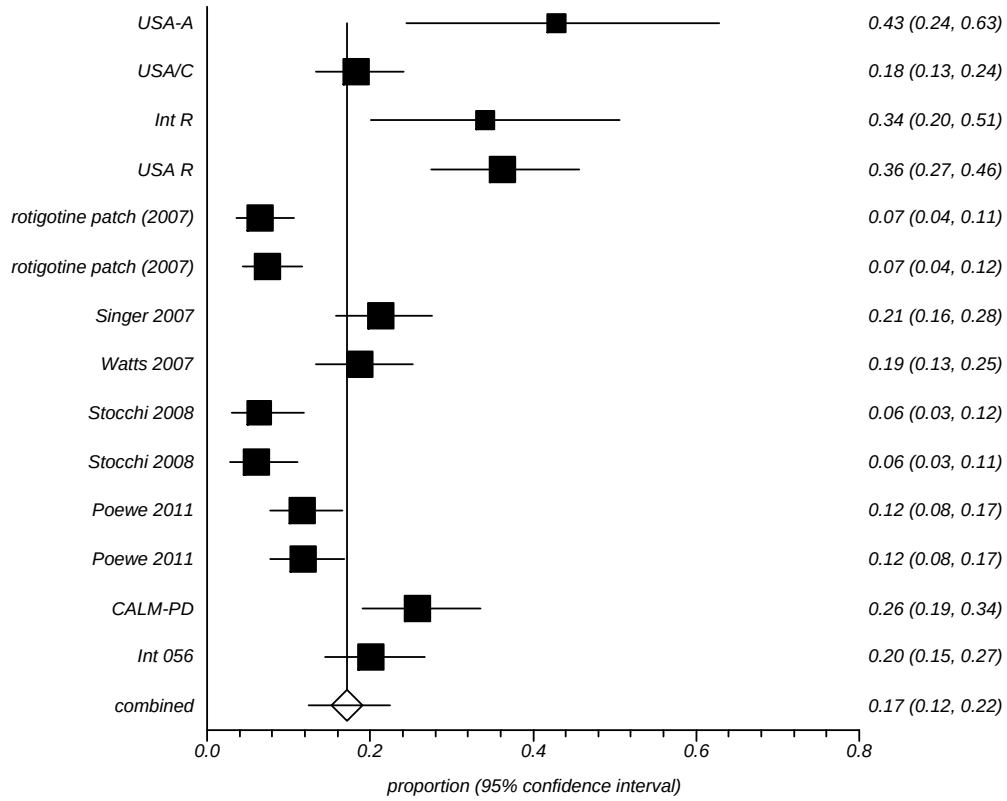
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.2b Dizziness Levopoda

Stratum	Responding	Total	
1	36	150	CALM-PD
2	17	89	Int 056
3	10	92	ELLDOPA
4	5	88	ELLDOPA
5	14	91	ELLDOPA

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.24	0.17410455	0.31645475	29.32038835	21.66621228	CALM-PD
2	0.19101124	0.11539083	0.28811769	17.47572816	19.53205494	Int 056
3	0.10869565	0.05336994	0.19082333	18.05825243	19.68690318	ELLDOPA
4	0.05681818	0.01870386	0.1276324	17.2815534	19.47868948	ELLDOPA
5	0.15384615	0.08674052	0.24463657	17.86407767	19.63614011	ELLDOPA

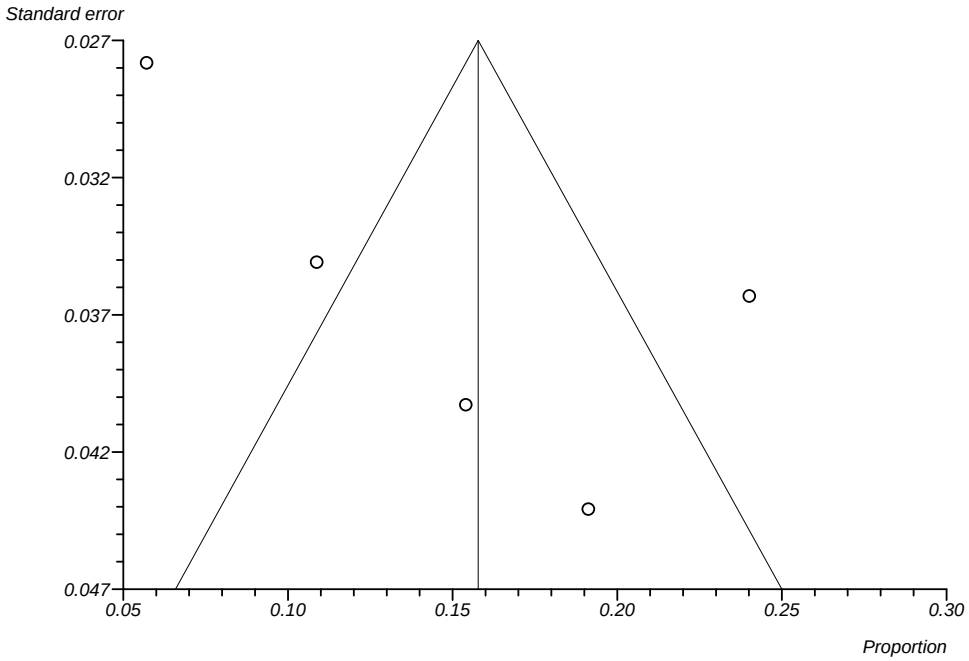
Fixed effects (inverse variance)
Pooled proportion = 0.15790921 (95% CI = 0.12772942 to 0.19063912)

Non-combinability of studies
Cochran Q = 18.00317541 (df = 4) P = 0.0012
Moment-based estimate of between studies variance = 0.03445762
I^2 (inconsistency) = 77.8% (95% CI = 24.4% to 89%)

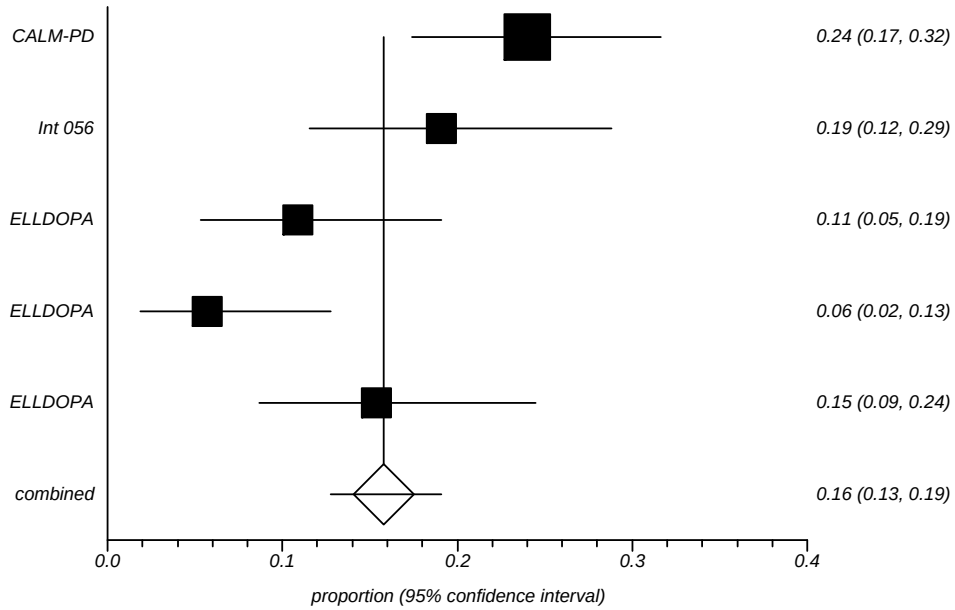
Random effects (DerSimonian-Laird)
Pooled proportion = 0.14952519 (95% CI = 0.08993562 to 0.22106372)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.6 P = 0.2333 (low power)
Egger: bias = 9.02224778 (95% CI = -5.71449973 to 23.75899529) P = 0.1465
Harbord: bias = -13.04664652 (92.5% CI = -29.18526777 to 3.09197472) P = 0.1188

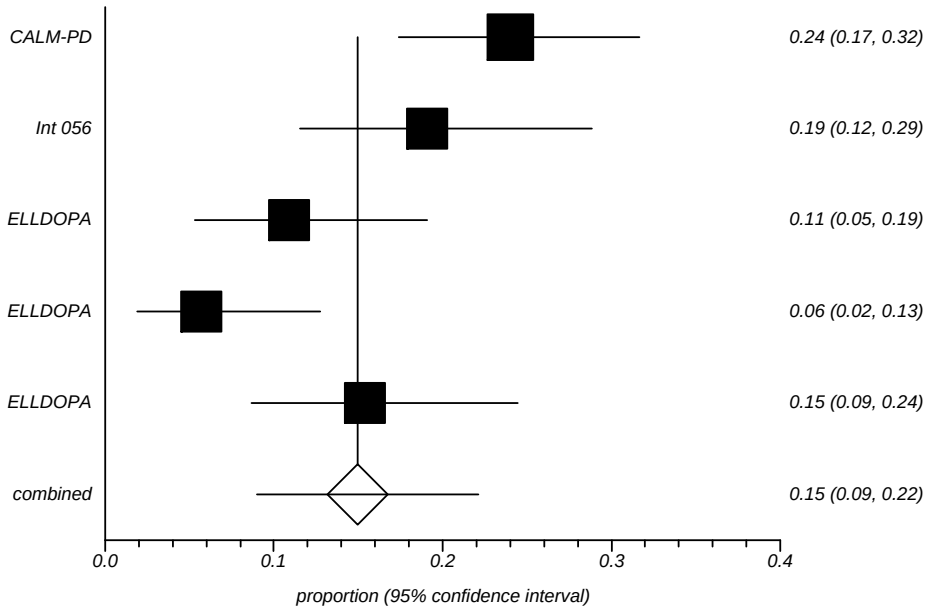
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.3a Oedema Dopamine agonists

Stratum	Responding	Total	
1	13	163	USA-B
2	10	202	Singer 2007
3	64	151	CALM-PD
4	25	179	Int 056

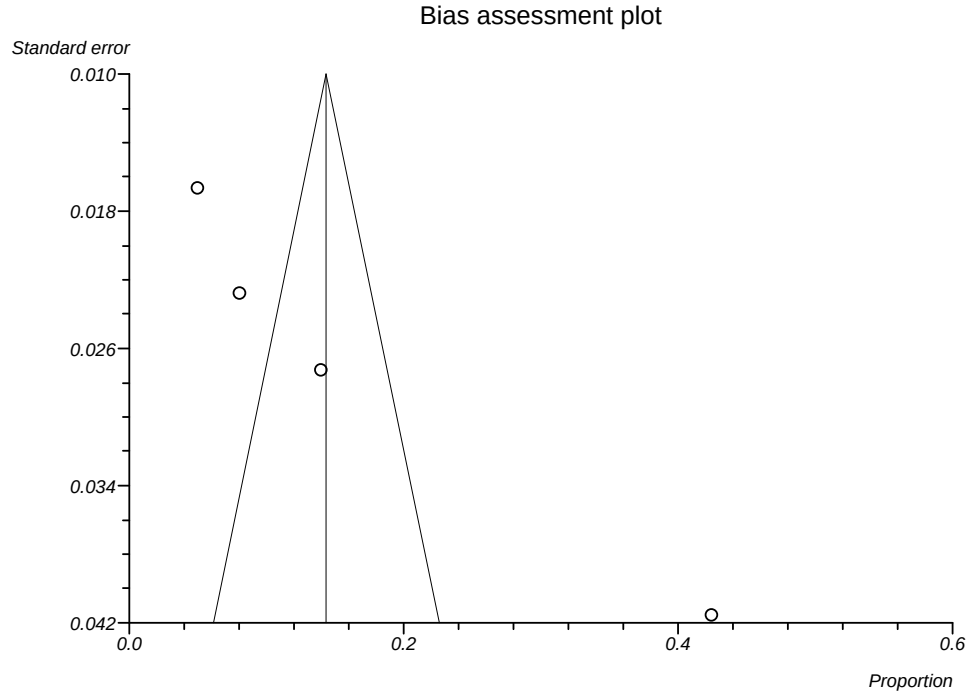
Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.0797546	0.043149	0.13252135	23.4620887	24.95481105	USA-B
2	0.04950495	0.02399165	0.089155	29.04148784	25.12630759	Singer 2007
3	0.42384106	0.34391824	0.50681242	21.7453505	24.88501454	CALM-PD
4	0.1396648	0.09246693	0.19923333	25.75107296	25.03386681	Int 056

