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Review

Dopamine agonists in animal models of Parkinson's disease: A systematic review and meta-analysis☆

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ABSTRACT

Background: Parkinson's disease (PD) can be a severely disabling condition in spite of therapies currently available. Systematic review and meta-analysis can provide an overview of a field of research and identify potential sources of bias and limits to efficacy. In this study we use these tools to describe the reported efficacy of dopamine agonists in animal models of PD.

Methods: Publications were identified by electronic searching of three online databases. Data were extracted for neurobehavioural outcome, for study design and for the reporting of measures to avoid bias. Standardised mean difference meta-analysis was used to provide summary estimates of efficacy, with the effects of study quality and study design explored using stratified meta-analysis.

Results: 253 publications reported the use of a dopamine agonist in an animal model of PD; of these 121 reported data suitable for inclusion in meta-analysis. 47 interventions were tested in 601 experiments using 4181 animals. Overall, neurobehavioural outcome was improved by 1.08 standard deviations (SD; 95% Confidence Interval (CI) 0.97−1.19). Reporting of measures to reduce bias was low and publications which reported the blinded assessment of outcome had significantly smaller effect sizes (0.85, 95% CI 0.64 to 1.07) than those which did not (1.18, 95% CI 1.05 to 1.31, $p < 0.005$).

Conclusions: While dopamine agonists do appear to have efficacy in animal models of PD the low prevalence of reporting of measures to avoid bias is of concern. Systematic review of individual interventions may be helpful in the design of future preclinical and clinical trials.

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1. Introduction

Treatment options for Parkinson's disease (PD) have continued to increase with the development of new classes of drugs and new formulations of existing drugs, but there remains a need to identify interventions which robustly achieve substantial efficacy while minimising adverse effects. With their comparatively smaller risk of motor side effects, dopamine agonists are commonly used as first line agents and have clear evidence for efficacy from meta-analysis of randomised controlled trials. However, in comparison to other agents they may have lower efficacy and increased rates of treatment limiting adverse effects [1]. Because of their documented clinical efficacy and the quantity of information available they provide a good exemplar of the animal data supporting a successful clinical treatment which we might use to inform the development of the next generation of drugs for PD.

In other domains systematic review and meta-analysis of preclinical (animal) literature has been used to identify the conditions of maximum efficacy in animals and to inform the design of clinical trials [2,3]. Moreover, this approach can also be used to summarise the quality of the studies (including the reporting of measures to avoid bias such as random allocation to group and blinded assessment of outcome) and to assess the impact of such biases. We have previously shown that for both stroke and multiple sclerosis (MS) preclinical research publications which do not report these measures have significantly larger effect sizes [4–7]. In addition, we have shown that publication bias is prevalent in the preclinical stroke literature and that when this is taken into account the overall efficacy of interventions falls from 31% to 24% [8].

Here we report a systematic review and meta-analysis of dopamine agonists in experimental models of PD. Specifically we aim to (1) identify publications reporting the use of a dopamine agonist in an animal model of PD; (2) report summary estimates of efficacy; (3) identify the impact of study design and study quality on the reported efficacy; and (4) assess for the presence and impact of any publication bias.

2. Methods

2.1. Search strategy

Studies reporting the use of a dopamine agonist in an animal model of PD were identified by electronic searching of Pubmed, Biosis and Embase up to and including September 2009. The following search strategy was used: [Parkinson's disease] AND ([1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine OR MPTP OR 1-methyl 4-phenyl pyridinium OR MPP+ OR 6-hydroxydopamine OR 6-OHDA OR Paraquat OR Maneb OR Rotenone OR 3-nitrotyrosine OR Alpha-synuclein OR Reserpine OR Methamphetamine]). Abstracts were independently screened by two investigators (ER, HV) to identify those meeting our inclusion criteria (see below), with differences clarified by discussion with a third investigator (ES).

