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Dopamine receptor agonist treatment of Parkinson's disease:

A systematic review and meta-analysis

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder which affects approximately 1% of individuals over 60 years of age. There has been a growing interest in dopamine agonists as a form of treatment for this disease. The aims of this systematic review and meta-analysis were to establish the efficacy of different subclasses of dopamine receptor agonist in the treatment of animal models of PD, to examine the relationship between details of the methods used in these studies and how effective the drug is reported to be, and to determine whether the species of the animal used has a bearing on the efficacy of dopamine agonist.

114 articles were included in this analysis, from which 600 comparisons were identified, using a total of 5687 animals. A methodological quality score was assigned to each paper, and this was shown to have significant bearing on how effective a drug was reported to be when the outcome was measured by subjective observation. This was not the case when outcome was measured by an automated system. The efficacy of a particular dopamine agonist also depended on the receptor subtype stimulated and the type of outcome measure used, be it motor activity contralateral turning or neurobehavioural scale. D3 receptor agonists showed the greatest improvement in outcome in terms of motor activity at 1.552 (95% CI 0.922-2.18), but proved detrimental to the neurobehavioural score -13.700 (-45.955-18.556). D2+D3 agonists significantly improved neurobehavioural score 51.648 (39.462-63.834), but a less marked improvement was seen in the promotion of contralateral turning behaviour 28.224 (-0.668-57.117), but Dopamine agonists also stimulated greater contralateral turning behaviour in mice 401.57 (264.994-538.59), and rats 213.357 (189.785-236.929), in comparison to monkey models 62.071 (47.191-76.950).

As well informing further research into the use of dopamine agonists in clinical practice, this analysis may also stimulate debate into the validity of animal models to inform the treatment of human disease.

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1- INTRODUCTION

1.1 – Parkinson's disease – a brief background:

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with the loss of dopaminergic nigrostriatal neurons. It is recognised as one of the most common neurological disorders, affecting approximately 1% of individuals over 60 years of age**. PD is 1.5 times more common in men than women**. The primary features of this disease include resting tremor, rigidity, bradykinesia, and postural instability.

The major neuropathologic findings in PD are a loss of pigmented dopaminergic (tyrosine hydroxylase positive) neurons in the substantia nigra, and the presents of Lewy bodies. 60-80% of dopamine neurons are lost before motor signs of PD become evident. Lewy bodies are concentric, eosinophilic, cytoplasmic inclusions with peripheral halos and dense cores. They are characteristic, but not pathonomonic of idiopathic PD. All Lewy bodies stain for α-synuclein, which was recently discovered to be their major structural component**.

The basal ganglia motor circuit modulates cortical output and is required for normal movement. It receives signals from the cerebral cortex and relays these through the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulate (SNr). This inhibitory output is directed to the thalamocortical pathway and suppresses movement. The basal ganglia circuit consists of the direct and indirect pathways (Figure 1). The direct pathway involves direct inhibition of the GPi and SNr by the striatum. The indirect pathway comprises inhibitory connections between the striatum and the external globus pallidus (GPe) and the subthamic nucleus (STN). The STN in turn exerts an excitatory influence on the GPi and SNr. The GPi and SNr inhibit the ventral lateral (VL) nucleus of the thalamus. Striatal neurons containing D1 receptors constitute the direct pathway and those containing D2 receptors are part of the indirect pathway. In PD decreased striatal dopamine (DA) causes increase inhibitory output from the GPi/SNr, which suppresses movement.