Fixed effects (inverse variance)
Pooled proportion = 0.14350133 (95% CI = 0.1185146 to 0.17044635)

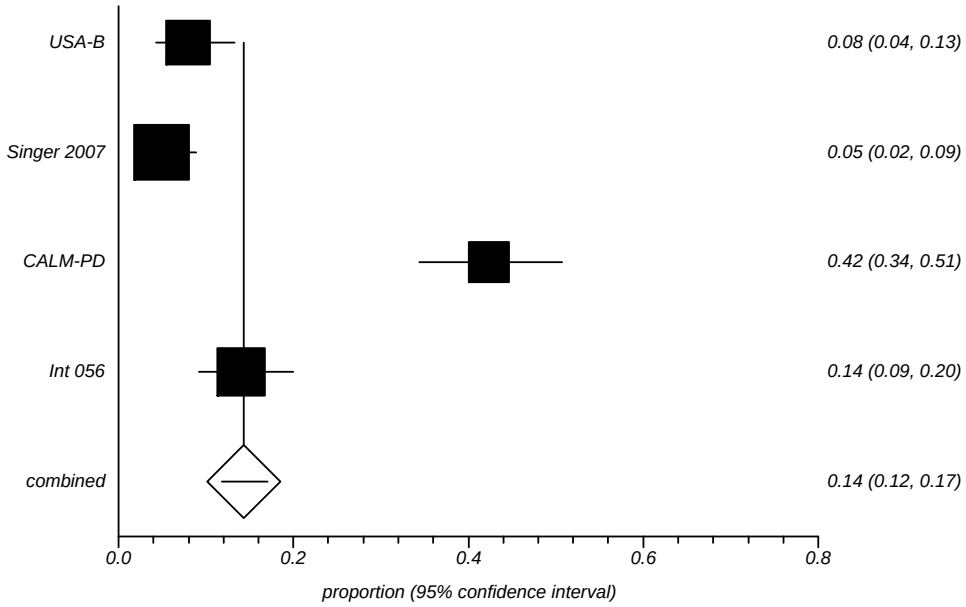
Non-combinability of studies
Cochran Q = 89.43592574 (df = 3) P < 0.0001
Moment-based estimate of between studies variance = 0.16553435
I^2 (inconsistency) = 96.6% (95% CI = 94.6% to 97.7%)

Random effects (DerSimonian-Laird)
Pooled proportion = 0.15408335 (95% CI = 0.0396931 to 0.32461164)

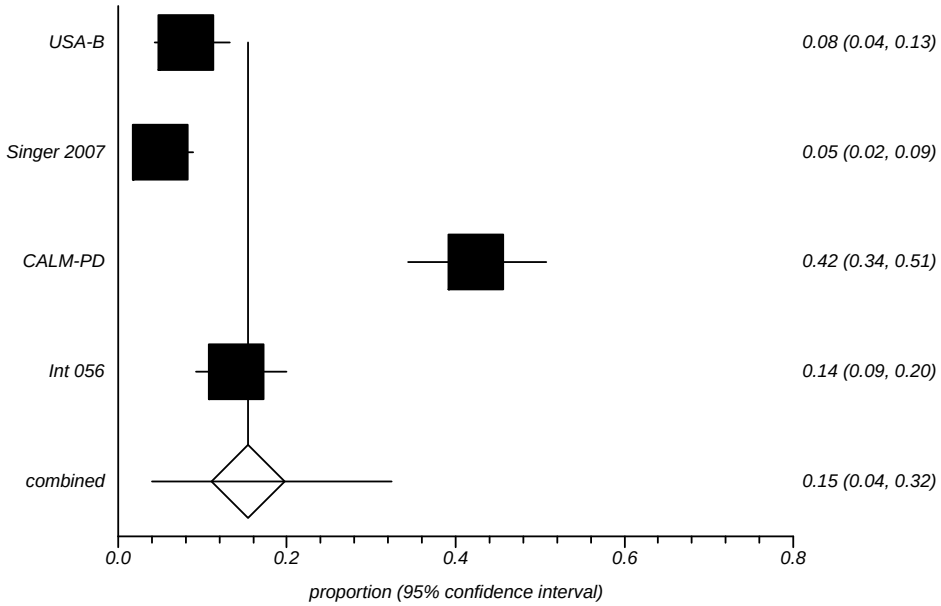
Bias indicators
Begg-Mazumdar: Kendall's tau = 1 P = 0.0833 (low power)
Egger: bias = 13.44610647 (95% CI = 0.13996564 to 26.75224731) P = 0.049
Harbord: bias = 75.2887949 (92.5% CI = -77.8850506 to 228.46264039) P = 0.2327



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.3b Oedema Levodopa

Stratum	Responding	Total	
1	22	150	CALM-PD
2	5	89	Int 056

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.14666667	0.09425508	0.21359422	62.65560166	52.60583838	CALM-PD
2	0.05617978	0.0184908	0.1262528	37.34439834	47.39416162	Int 056

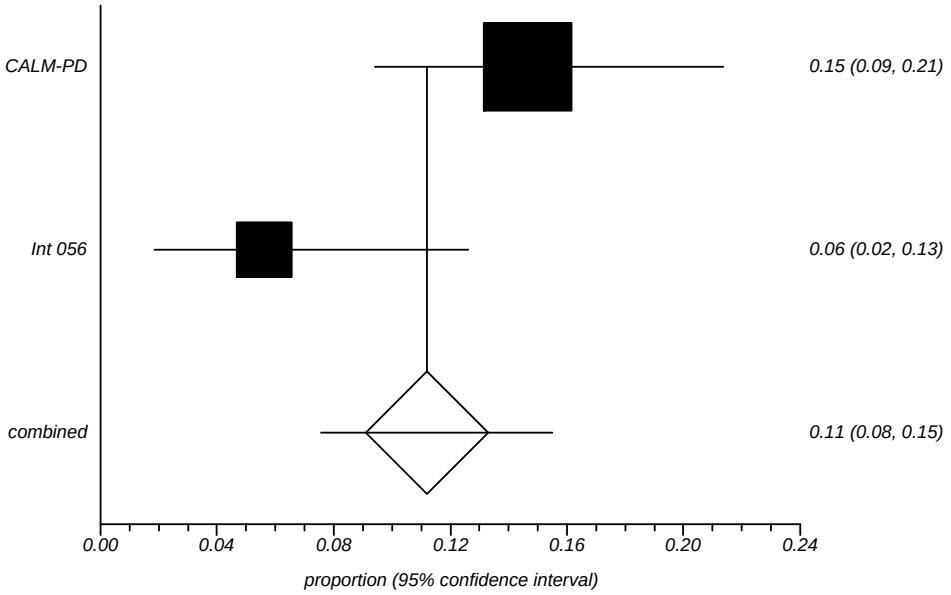
Fixed effects (inverse variance)
Pooled proportion = 0.11215072 (95% CI = 0.0755043 to 0.15497112)

Non-combinability of studies
Cochran Q = 4.85663338 (df = 1) P = 0.0275
Moment-based estimate of between studies variance = 0.03419605
I^2 (inconsistency) = *% (95% CI = *% to *%)

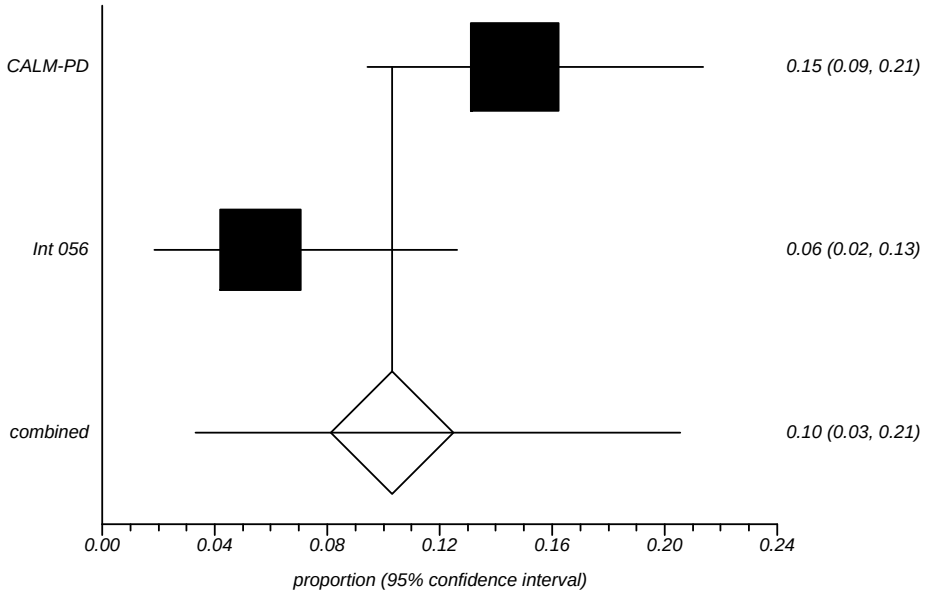
Random effects (DerSimonian-Laird)
Pooled proportion = 0.1030141 (95% CI = 0.03316616 to 0.20538392)

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *
Harbord: bias = -11.77643212 (92.5% CI = * to *) P = *

Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.4a Somnolence Dopamine agonists

Stratum	Responding	Total	
1	30	163	USA-B
2	58	213	USA/C
3	23	41	int R
4	42	116	USA R
5	23	215	rotigotine patch (2007)
6	28	228	rotigotine patch (2007)
7	63	202	Singer 2007
8	60	181	Watts 2007
9	16	140	Stocchi 2008
10	22	149	Stocchi 2008
11	34	106	Hauser 2010
12	34	103	Hauser 2010
13	81	223	Poewe 2011
14	70	213	Poewe 2011
15	56	151	CALM-PD
16	49	179	Int 056

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.18404908	0.12775673	0.25219684	6.21447518	6.33943384	USA-B
2	0.27230047	0.21372492	0.33733444	8.10913225	6.48359128	USA/C
3	0.56097561	0.39749844	0.71531292	1.59151194	4.966558	int R
4	0.36206897	0.27488696	0.45647842	4.43349754	6.10601543	USA R
5	0.10697674	0.0690331	0.15618564	8.18491853	6.48807205	rotigotine patch (2007)
6	0.12280702	0.0831776	0.1725796	8.67752937	6.51542291	rotigotine patch (2007)
7	0.31188119	0.24871441	0.38066871	7.69230769	6.45749246	Singer 2007
8	0.33149171	0.26343073	0.40517726	6.89655172	6.39966533	Watts 2007
9	0.11428571	0.06675369	0.17895149	5.34293293	6.24253141	Stocchi 2008
10	0.14765101	0.09490444	0.21496986	5.6839712	6.28362382	Stocchi 2008
11	0.32075472	0.23339122	0.4184293	4.05456612	6.03356832	Hauser 2010
12	0.33009709	0.24057772	0.42967501	3.9408867	6.00950389	Hauser 2010
13	0.3632287	0.30006558	0.43008173	8.48806366	6.50525219	Poewe 2011
14	0.3286385	0.26599828	0.39612726	8.10913225	6.48359128	Poewe 2011
15	0.37086093	0.29374719	0.45314982	5.75975748	6.29216197	CALM-PD
16	0.27374302	0.20988445	0.3452599	6.82076544	6.3935158	Int 056

Fixed effects (inverse variance)
Pooled proportion = 0.25657722 (95% CI = 0.24009533 to 0.27341341)