2.2. Inclusion and exclusion criteria and data extraction

We included studies that described the use of a dopamine agonist in an animal model of PD and reported the number of animals per group, a neurobehavioural outcome, and the mean outcome and its variance (standard error of the mean or standard deviation). We defined a dopamine agonist as a drug with reported agonism at atleast one class of dopamine receptor irrespective of actions at other dopamine or other receptor classes. We therefore made no judgement as to whether dopamine agonism was the principle mechanism of action. Indirect dopamine agonists (e.g. the dopamine precursor L-DOPA) were specifically excluded. We also excluded studies where apomorphine was used exclusively to confirm successful lesioning as part of an experimental protocol not testing the efficacy of dopamine agonists, and experiments where the pooled sample size was 4 or fewer (this precludes standardised mean difference meta-analysis). Data were extracted to the CAMARADES Database [7]. Neurobehavioural outcome measures used were categorised into one of seven groupings for further analyses (Table 1). Where outcomes were measured repeatedly we chose the time at which efficacy was greatest. Where outcomes were expressed graphically, data were measured using digital ruler software (Universal Desktop Ruler). Information was extracted for aspects of quality (see below) and experimental design (animal species and strain, sex, intervention tested, anaesthetic used during disease induction). For neurobehavioural outcomes the number of animals, mean and variance (standard error of the mean or standard deviation) for the treatment and control group were extracted as well as the dose, route of administration and time of administration and assessment. The time of lesioning was set to zero and the time of drug administration expressed relative to this.

3. Methodological quality

We used a six point checklist based on published criteria [9–11] to assess the methodological quality of publications. These items included publication in a peer reviewed journal, the reporting of

Table 1
Grouping of the different outcome measures to one of six categories for analysis.

Neurobehavioural outcome	Description
Motor activity requiring sensory input (MASI)	Number of mistakes or "no response" errors; pellets eaten; steps reached; reaction time (correct responses); startle response.
Spontaneous activity	Locomotor/spontaneous activity (measured as beam crossings); time spent in: body displacement, shuffling, head movement, locomotor activity, grooming, jumping, rearing.
Skilled motor activity	Catalepsy; errors per step, number of steps or time to traverse on a beam; retention time on rotarod; initiation time for stepping; grasping time or hanging time.
Rotational Behaviour	Number of spontaneous or drug induced rotations.
Limb asymmetry	Right biased swing; goal directed limb movements; contralateral turns or pivots; adjusting steps in backhand or forehand direction; turns to the right in a maze; ipsilateral rotations; right hand use.
Parkinson's disability rating	Akinesia score; Parkinson's rating score (usually out of 5); disability score; bradykinesia score.
Balance and gait	Stepping length or width (gait); ankle extension or flexion; posture; balance; rigidity.

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random allocation to group, blinded assessment of outcome, a sample size calculation, compliance with animal welfare regulations and a statement of a potential conflict of interest.

4. Data analysis

For each comparison we calculated the standardised effect size and its standard error [12]. This allows comparison between effects measured on different scales. Data were aggregated using a weighted mean difference method where greater weight is given to more precise studies. When a control group served more than one experimental group, the number of observations in that control group was, for the purpose of the meta-analysis, divided by the number of experimental groups served. To account for anticipated heterogeneity we used the random effects model of Dersimonian and Laird [13] which is more conservative than fixed effects meta-analysis. The weighting given to individual comparisons depends on the variance within those comparisons and on overall heterogeneity. The significance of differences between n groups was assessed by partitioning heterogeneity and by using the χ^2 distribution with $n-1$ degrees of freedom (df). When stratifying heterogeneity according to study quality and design, the different neurobehavioural outcome measures were analysed together to establish the overall impact of study quality; we used meta-regression to explore whether study quality items had a particular influence on particular outcome measures. To allow for multiple comparisons we adjusted our significance level to $p < 0.005$ using Bonferroni correction. We looked for publication bias using funnel plotting [14], Egger regression [15] and "trim and fill" [16].

5. Results

5.1. Search results

We identified 252 published articles (215 full publications and 37 abstracts) from the electronic search, and hand searching identified one unpublished thesis. Together these reported the use of 74 unique dopamine agonists in animal models of PD (Fig. 1 and Supplementary material 1). 132 publications were excluded from the meta-analysis because (1) they did not report critical information such as results from a control group (82 publications); data were insufficient or had subsequently been published in greater detail (37 publications, mostly abstracts), or they used apomorphine as a screening tool to assess the level of dopamine depletion (13 publications). The remaining 121 publications (116 full publications and 5 abstracts) using 47 dopamine agonists reported at least one neurobehavioural outcome in sufficient detail to allow meta-analysis. 46 of 121 publications described crossover studies, where each animal served as its own control, with performance under control conditions generally assessed before the treatment phase.

This review is therefore based on data from 253 sources, and we have been able to perform meta-analysis on a subset of 121 publications which included data from 601 experiments involving 4181 animals.