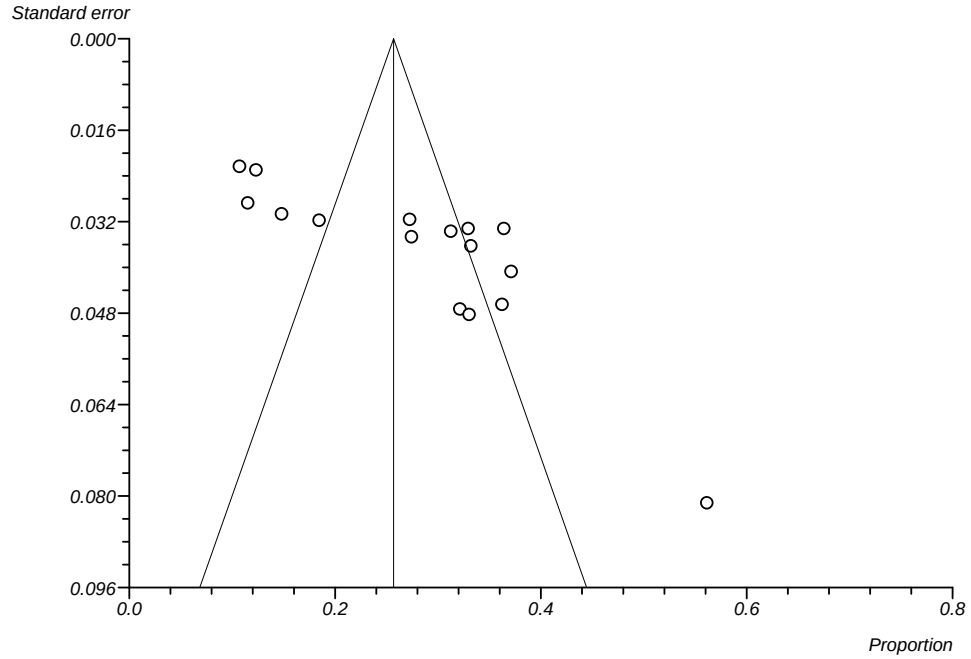
Non-combinability of studies
Cochran Q = 157.50855376 (df = 15) P < 0.0001
Moment-based estimate of between studies variance = 0.05797778
I^2 (inconsistency) = 90.5% (95% CI = 86.7% to 92.8%)

Random effects (DerSimonian-Laird)
Pooled proportion = 0.27032169 (95% CI = 0.21677696 to 0.32744568)

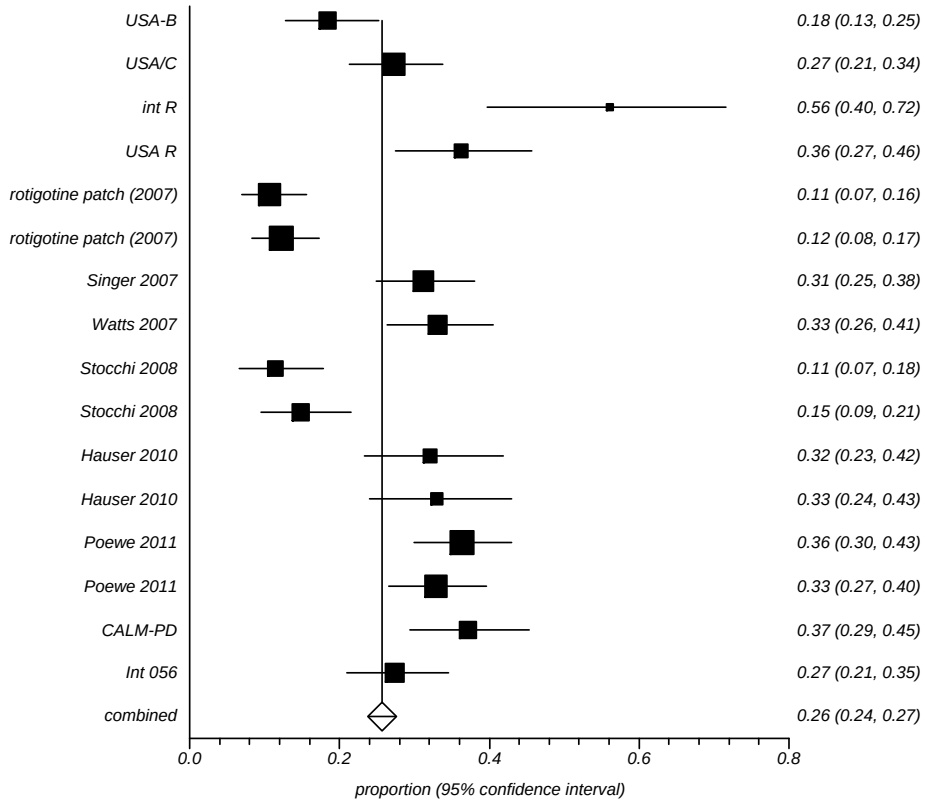
Bias indicators

Begg-Mazumdar: Kendall's tau = 0.55 P = 0.0024
Egger: bias = 9.92011356 (95% CI = 5.89707798 to 13.94314913) P = 0.0001
Harbord: bias = 6.47839532 (92.5% CI = -1.63436382 to 14.59115447) P = 0.1468

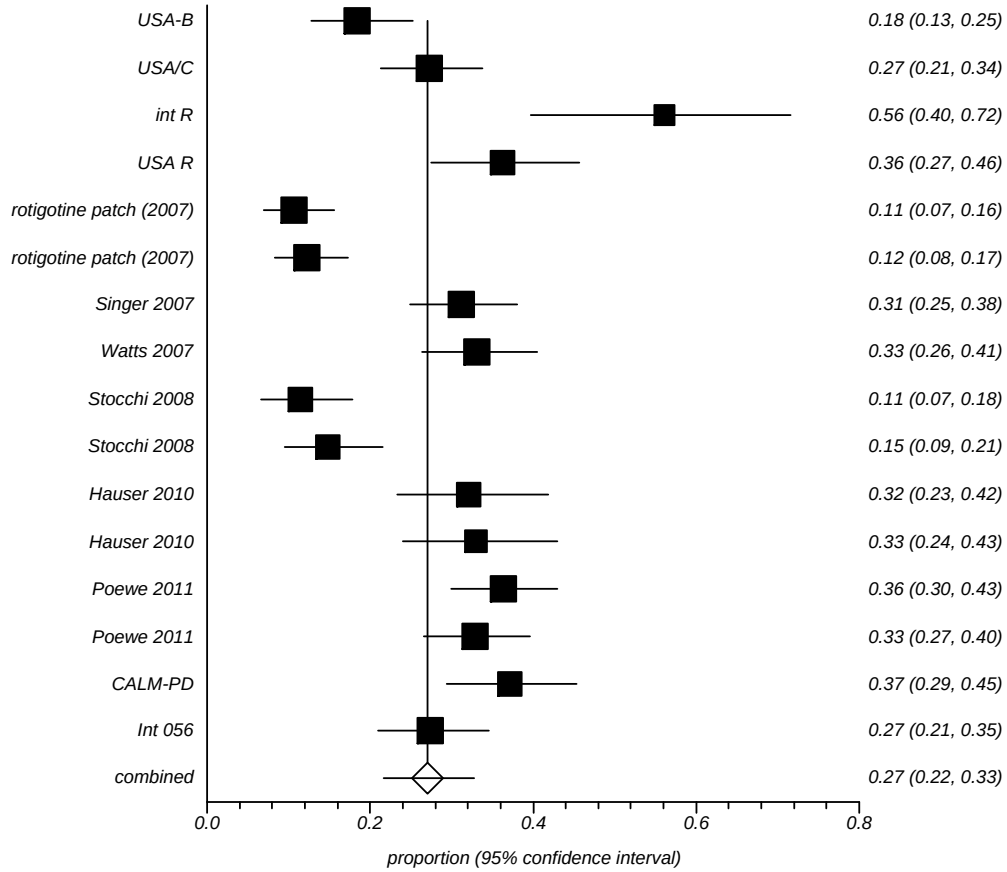
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.4b Somnolence - Levodopa

Stratum	Responding	Total	
1	32	150	CALM-PD
2	17	89	Int 056
3	0	92	ELLDOPA
4	5	88	ELLDOPA
5	5	91	ELLDOPA

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.21333333	0.15073024	0.28760662	29.32038835	20.54541239	CALM-PD
2	0.19101124	0.11539083	0.28811769	17.47572816	19.84570324	Int 056
3	0	0	0.03930329	18.05825243	19.89982068	ELLDOPA
4	0.05681818	0.01870386	0.1276324	17.2815534	19.8269224	ELLDOPA
5	0.05494505	0.01807893	0.12358108	17.86407767	19.88214129	ELLDOPA

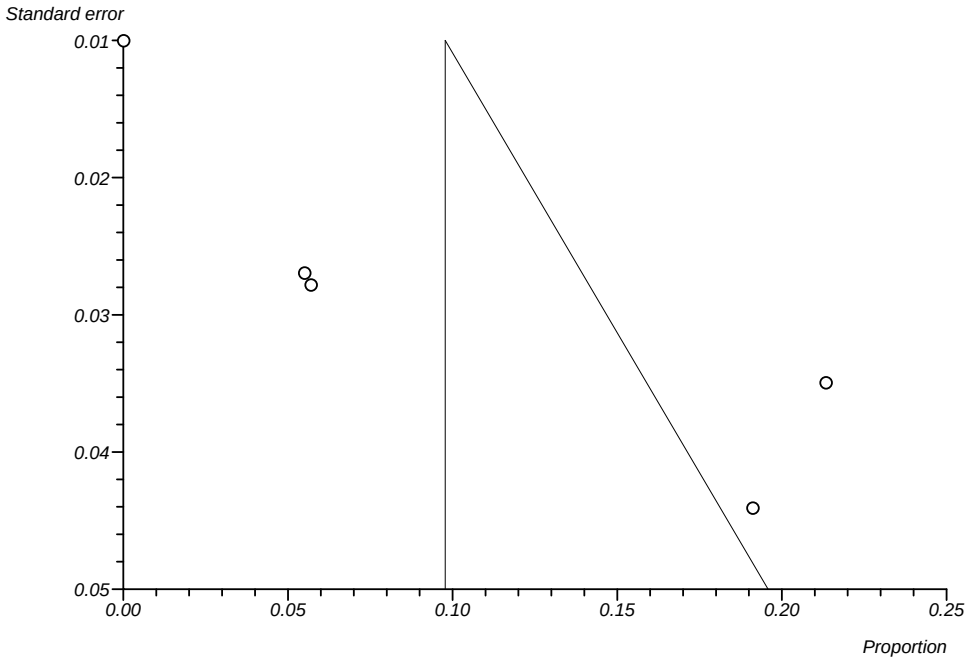
Fixed effects (inverse variance)
Pooled proportion = 0.09780847 (95% CI = 0.07368383 to 0.12493126)

Non-combinability of studies
Cochran Q = 53.04560564 (df = 4) P < 0.0001
Moment-based estimate of between studies variance = 0.12068654
I^2 (inconsistency) = 92.5% (95% CI = 85.7% to 95.2%)

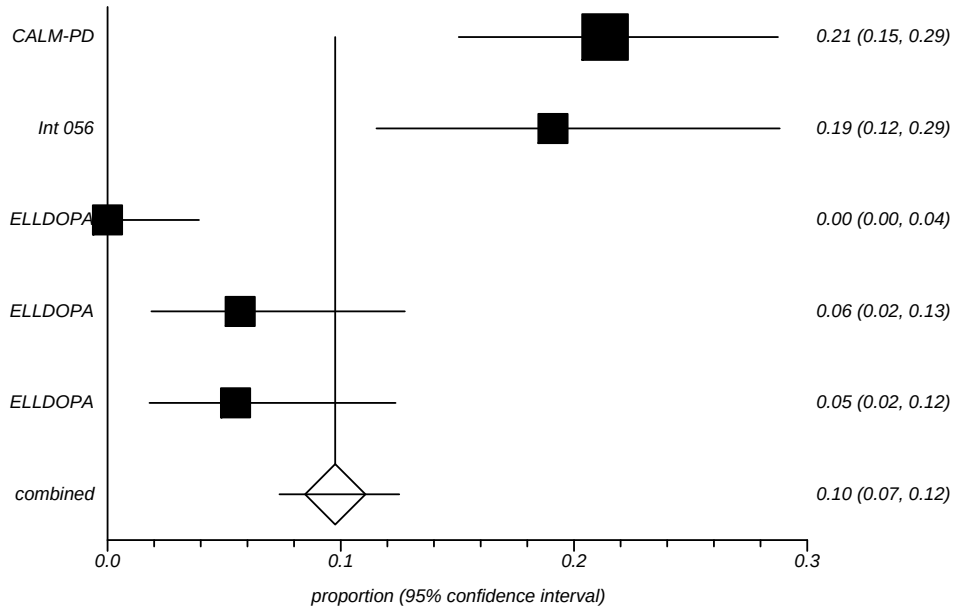
Random effects (DerSimonian-Laird)
Pooled proportion = 0.08670916 (95% CI = 0.01958397 to 0.19501437)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.8 P = 0.0833 (low power)
Egger: bias = 5.53425079 (95% CI = 0.91763885 to 10.15086272) P = 0.0317
Harbord: bias = -18.76245781 (92.5% CI = -48.38555878 to 10.86064316) P = 0.1881

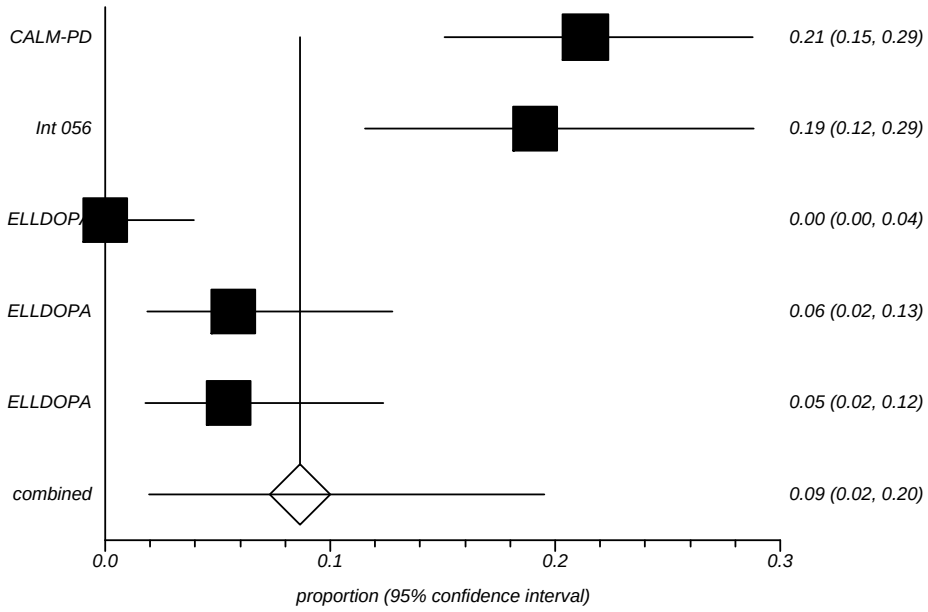
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.5a Insomnia Dopamine agonists

Stratum	Responding	Total	
1	6	26	USA-A
2	42	163	USA-B
3	16	213	USA/C
4	13	116	USA R
5	6	215	rotigotine patch (2007)
6	6	228	rotigotine patch (2007)
7	9	202	Singer 2007
8	17	181	Watts 2007
9	45	179	Int 056
10	39	151	CALM-PD

Stratum	Proportion	95% CI (exact)		% Weights		Source
				fixed	random	
1	0.23076923	0.08974011	0.4364751	1.60332542	7.69200966	USA-A
2	0.25766871	0.19244578	0.33192298	9.73871734	10.20645466	USA-B
3	0.07511737	0.04354383	0.11912088	12.70783848	10.36243271	USA/C
4	0.11206897	0.061039	0.18401534	6.94774347	9.94897909	USA R
5	0.02790698	0.01030879	0.05974909	12.82660333	10.36724444	rotigotine patch (2007)
6	0.02631579	0.00971734	0.05639548	13.59857482	10.39656836	rotigotine patch (2007)
7	0.04455446	0.02057264	0.08289077	12.05463183	10.33436268	Singer 2007
8	0.09392265	0.05566956	0.14611878	10.80760095	10.27190284	Watts 2007
9	0.25139665	0.1896629	0.32155687	10.6888361	10.26523906	Int 056
10	0.25827815	0.19055408	0.33573966	9.02612827	10.1548065	CALM-PD

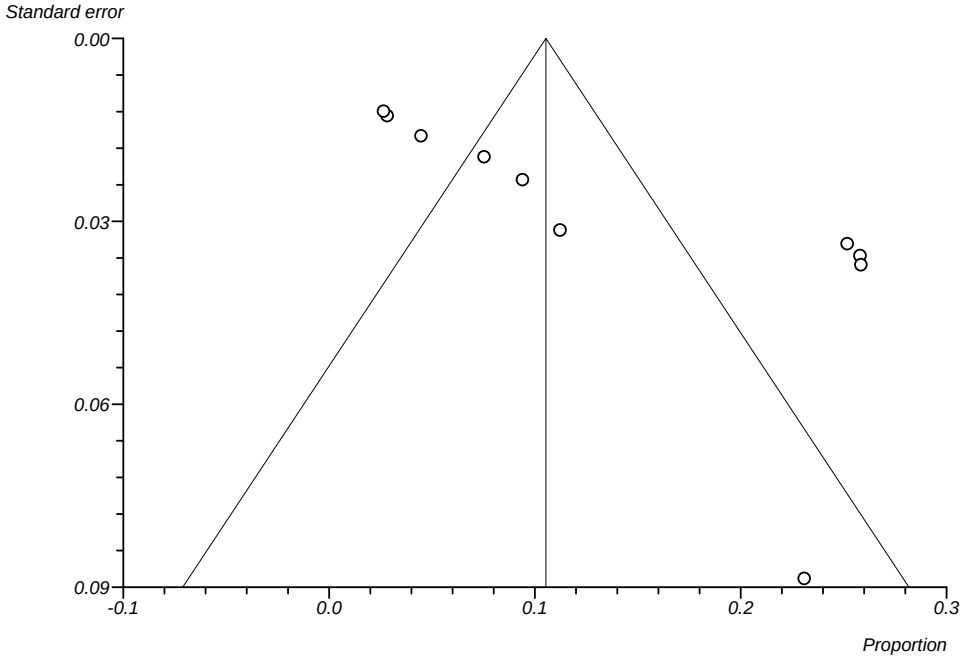
Fixed effects (inverse variance)
Pooled proportion = 0.10521785 (95% CI = 0.0910188 to 0.12031729)

Non-combinability of studies
Cochran Q = 141.50000971 (df = 9) P < 0.0001
Moment-based estimate of between studies variance = 0.08855026
I^2 (inconsistency) = 93.6% (95% CI = 90.9% to 95.3%)

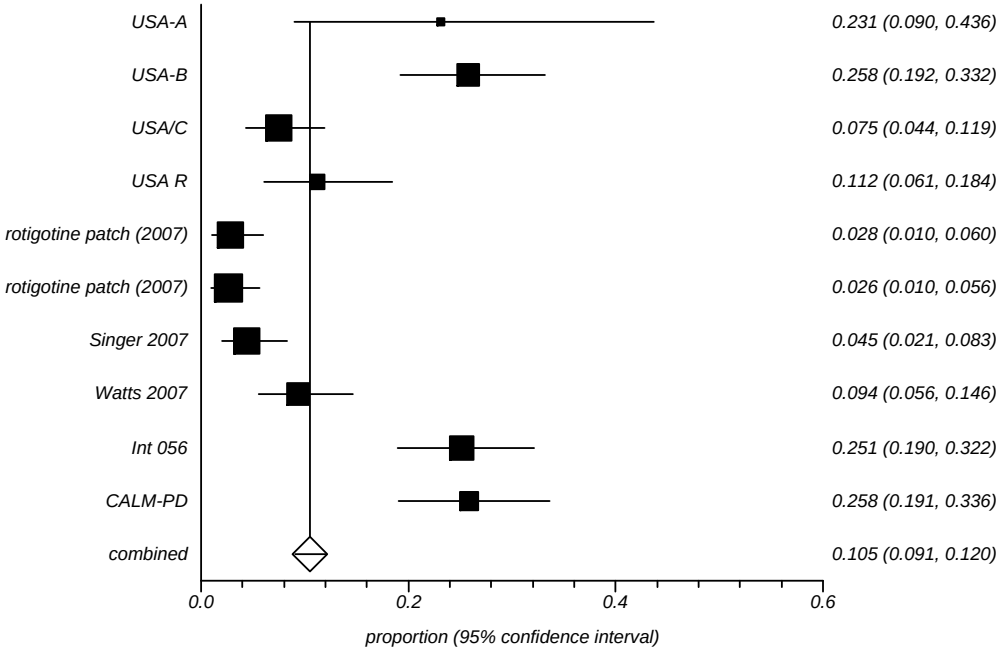
Random effects (DerSimonian-Laird)
Pooled proportion = 0.121813 (95% CI = 0.0661915 to 0.19142537)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.73333333 P = 0.0022 (low power)
Egger: bias = 6.56311844 (95% CI = 3.59130793 to 9.53492895) P = 0.0009
Harbord: bias = 6.93233268 (92.5% CI = -5.41386654 to 19.27853191) P = 0.2839

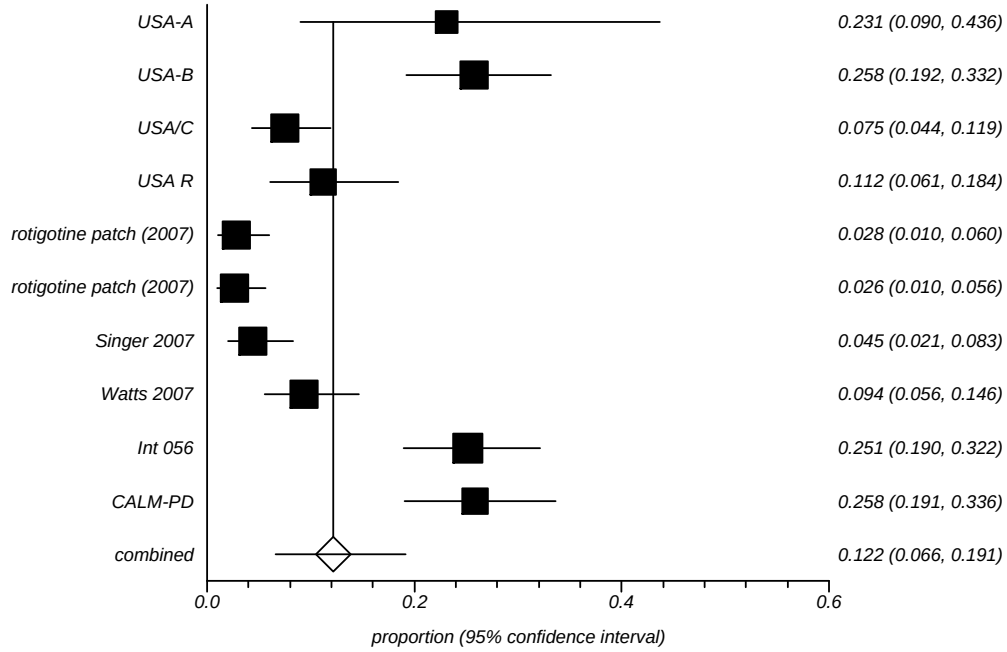
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.5b Insomnia Levodopa

Stratum	Responding	Total	
1	21	89	Int 056
2	33	150	CALM-PD
3	8	92	ELLDOPA
4	4	88	ELLDOPA
5	5	91	ELLDOPA

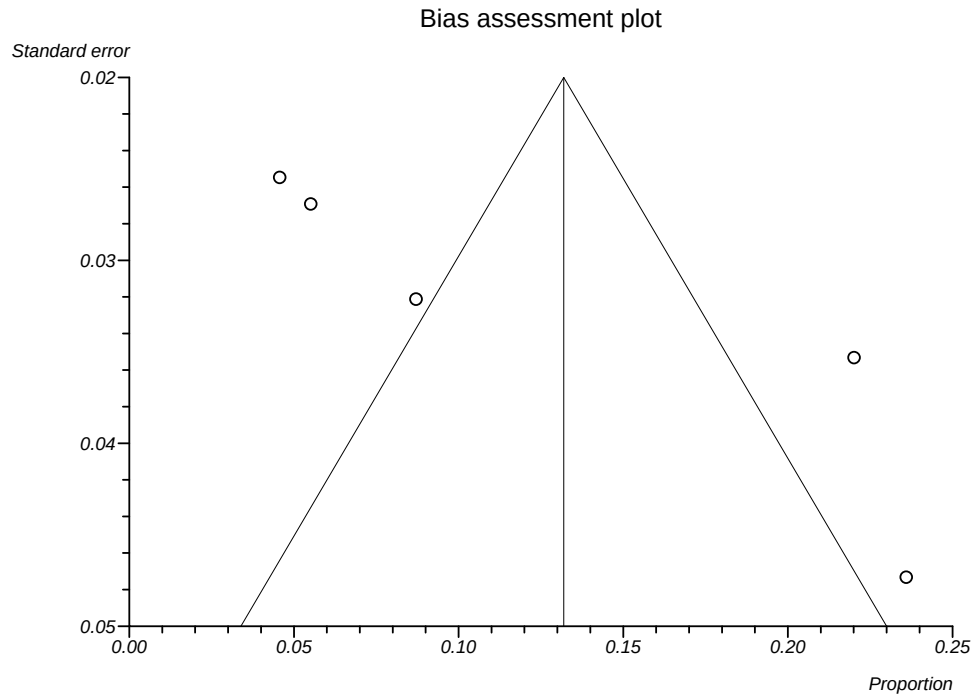
Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.23595506	0.15238129	0.33778766	17.47572816	19.72667	Int 056
2	0.22	0.15653734	0.29485407	29.32038835	20.96891793	CALM-PD
3	0.08695652	0.03829206	0.16416675	18.05825243	19.82043285	ELLDOPA
4	0.04545455	0.01252182	0.11230925	17.2815534	19.69421899	ELLDOPA
5	0.05494505	0.01807893	0.12358108	17.86407767	19.78976022	ELLDOPA