5.2. Efficacy of dopamine agonists

Overall, neurobehavioural outcome was improved by 1.10 SD (95% CI 0.99 to 1.22). The efficacy of 47 individual interventions ranged from an improvement of 6.57 SDs (0.75–12.4) for BAM-1110 to a significant worsening of −1.35 (−2.49 to −0.21) for amantadine (Fig. 2 and Table 2). Overall 29 interventions significantly improved outcome, only 1 made it significantly worse, and 17 drugs had no significant effect on outcome. We grouped the outcome measures used into seven broad categories (Table 1), and this accounted for a significant proportion of the between study heterogeneity, with largest effects seen when outcome was measured on various Parkinsonism disability rating scales ($\chi^2 = 136.6$, df = 6, $p < 0.005$, Fig. 3a).

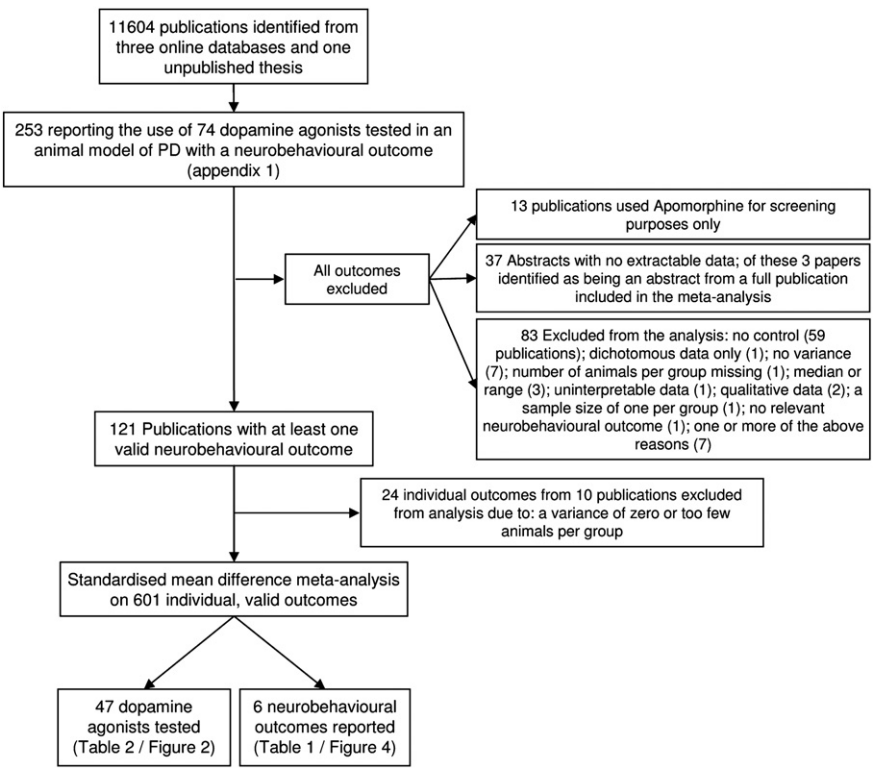

Fig. 1. A quorum diagram of the progression from the literature search to the data analysis.

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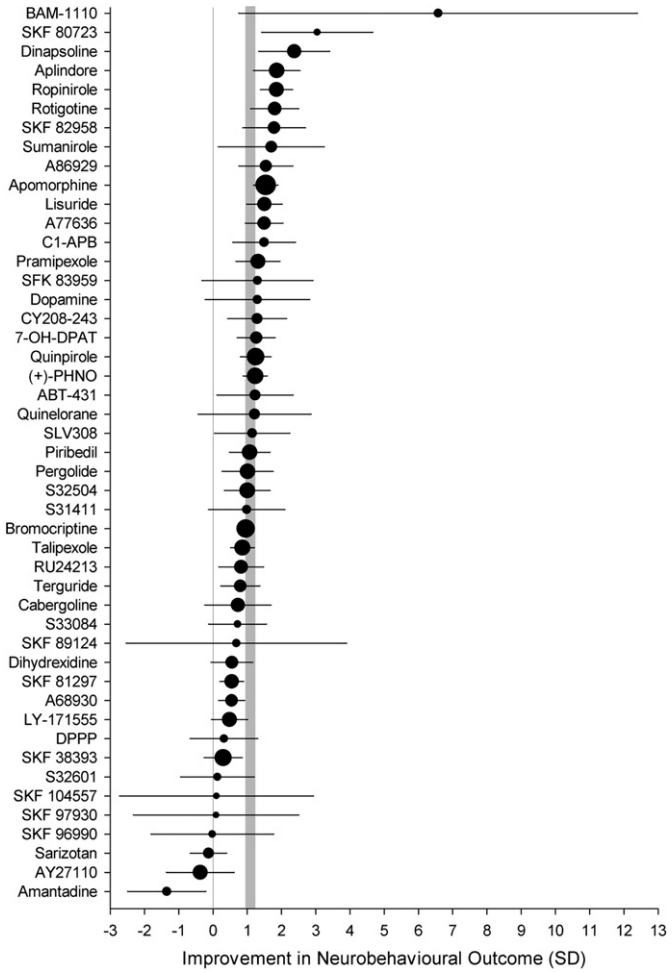