Fixed effects (inverse variance)
Pooled proportion = 0.13190881 (95% CI = 0.10409146 to 0.16247011)

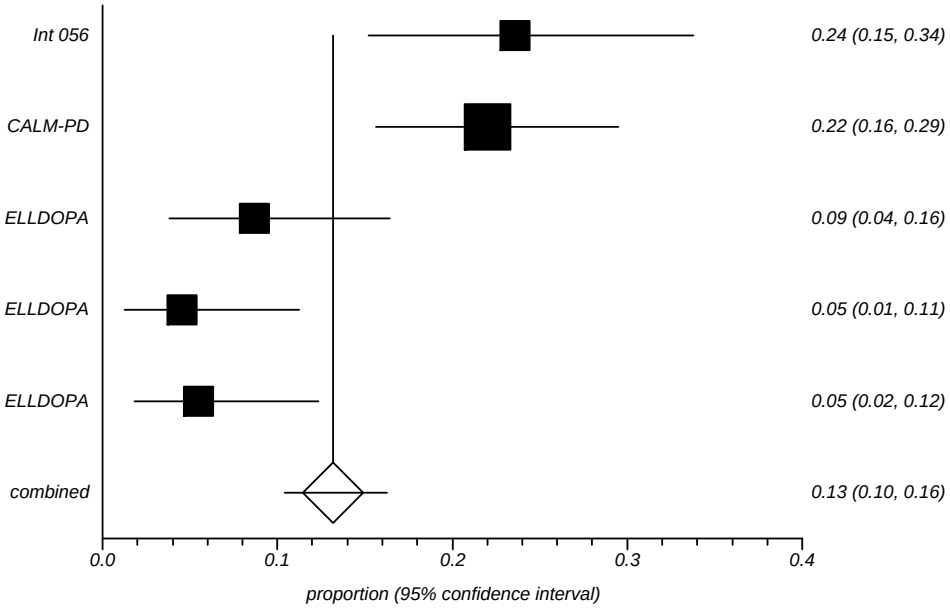
Non-combinability of studies
Cochran Q = 30.27525985 (df = 4) P < 0.0001
Moment-based estimate of between studies variance = 0.06465554
I^2 (inconsistency) = 86.8% (95% CI = 67.7% to 92.6%)

Random effects (DerSimonian-Laird)
Pooled proportion = 0.12268553 (95% CI = 0.05560381 to 0.21132744)

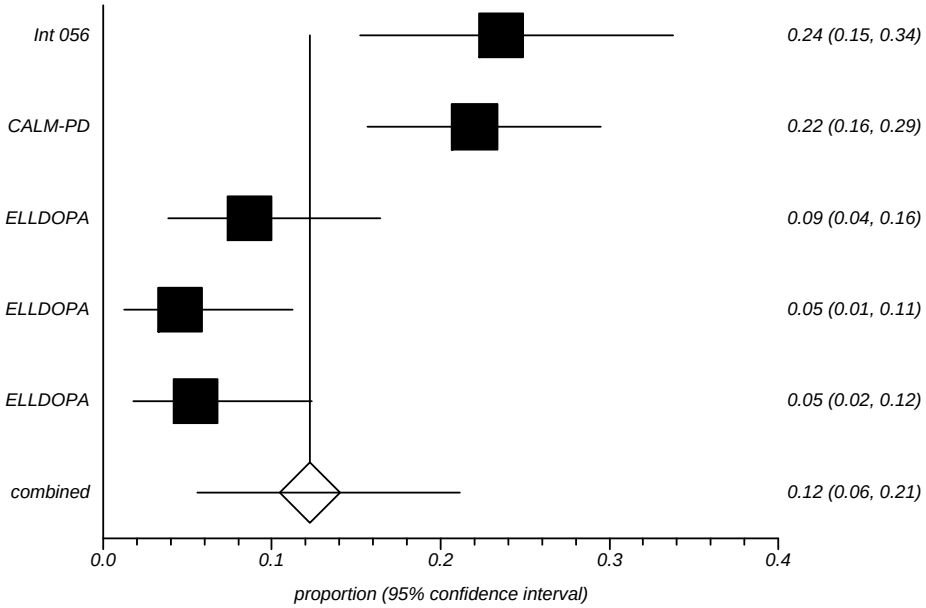
Bias indicators
Begg-Mazumdar: Kendall's tau = 0.8 P = 0.0833 (low power)
Egger: bias = 10.33752974 (95% CI = 0.72869542 to 19.94636407) P = 0.0417
Harbord: bias = -13.90771703 (92.5% CI = -41.29011057 to 13.47467651) P = 0.2666



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.6a Nausea Dopamine agonist

Stratum	Responding	Total	
1	6	28	USA-A
2	64	163	USA-B
3	42	213	USA/C
4	28	41	Int R
5	61	116	USA R
6	29	215	rotigotine patch (2007)
7	36	228	rotigotine patch (2007)
8	70	202	Singer 2007
9	75	181	Watts 2007
10	27	140	Stocchi 2008
11	30	149	Stocchi 2008
12	22	106	Hauser 2010
13	22	103	Hauser 2010
14	48	223	Poewe 2011
15	51	213	Poewe 2011
16	55	151	CALM-PD
17	87	179	Int 056

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.21428571	0.08296061	0.40953103	1.08695652	4.47590241	USA-A
2	0.39263804	0.31718599	0.47206891	6.14692654	6.04127441	USA-B
3	0.1971831	0.14596303	0.25703978	8.02098951	6.14921305	USA/C
4	0.68292683	0.51913361	0.8191506	1.57421289	4.95906456	Int R
5	0.52586207	0.43105486	0.61931703	4.38530735	5.86429253	USA R
6	0.13488372	0.09222971	0.18793929	8.09595202	6.15255157	rotigotine patch (2007)
7	0.15789474	0.11310393	0.21183053	8.5832084	6.17290866	rotigotine patch (2007)
8	0.34653465	0.28113134	0.41651769	7.60869565	6.12974773	Singer 2007
9	0.41436464	0.34177713	0.48980446	6.82158921	6.0864985	Watts 2007
10	0.19285714	0.13110862	0.26805161	5.28485757	5.96813548	Stocchi 2008
11	0.20134228	0.14015934	0.27478225	5.62218891	5.99920834	Stocchi 2008
12	0.20754717	0.134876	0.29719412	4.01049475	5.80879818	Hauser 2010
13	0.21359223	0.13896186	0.30532933	3.89805097	5.79030514	Hauser 2010
14	0.21524664	0.16317721	0.27505402	8.3958021	6.16534294	Poewe 2011
15	0.23943662	0.18377494	0.30250376	8.02098951	6.14921305	Poewe 2011
16	0.36423841	0.28754322	0.4463752	5.69715142	6.00565398	CALM-PD
17	0.48603352	0.41079409	0.5617431	6.74662669	6.08188948	Int 056

Fixed effects (inverse variance)
Pooled proportion = 0.27827253 (95% CI = 0.2614312 to 0.29543307)

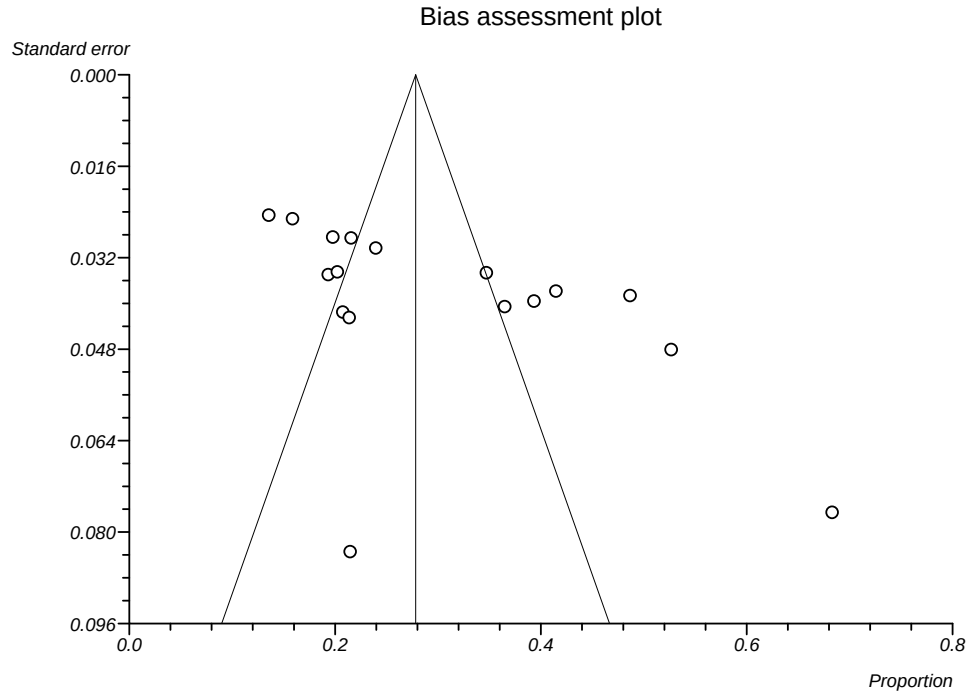
Non-combinability of studies
Cochran Q = 202.80924771 (df = 16) P < 0.0001
Moment-based estimate of between studies variance = 0.07506486
I^2 (inconsistency) = 92.1% (95% CI = 89.4% to 93.9%)

Random effects (DerSimonian-Laird)

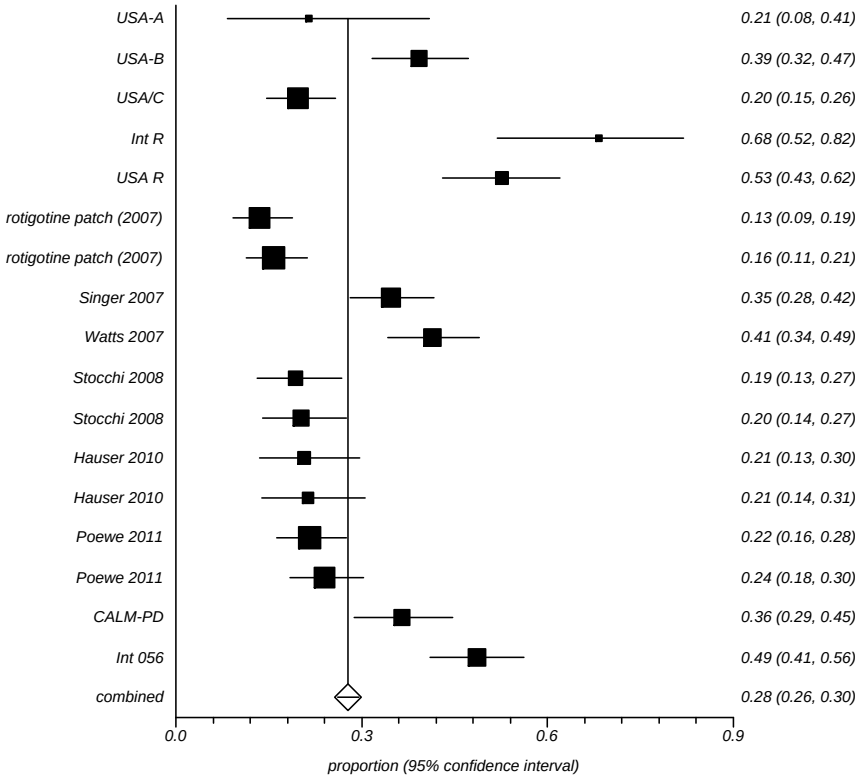
Pooled proportion = 0.29589253 (95% CI = 0.23536469 to 0.36025884)