Fig. 2. Estimate of efficacy of 47 dopamine agonists. Horizontal error bars represents the 95% CI; vertical grey bar represents the global estimate of efficacy and its 95% CI; symbol size represents the log of the number of animals for that intervention.

5.3. Methodological quality

Few studies reported measures to avoid bias; the median number of quality items scored was 2 out of a possible 6 (interquartile range 1–2) (Supplementary material 2). 207 publications (81%) were published in a peer reviewed journal, random allocation to group was reported by 40 publications (16%), blinded assessment of outcome by 38 publications (15%), and a sample size calculation by only 1 publication (<1%). Compliance with animal welfare regulations was reported by 100 publications (40%) and a potential conflict of interest by 6 publications (2%).

Collectively for all neurobehavioural outcomes there was an inverse relationship between study quality and effect size (Fig. 3b) ($\chi^2 = 102.3$, df = 4, $p < 0.005$). Reporting of blinded assessment of outcome was associated with significantly smaller effect sizes (0.85 SD, 95% CI 0.64 to 1.07, 144 comparisons) than those that did not (1.18 SD, 95% CI 1.05 to 1.31, 457 comparisons; $\chi^2 = 64.4$, df = 1, $p < 0.005$); however, the impact of blinding was different for different outcomes measures (Fig. 3c).

The median number of animals was 5 in the treatment group (IQR 4–8) and 2 in the control group (IQR 1–4). The number of animals per group accounted for a significant proportion of between group heterogeneity ($\chi^2 = 57.4$, df = 4, $p < 0.005$); however there was no clear trend between the sample size and reported effect size (Fig. 3d).

5.4. Publication bias

Funnel plot inspection suggested a preponderance of imprecise studies overstating efficacy consistent with publication bias (Fig. 3e), but this was not confirmed by the "trim and fill" iterative approach.

5.5. Parkinson's disease model

Of the 253 publications identified in the systematic review, ten different methods of inducing experimental PD were reported. The most common were: 6-hydroxydopamine striatal lesioning was reported in 136 publications, followed by MPTP (105) and reserpine (22). Seven lesioning methods were used in the 121 studies included in the meta-analysis, and the method of lesioning accounted for a significant proportion of the between study heterogeneity ($\chi^2 = 197.7$, df = 6, $p < 0.005$); interventions were most effective when disease was modelled by rotenone lesioning, whereas dopamine agonists did not improve outcome when the lesion was induced in a transgenic mouse model by over-expression of mutated alpha synuclein (Fig. 4a and Supplementary material 3).

5.6. Design characteristics

Dopamine agonists were tested in rats (141 publications), non-human primates (101), mice (21) and guinea pigs (1) and in one publication the species used was not reported. The animal species ($\chi^2 = 44.1$, df = 3, Fig. 4b), sex ($\chi^2 = 58.7$, df = 3, Fig. 4c), type of anaesthetic used during lesioning ($\chi^2 = 52.1$, df = 10, Supplementary Fig. 1a), time of drug administration relative to lesioning ($\chi^2 = 35.4$, df = 6, Supplementary Fig. 1b) and route of administration ($\chi^2 = 25.7$, df = 7, Supplementary Fig. 1c) all seemed to influence the reported efficacy as they accounted for a significant proportion of the between study heterogeneity (for each comparison $p < 0.005$).

The median interval between lesioning and treatment was 28 days (IQR 13–70) but there was no relationship between the age of the lesion and efficacy.

6. Discussion

6.1. Efficacy of dopamine agonists

Dopamine agonists are routinely used in the management of PD, and we have shown here that several are reported to have substantial efficacy in relevant animal models. Of the ten interventions with at least some dopamine agonist activity used clinically (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, peribidel, pramipexole, ropinirole and rotigotine), all had significant efficacy save cabergoline, which was without effect, and amantadine, which resulted in a significant worsening of outcome. Interventions with the highest (BAM-110) and lowest (amantadine) efficacy each were reported in only one publication, and because of this and the absence of head-to-head comparisons no reliable conclusions about the rank order of potency can be drawn.

6.2. Study characteristics

Our results suggest that dopamine agonists were most potent when tested in male animals, in guinea pigs, using the subcutaneous route of delivery and when rotenone was used as the experimental model and when of isoflurane, chloral hydrate and pentobarbital anaesthesia was used. No improvement was seen in

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Table 2
A summary of the dopamine agonists tested in animal models of PD and where available, point estimates of efficacy. Highlighted interventions are those used clinically.

Intervention	Number of publications[a]	First tested in year:	Average quality score	Number of experiments*	Effect size	Lower 95% CI	Upper 95% CI
(−)3PPP	1	1990	1.0	n/a	n/a	n/a	n/a
(+)3PPP	1	1990	1.0	n/a	n/a	n/a	n/a
(+)Dinapsoline	1	2002	0.0	n/a	n/a	n/a	n/a
(+)Dinapsoline	1	2002	0.0	n/a	n/a	n/a	n/a
(+)-PHNO	11	1986	0.4	38	1.23	0.88	1.59
18Dinapsoline	1	2002	0.0	n/a	n/a	n/a	n/a
5-OH-DPAT	1	1997	0.0	n/a	n/a	n/a	n/a
7-OH-DPAT	2	1995	0.5	5	1.26	0.71	1.82
A68930	1	1997	1.0	5	0.54	0.16	0.92
A77636	5	1992	0.6	16	1.50	0.95	2.05
A86929	5	1996	0.4	10	1.55	0.76	2.34
ABT-431	2	1996	0.0	8	0.90	−0.14	1.95
Alpha-DHEC	1	1995	1.0	n/a	n/a	n/a	n/a
Amantadine	1	2008	1.0	4	−1.35	−2.49	−0.21
Aplindore	1	2006	1.0	6	1.86	1.18	2.54
Apomorphine	123	1975	0.6	89	1.54	1.19	1.90
AY27110	2	1984	0.0	8	−0.37	−1.36	0.62
BAM-1110	1	1998	0.0	3	6.57	0.75	12.40