Bias indicators

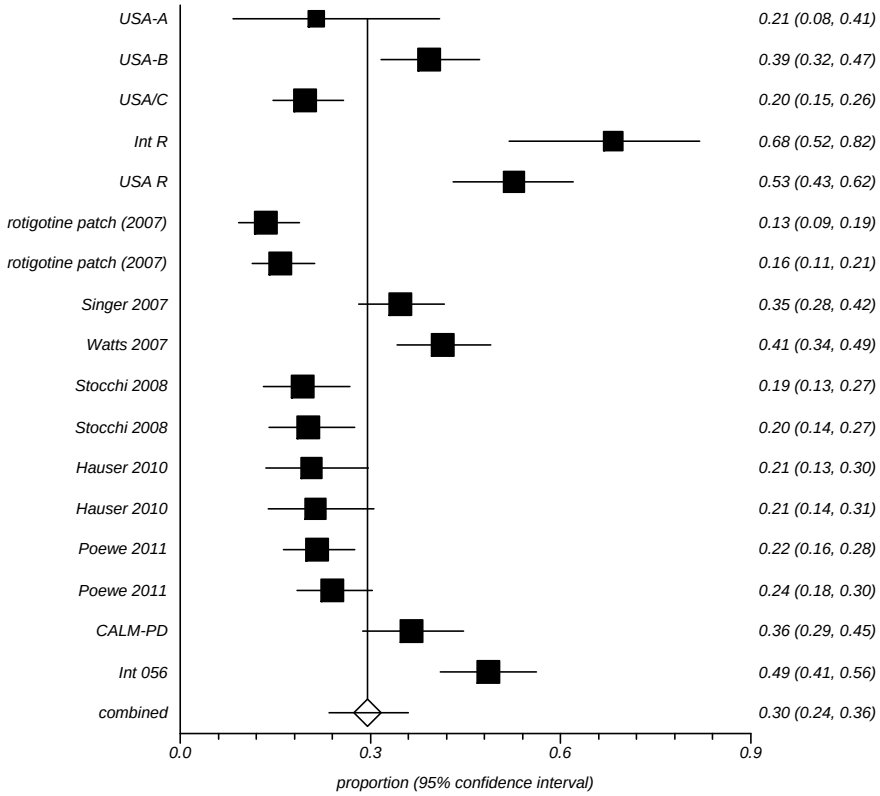
Begg-Mazumdar: Kendall's tau = 0.51470588 P = 0.0033
Egger: bias = 8.07169773 (95% CI = 2.79878777 to 13.34460768) P = 0.0052
Harbord: bias = 4.94270341 (92.5% CI = -2.45599471 to 12.34140154) P = 0.2206



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.6b Nausea Levodopa

Stratum	Responding	Total	
1	55	150	CALM-PD
2	44	89	Int 056
3	29	215	Hauser 2009
4	15	92	ELLDOPA
5	23	88	ELLDOPA
6	29	91	ELLDOPA

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.36666667	0.28956317	0.44915024	20.65663475	17.10530907	CALM-PD
2	0.49438202	0.3866645	0.60248388	12.3119015	16.33658644	Int 056
3	0.13488372	0.09222971	0.18793929	29.54856361	17.47029908	Hauser 2009
4	0.16304348	0.09422516	0.25461913	12.72229822	16.39542293	ELLDOPA
5	0.26136364	0.17344877	0.36593174	12.1751026	16.31619186	ELLDOPA
6	0.31868132	0.22487385	0.4246703	12.58549932	16.37619061	ELLDOPA

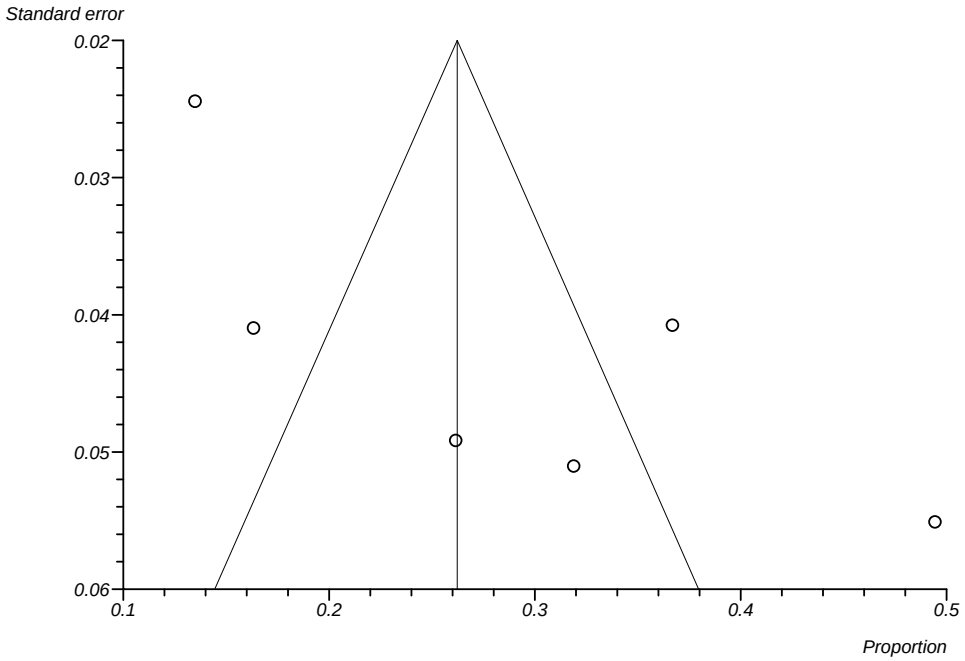
Fixed effects (inverse variance)
Pooled proportion = 0.26201438 (95% CI = 0.23079045 to 0.2944884)

Non-combinability of studies
Cochran Q = 57.43099602 (df = 5) P < 0.0001
Moment-based estimate of between studies variance = 0.0887673
I^2 (inconsistency) = 91.3% (95% CI = 84% to 94.4%)

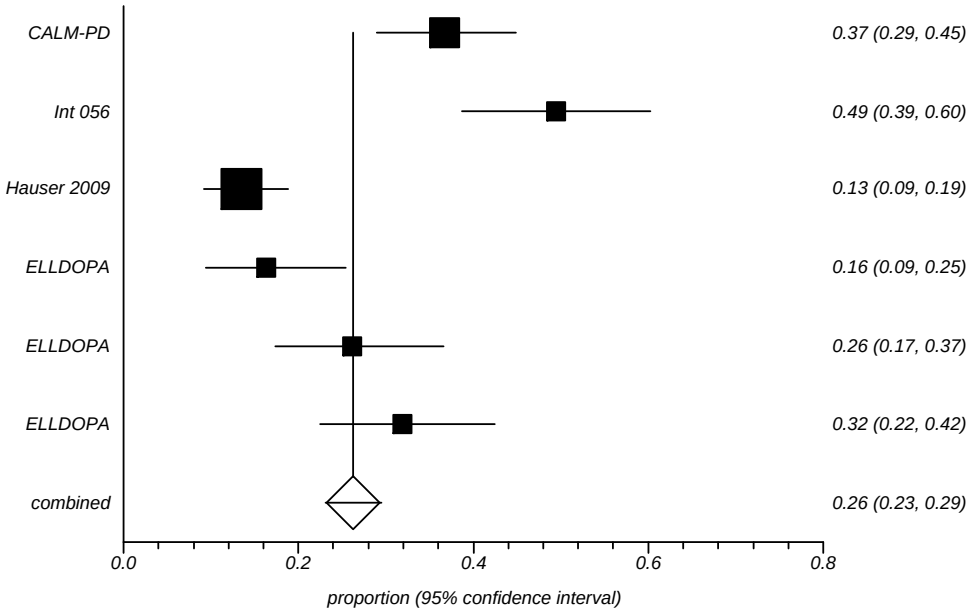
Random effects (DerSimonian-Laird)
Pooled proportion = 0.28261832 (95% CI = 0.17783943 to 0.40095168)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.6 P = 0.1361 (low power)
Egger: bias = 8.29401189 (95% CI = -0.11538832 to 16.70341209) P = 0.052
Harbord: bias = 8.53915745 (92.5% CI = -9.05006362 to 26.12837853) P = 0.3101

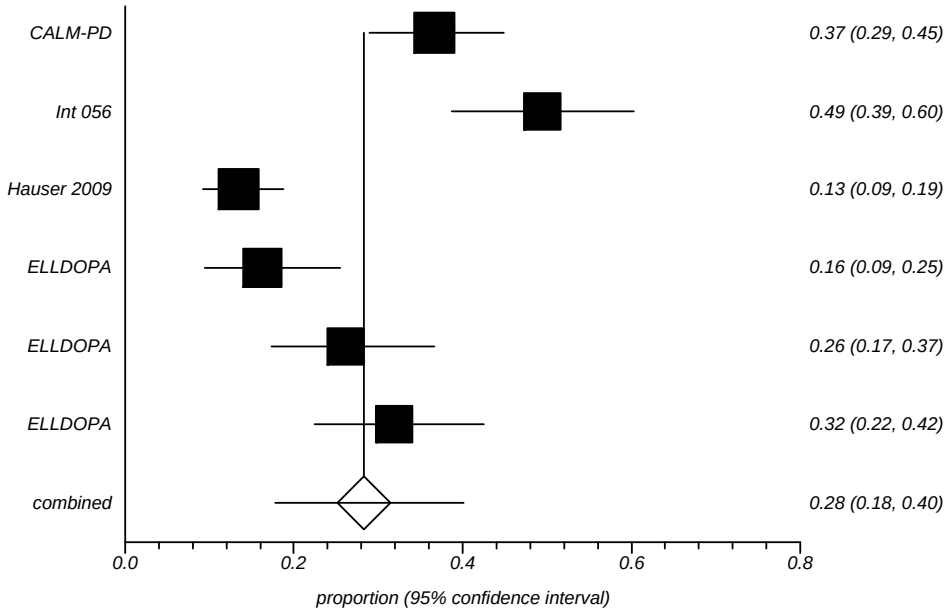
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.7a Hallucinations Dopamine agonists

Stratum	Responding	Total	
1	4	28	USA-A
2	19	163	USA-B
3	14	213	USA/C
4	1	41	Int R
5	2	116	USA R
6	31	179	Int 056
7	22	151	CALM-PD

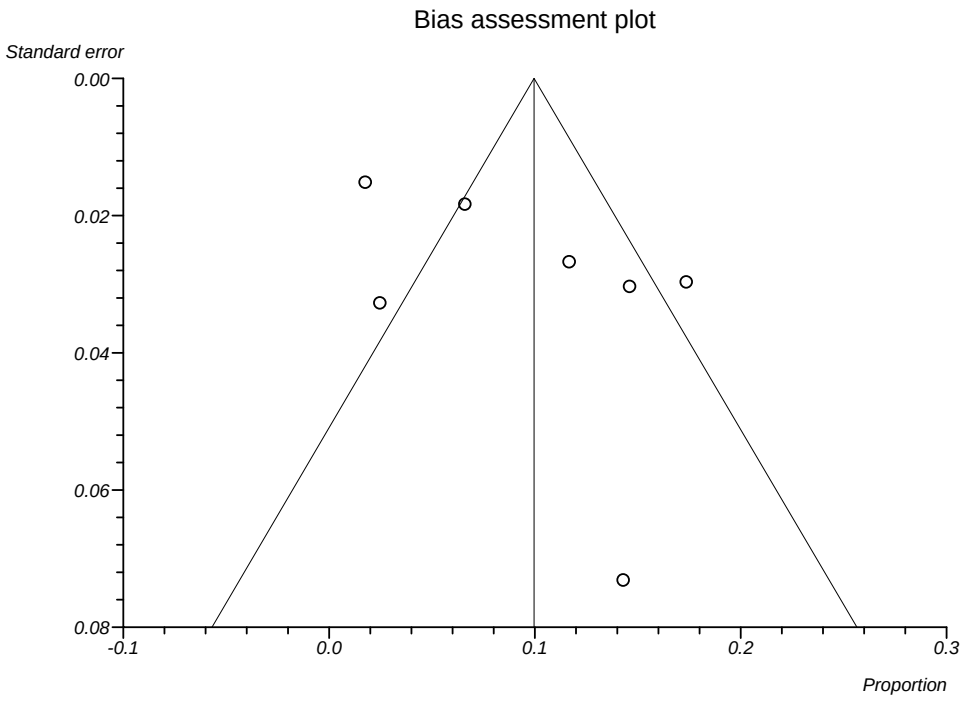
Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.14285714	0.04033563	0.32665267	3.22939866	9.62551832	USA-A
2	0.11656442	0.07165772	0.17603357	18.26280624	15.87163513	USA-B
3	0.0657277	0.03639682	0.10782167	23.83073497	16.40596343	USA/C
4	0.02439024	0.00061732	0.12855402	4.67706013	11.2972443	Int R
5	0.01724138	0.00209487	0.06089484	13.02895323	15.0300049	USA R
6	0.17318436	0.12080724	0.23672226	20.04454343	16.07076399	Int 056
7	0.14569536	0.09361456	0.21223603	16.92650334	15.69886993	CALM-PD