BP897	1	2004	1.0	n/a	n/a	n/a	n/a
Bromocriptine	32	1982	0.4	58	0.96	0.73	1.19
C1-APB	2	1997	0.0	1	1.49	0.58	2.41
Cabergoline	11	1994	0.6	13	0.73	−0.24	1.70
CY208-243	3	1989	0.0	4	1.29	0.43	2.15
D145	1	1975	0.0	n/a	n/a	n/a	n/a
Dihydrexidine	5	1994	0.4	15	0.55	−0.06	1.17
Dinapsoline	1	2001	1.0	9	2.37	1.34	3.41
Dopamine	4	1988	0.5	3	1.30	−0.23	2.82
DPPP	1	1986	0.0	1	0.32	−0.67	1.31
DU127090	1	2003	0.0	n/a	n/a	n/a	n/a
Hexahydrothieno[c]benzo[f]quinoline[f]quinolines	1	1997	0.0	n/a	n/a	n/a	n/a
Lergotrile	1	1982	0.0	n/a	n/a	n/a	n/a
Lisuride	8	1984	0.1	10	1.50	0.98	2.03
LY-171555	10	1988	0.7	19	0.48	−0.05	1.01
N-0498	1	1986	0.0	n/a	n/a	n/a	n/a
N-0499	1	1986	0.0	n/a	n/a	n/a	n/a
N-0500	1	1986	0.0	n/a	n/a	n/a	n/a
N-0923	2	1992	0.5	n/a	n/a	n/a	n/a
N-0924	1	1994	1.0	n/a	n/a	n/a	n/a
N-Ethylnorapomorphine	1	1976	0.0	n/a	n/a	n/a	n/a
N-Methylcyclopropylnorapomorphine	1	1976	0.0	n/a	n/a	n/a	n/a
NNDipropylA56DTN	1	1990	1.0	n/a	n/a	n/a	n/a
N-n-Proplynorapomorphine	1	1976	0.0	n/a	n/a	n/a	n/a
Norapomorphine	1	1976	0.0	n/a	n/a	n/a	n/a
PD128,907	1	1997	1.0	n/a	n/a	n/a	n/a
Pergolide	13	1980	0.5	14	1.01	0.26	1.76
Piribedil	8	1992	0.8	26	1.07	0.48	1.66
Pramipexole	7	1992	0.6	14	1.31	0.67	1.96
Quinelorane	2	2000	1.0	5	1.22	−0.43	2.86
Quinpirole	33	1990	0.6	30	1.25	0.80	1.70
Ropinirole	16	1991	0.7	23	1.85	1.39	2.32
Rotigotine	4	2007	1.5	10	1.80	1.10	2.51
RU24213	2	1994	0.0	6	0.82	0.17	1.48
RU29717	1	1986	0.0	n/a	n/a	n/a	n/a
S31411	1	2004	1.0	3	0.99	−0.13	2.11
S32504	4	2001	0.5	23	1.00	0.33	1.67
S32601	1	2004	1.0	2	0.13	−0.95	1.21
S33084	2	2002	0.5	1	0.72	−0.13	1.57
Sarizotan	1	2009	1.0	6	−0.13	−0.66	0.40
SFK 83959	5	1995	1.2	2	1.30	−0.32	2.93
SKF 104557	1	2000	1.0	2	0.10	−2.73	2.93
SKF 38393	32	1985	0.6	27	0.30	−0.26	0.86
SKF 75670	1	1995	2.0	n/a	n/a	n/a	n/a
SKF 80723	2	1995	1.5	1	3.04	1.42	4.67
SKF 81297	9	1993	1.0	17	0.55	0.20	0.90
SKF 82958	12	1993	0.5	7	1.79	0.87	2.71
SKF 89124	1	2000	1.0	4	0.68	−2.54	3.90
SKF 96990	1	2000	1.0	3	−0.02	−1.81	1.77
SKF 97930	1	2000	1.0	2	0.09	−2.33	2.51
SLV308	3	2001	0.0	5	1.14	0.04	2.25
SLV318	1	2003	0.0	n/a	n/a	n/a	n/a
Sumanirole	2	2005	1.5	8	1.70	0.15	3.25
Talipexole	7	1993	0.4	28	0.86	0.51	1.21
Terguride	4	1988	0.5	7	0.80	0.22	1.37
U91356A	2	1992	0.0	n/a	n/a	n/a	n/a