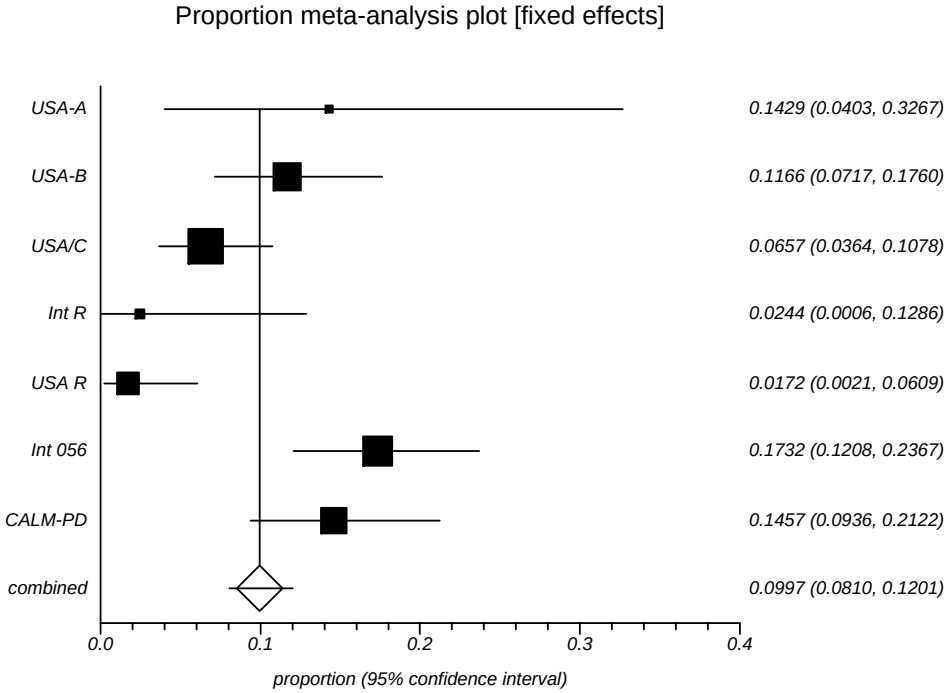
Fixed effects (inverse variance)
Pooled proportion = 0.09969027 (95% CI = 0.08096574 to 0.12012663)

Non-combinability of studies
Cochran Q = 33.74818319 (df = 6) P < 0.0001
Moment-based estimate of between studies variance = 0.03764518
I^2 (inconsistency) = 82.2% (95% CI = 59.8% to 89.7%)

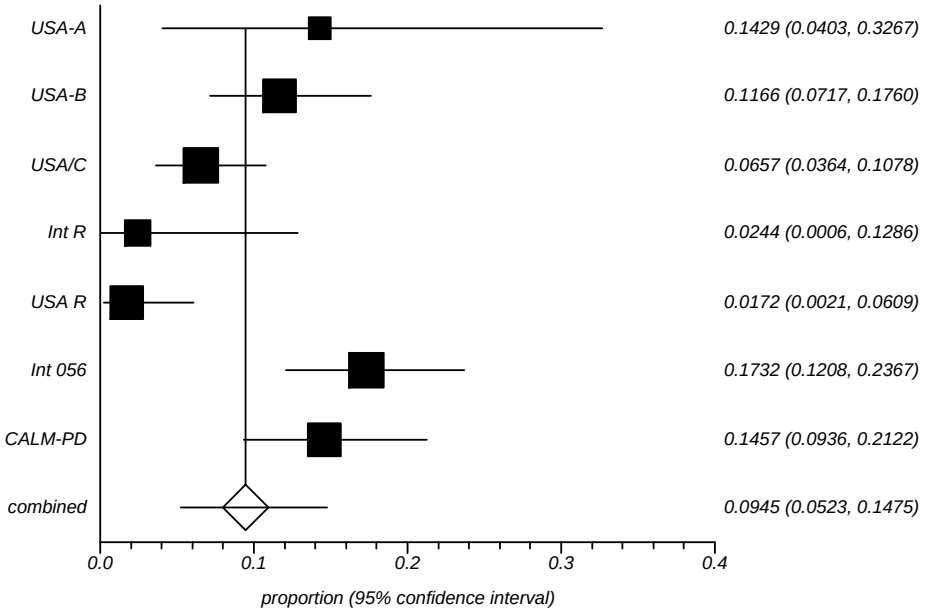
Random effects (DerSimonian-Laird)
Pooled proportion = 0.09449628 (95% CI = 0.05233273 to 0.14745062)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.23809524 P = 0.5619 (low power)
Egger: bias = 3.71796718 (95% CI = -1.68855642 to 9.12449078) P = 0.1373
Harbord: bias = -1.25672656 (92.5% CI = -8.13287424 to 5.61942111) P = 0.6989


Bias assessment plot
Standard error
0.00
0.02
0.04
0.06
0.08
-0.1
0.0
0.1
0.2
0.3
Proportion


Proportion meta-analysis plot [fixed effects]
USA-A
USA-B
USA/C
Int R
USA R
Int 056
CALM-PD
combined
0.1429 (0.0403, 0.3267)
0.1166 (0.0717, 0.1760)
0.0657 (0.0364, 0.1078)
0.0244 (0.0006, 0.1286)
0.0172 (0.0021, 0.0609)
0.1732 (0.1208, 0.2367)
0.1457 (0.0936, 0.2122)
0.0997 (0.0810, 0.1201)
0.0
0.1
0.2
0.3
0.4
proportion (95% confidence interval)

Proportion meta-analysis plot [random effects]



A.3.7b Hallucinations Levodopa

Stratum	Responding	Total	
1	5	89	Int 056
2	12	150	CALM-PD

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.05617978	0.0184908	0.1262528	37.34439834	37.34439834	Int 056
2	0.08	0.04202026	0.13557389	62.65560166	62.65560166	CALM-PD

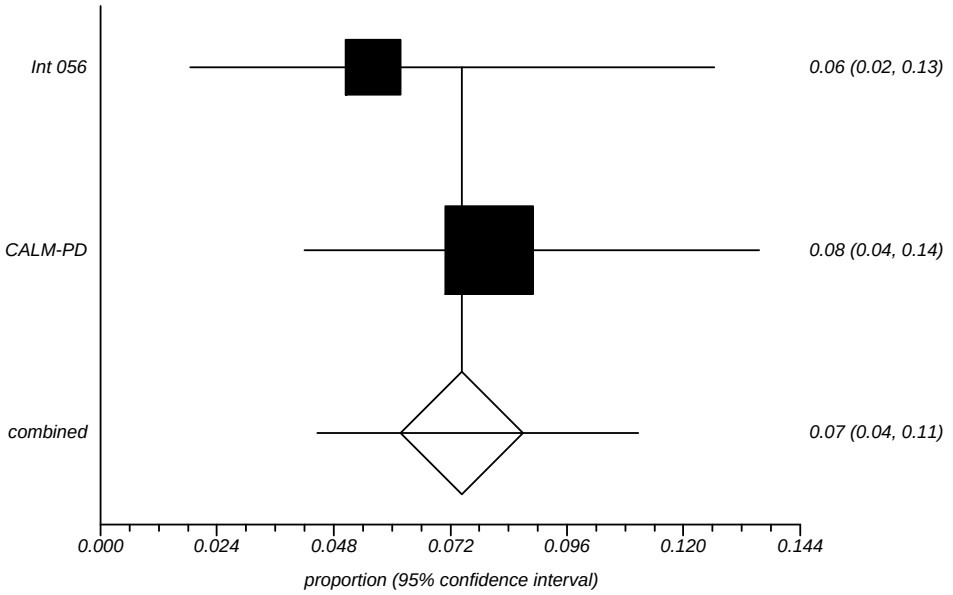
Fixed effects (inverse variance)
Pooled proportion = 0.07426879 (95% CI = 0.04464081 to 0.11067377)

Non-combinability of studies
Cochran Q = 0.40242792 (df = 1) P = 0.5258
Moment-based estimate of between studies variance = 0
I^2 (inconsistency) = *% (95% CI = *% to *%)

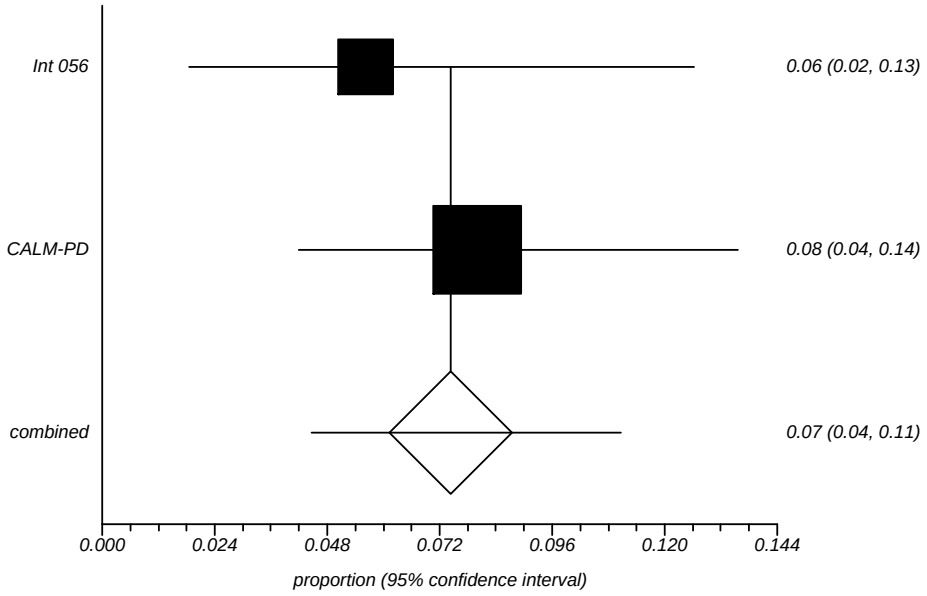
Random effects (DerSimonian-Laird)
Pooled proportion = 0.07426879 (95% CI = 0.04464081 to 0.11067377)

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *
Harbord: bias = -3.73077408 (92.5% CI = * to *) P = *

Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.8a Headache: Dopamine agonists

Stratum	Responding	Total	
1	9	28	USA-A
2	24	213	USA/C
3	20	116	USA R
4	10	215	rotigotine patch (2007)
5	9	228	rotigotine patch (2007)
6	29	181	Watts 2007
7	8	140	Stocchi 2008
8	8	149	Stocchi 2008
9	25	179	Int 056
10	31	151	CALM-PD

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.32142857	0.15877604	0.52351641	1.80124224	6.43068254	USA-A
2	0.11267606	0.07354219	0.16300255	13.29192547	10.68431287	USA/C
3	0.17241379	0.10861267	0.25364242	7.26708075	9.83855485	USA R
4	0.04651163	0.02252639	0.08387117	13.41614907	10.69458047	rotigotine patch (2007)
5	0.03947368	0.01820615	0.07360836	14.22360248	10.75737478	rotigotine patch (2007)
6	0.16022099	0.11000489	0.22193062	11.30434783	10.493016	Watts 2007
7	0.05714286	0.02499018	0.10948885	8.75776398	10.13997378	Stocchi 2008
8	0.05369128	0.02346213	0.10305083	9.31677019	10.23166152	Stocchi 2008
9	0.1396648	0.09246693	0.19923333	11.18012422	10.47907463	Int 056
10	0.20529801	0.14395655	0.27856565	9.44099379	10.25076858	CALM-PD

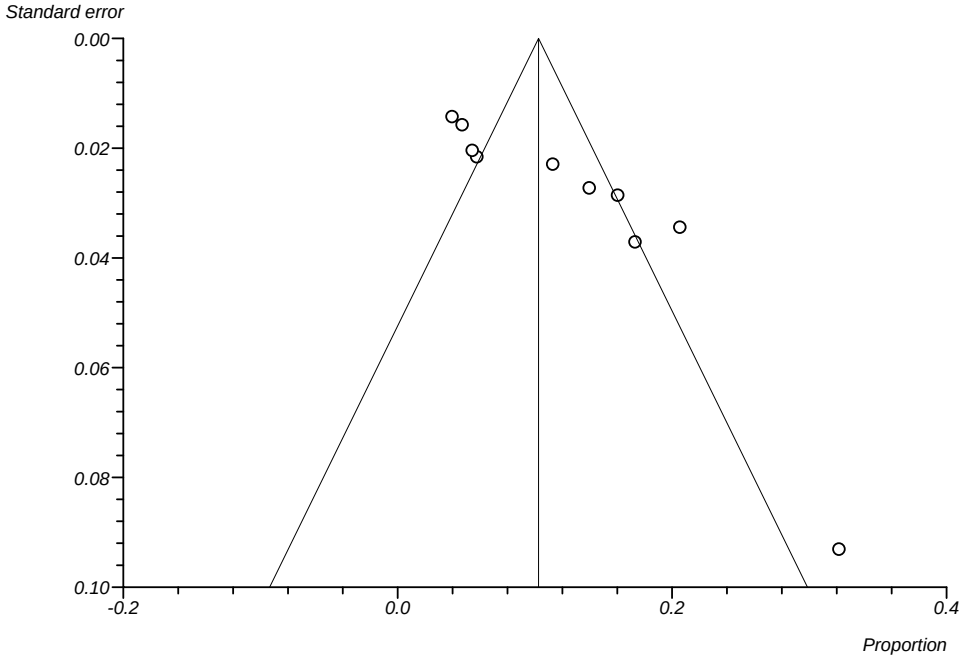
Fixed effects (inverse variance)
Pooled proportion = 0.10251384 (95% CI = 0.08817752 to 0.11779838)

Non-combinability of studies
Cochran Q = 66.74750798 (df = 9) P < 0.0001
Moment-based estimate of between studies variance = 0.04039396
I^2 (inconsistency) = 86.5% (95% CI = 76.8% to 91%)

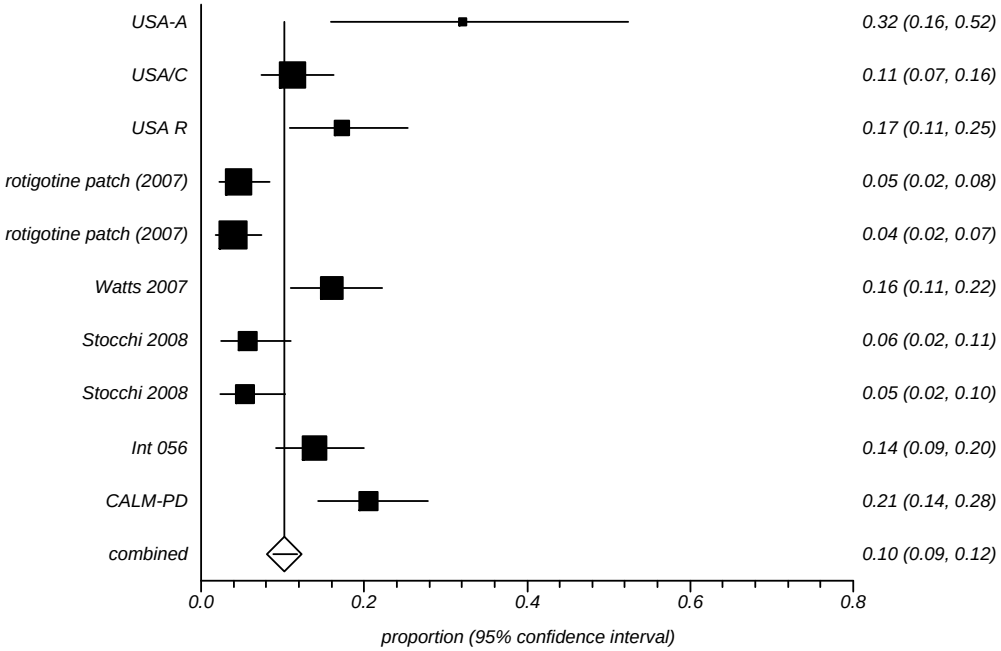
Random effects (DerSimonian-Laird)
Pooled proportion = 0.11530582 (95% CI = 0.07555372 to 0.16216262)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.82222222 P = 0.0004 (low power)
Egger: bias = 5.63730993 (95% CI = 3.31741001 to 7.95720986) P = 0.0005
Harbord: bias = 7.21873538 (92.5% CI = -0.16653405 to 14.60400482) P = 0.0806

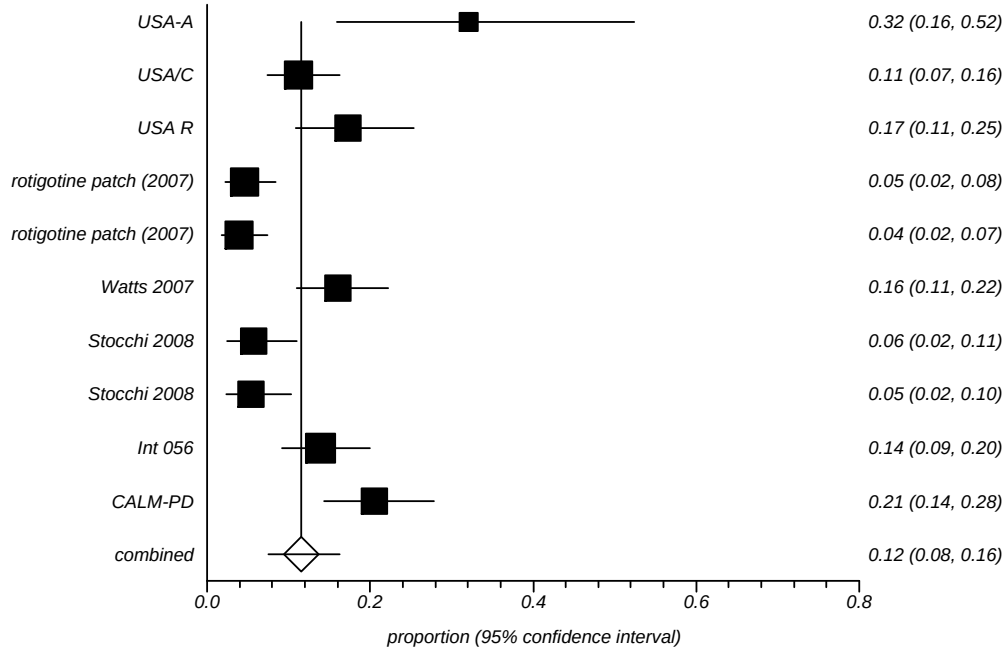
Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]



A.3.8b Headache Levodopa

Stratum	Responding	Total	
1	16	89	Int 056
2	23	150	CALM-PD
3	7	92	ELLDOPA
4	5	88	ELLDOPA
5	12	91	ELLDOPA

Stratum	Proportion	95% CI (exact)		% Weights		Source
				Fixed	Random	
1	0.17977528	0.1063943	0.27546281	17.47572816	19.12362289	Int 056
2	0.15333333	0.09975195	0.22113973	29.32038835	23.14772931	CALM-PD
3	0.07608696	0.03113777	0.15050263	18.05825243	19.39283072	ELLDOPA
4	0.05681818	0.01870386	0.1276324	17.2815534	19.03160051	ELLDOPA
5	0.13186813	0.07003549	0.21902016	17.86407767	19.30421656	ELLDOPA

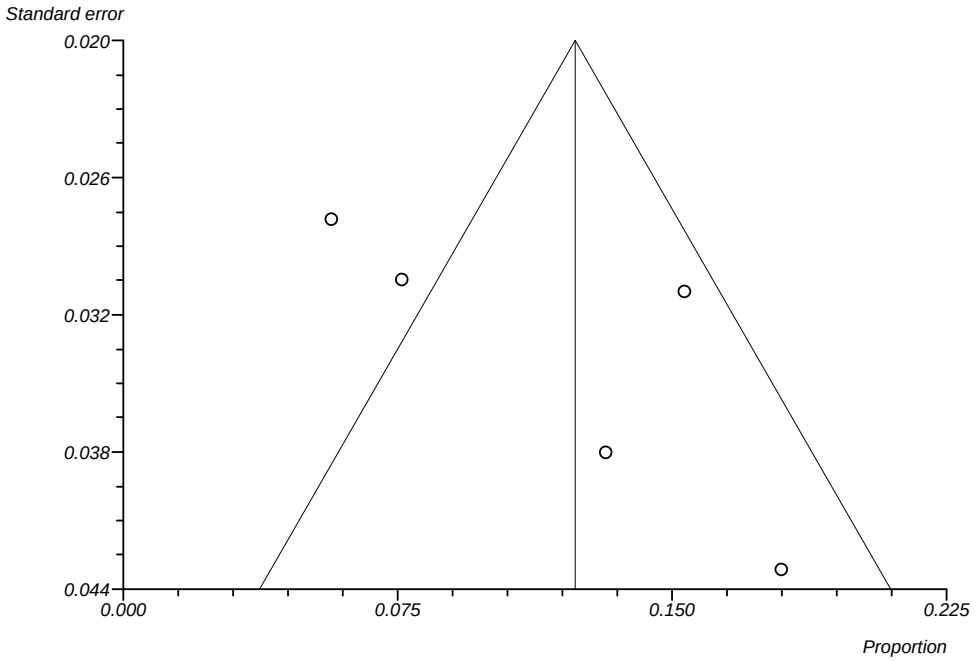
Fixed effects (inverse variance)
Pooled proportion = 0.12342678 (95% CI = 0.0964575 to 0.15320324)

Non-combinability of studies
Cochran Q = 9.97735386 (df = 4) P = 0.0408
Moment-based estimate of between studies variance = 0.01470848
I^2 (inconsistency) = 59.9% (95% CI = 0% to 82.9%)

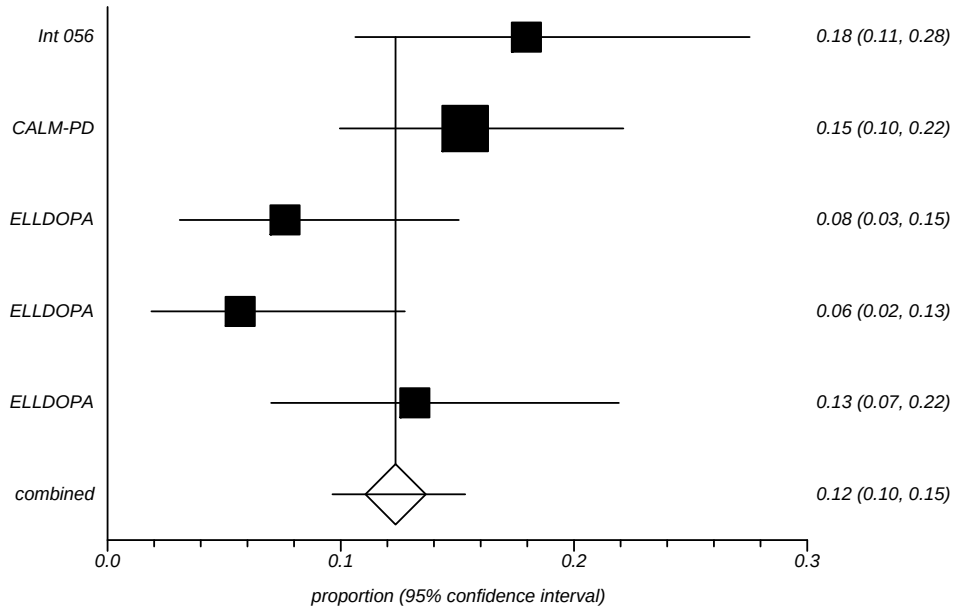
Random effects (DerSimonian-Laird)
Pooled proportion = 0.12076132 (95% CI = 0.07961689 to 0.16908769)

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.8 P = 0.0833 (low power)
Egger: bias = 6.91107914 (95% CI = -4.06075648 to 17.88291476) P = 0.1387
Harbord: bias = -5.34877274 (92.5% CI = -22.88226801 to 12.18472254) P = 0.4734

Bias assessment plot



Proportion meta-analysis plot [fixed effects]



Proportion meta-analysis plot [random effects]