[a] For references see Supplementary material 3.

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the alpha-synuclein transgenic model; however it is unclear whether this is a biological phenomenon, or these associations are confounded by the quality of the literature.

6.3. Study quality

Measures to avoid bias were infrequently reported. While it is possible that some authors might have taken such measures but not reported them, in the experimental stroke literature there were no significant differences between actual and reported study quality [17], and the same may hold here. This is important because we have shown that across a range of animal experiments modelling stroke and multiple sclerosis, publications which do not report such measures substantially overstate efficacy [4–7]. Here we have shown that the same holds for animal experiments modelling PD. Because of this our findings for efficacy should be interpreted with some caution, and a more detailed review would be required fully to assess the impact of these factors.

In addition to these concerns about the quality of studies included in the review a further 83 publications could not be included because they had no control group, they reported data without reporting its variance, it was not possible to interpret the data as presented or the pooled sample size was 3 or less.

6.4. Sample size

Animal experiments should be designed to be large enough to have a reasonable prospect of detecting a biologically significant

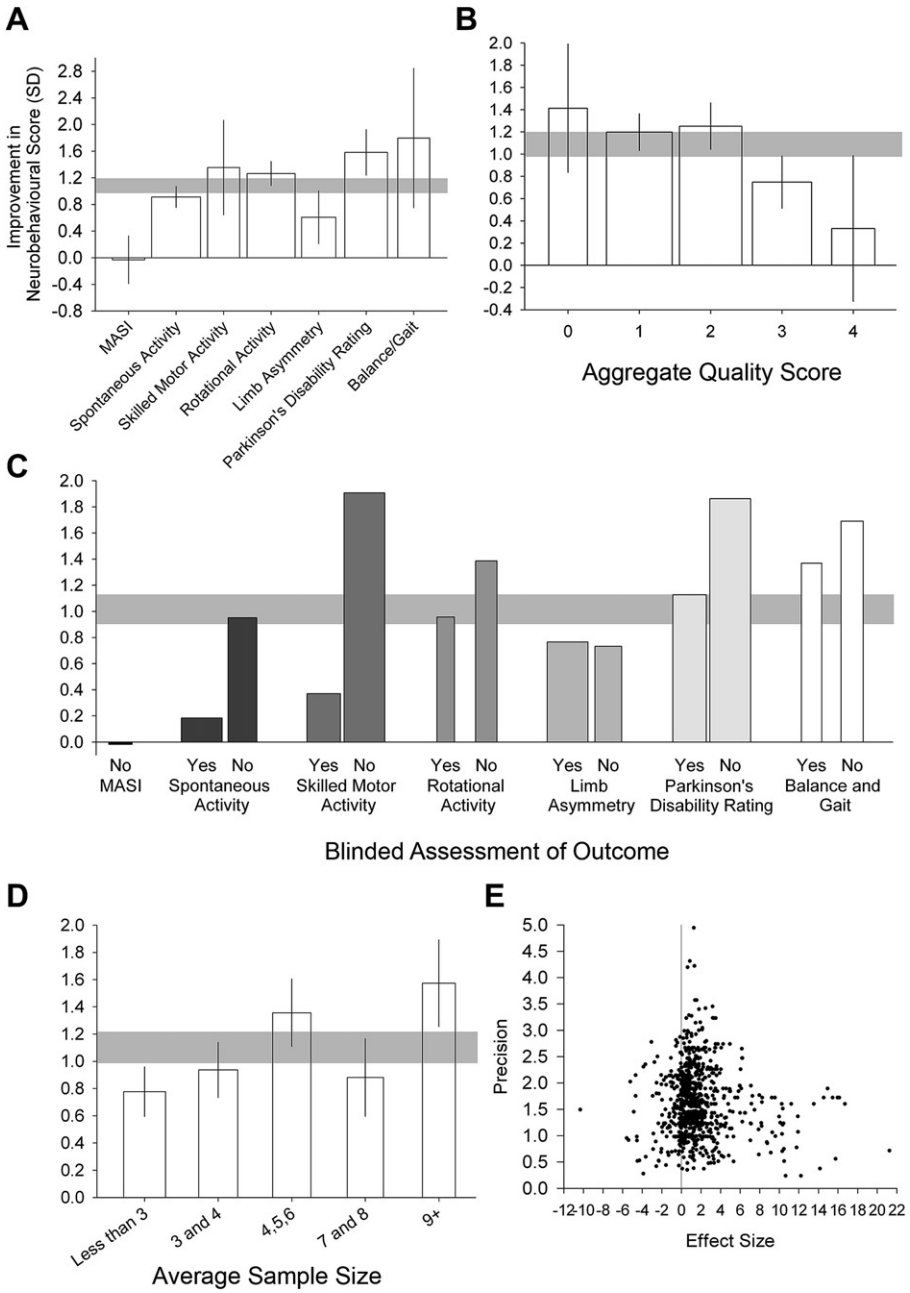

Fig. 3. Improvement in neurobehavioural outcome (A) and the effect of aggregate quality score (B) blinded assessment of outcome (C) and mean sample size (D) on the estimates of effect size, and a funnel plot (E) to test for the presence of publication bias. In A–D horizontal error bars represents the 95% CI of overall efficacy; bar width reflects the number of animals used. In E the vertical grey bar represents the line of no effect.

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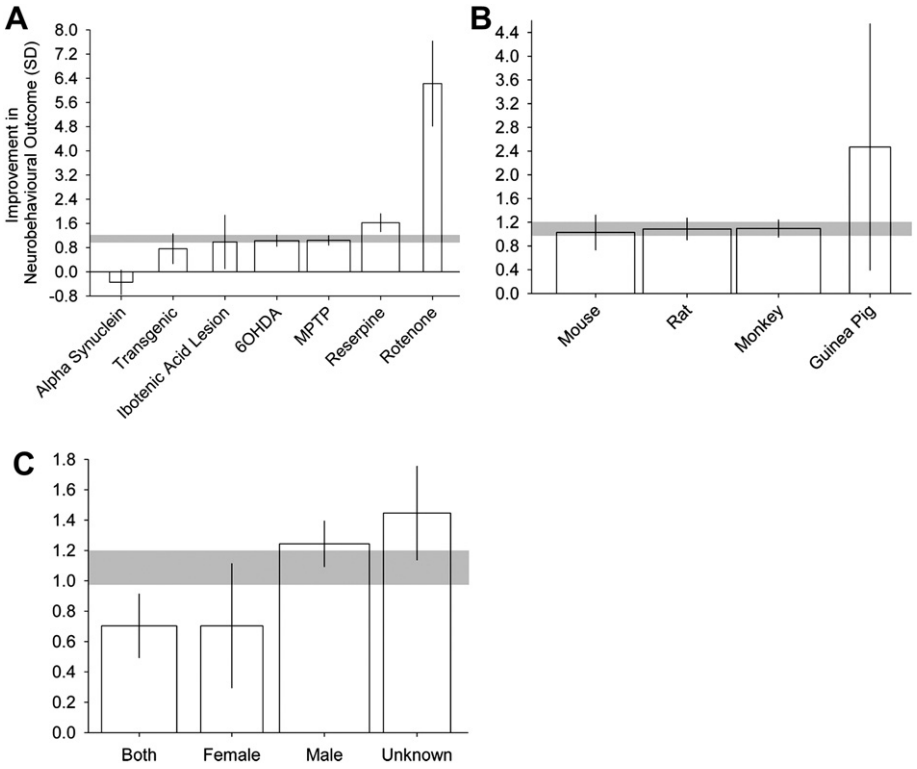

Fig. 4. Effect of the method of induction of injury (A), animal species (B) and sex (C) on the estimates of effect size. Horizontal error bars represents the 95% CI; vertical grey bar represents the global estimate of efficacy and its 95% CI; symbol size represents the log of the number of animals for that intervention.

difference yet small enough to minimise unnecessary use of animals. The required size can be estimated using a sample size or "power" calculation, but only one publication reported a sample size calculation. Overall the median number of animals per group was five for the treatment groups (IQR 4–8) and 2 for the control groups (IQR 1–4). Post-hoc power calculations have limited validity, but with a median effect size of 1.12 SD and a pooled variance of 0.648, 50% of experiments included in this analysis were powered at 40% or less, that is to say they only had a two in five chance of detecting the outcomes reported.

Taken together, these findings provide further support for the development of guidelines regarding the conduct [18] and reporting [19] of animal studies.

6.5. Publication bias

Both funnel plotting and Egger regression suggested publication bias, but this was not confirmed by "trim and fill" analysis, in contrast to the experimental stroke literature [8]. This analysis is based on the subset of 121 studies included in the meta-analysis, and it may be that were it possible to include the other studies then publication bias might indeed have been found. Furthermore, it has been suggested that trim and fill is an overly conservative statistical approach to the detection of publication bias [20], and it may be that with other techniques such as the Copas selection model, or a larger dataset, publication bias would be seen. Research summaries and considerations about taking novel treatments to clinical trial can only assess available data, and given the suggestion that publication bias may exist in this literature we advocate the development of research registries similar to those adopted in clinical research, that such unpublished sources of data might be identified in the development of research summaries.

6.6. Limitations

There are a number of limitations to our approach: firstly, as described above, our analysis can only include published data, and since positive studies are more likely to be published, it is conceivable that our estimates of effect size reported here are overstated. In addition, although we have accounted for multiple comparisons in our statistical evaluation, it is possible that some results occurred by chance. Moreover, there may be collinearity between certain variables, and in particular ones which have the fewest outcomes. A post-hoc analysis of multi-collinearity identified that there may be a relationship between some interventions and their route of delivery and/or anaesthetic used.

7. Conclusions

Here we have shown that several dopamine agonists have efficacy in animal models of PD including a number which are not currently in clinical use. However, we found reported study quality to be limited, and that reported efficacy fell as reported study quality increased. We have also found evidence suggesting the presence of publication bias, although we have not been able to quantify its impact. The use of systematic review and meta-analysis and the data presented here provide a framework for an evidence-based approach to the development of new treatments for PD and for the design of future animal and clinical studies. However, further work is required to fully to elucidate the impact of study quality and design factors on the animal modelling of PD.

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None declared.

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Appendix. Supplementary material

Supplementary material related to this article can be found online at doi:10.1016/j.parkreldis.2011.02.010.

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