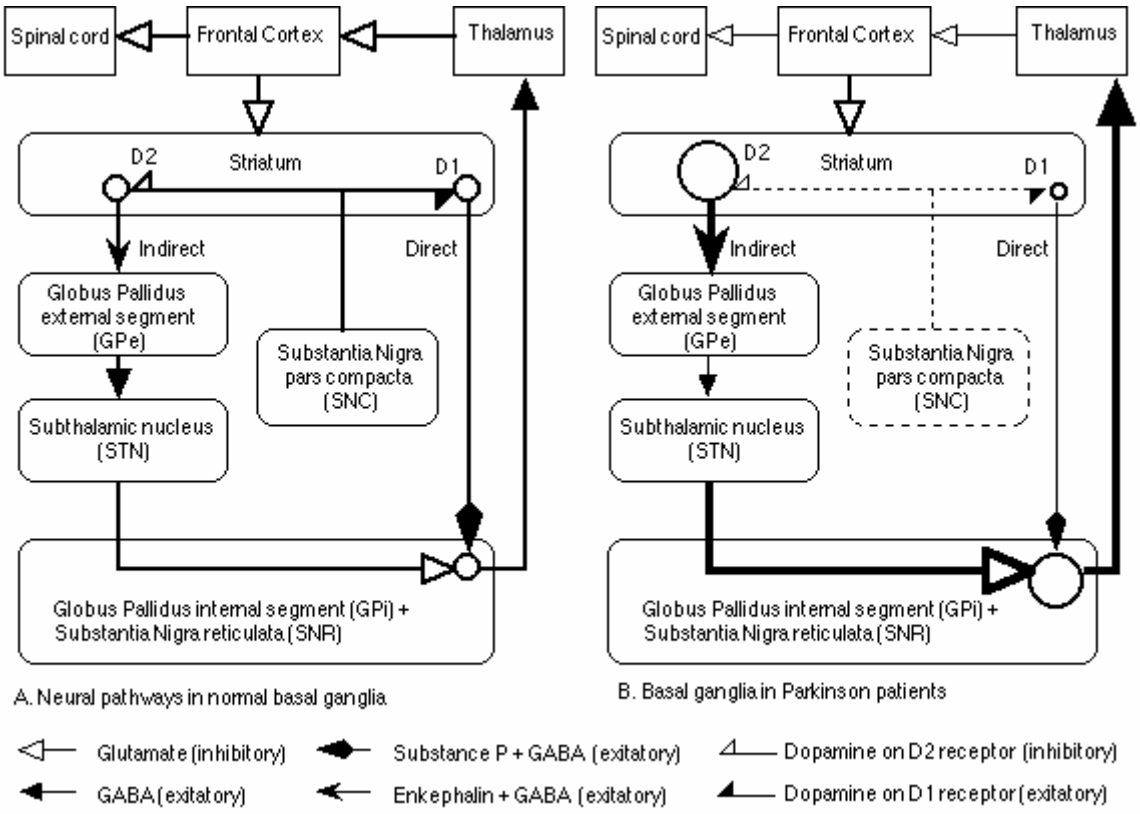


Figure 1: Schematic representation of the basal ganglia-thalamocortical motor circuit and the relative change in neuronal activity in Parkinson's disease**

1.2 – Dopamine agonists and the treatment of Parkinson's disease:

There is growing evidence that Levodopa, the gold standard for PD treatment over the past 30 years, is in fact toxic to dopaminergic cell cultures** . It is also well known that long term use of Levodopa generates motor complications such as dyskinesia**. This has lead to an increase interest in alternative therapies. Preclinical studies suggest that dopamine agonists reduce the loss of dopaminergic neurons, and slow the rate of PD progression******. They exert their antiparkinsonian effects by acting directly on dopamine receptors (D1, D2, D3, D4 and D5) and mimicking the endogenous neurotransmitter. They are also associated with fewer long-term side-effects**. This growing body of evidence has led to the use dopamine agonist monotherapy as well their use as a co-treatment with Levodopa**. Most dopamine agonists currently used in humans are D2 agonists, with or without D1 agonist properties.

1.3 – Animal models of Parkinson's disease:

There are a number of animal models of PD. Table 1 lists the main PD animal models used and describes the similarities and differences between these model and human disease characteristics.

Model:	Symptoms:	Histopathology:	Pathogenic relevance:	Applications:	Disadvantages:	Similarities to human disease:	Differences from human disease:	Comments:
MPTP	Akinesia, rigidity, tremor in some species	Decrease striatal TH-immunoreactivity, degeneration of TH-immunoreactive neurons in SNc, some loss of locus ceruleus neurons, alpha-synuclein aggregation	Environmental toxin, oxidative stress, inhibition of mitochondrial complex I	Preclinical testing of therapies to improve symptoms, screen drug therapies designed to protect DA neurons	Generally acute, non-progressive or reversible, inclusion bodies are rare	Parkinsonism, loss of DA neurons in SN, alpha-synuclein-immunoreactive cytoplastic inclusions, good response to DA receptor agonists	Acute or subacute process, no typical Lewy bodies	Rodents are less sensitive to MPTP
6-OHDA	Unilateral: rotation after dopamine agonist administration Bilateral: akinesia	Decreased striatal TH-immunoreactivity, degeneration of TH-immunoreactive neurons in SNc	Oxidative stress	Preclinical testing of therapies		Loss of DA neurons in SN, good response to DA receptor agonists, locomotor dysfunction	No Lewy bodies	Effective in rats, mice, cats and primates
Reserpine	Akinesia, cataplexy	None	Pharmacological dopamine depletion	Preclinical testing of therapies to improve symptoms	Nonspecific liberation of monomine transmitters, hypothermia	-	-	-
Rotenone	Akinesia, rigidity, tremor, flexed posture	Decrease striatal TH-immunoreactivity, decrease TH-immunoreactive neurons in SNc, some loss of locus ceruleus neurons, inclusions reminiscent of Lewy bodies	Chronic environmental toxin, chronic oxidative stress, chronic inhibition of mitochondrial complex I	Screen drug therapies designed to protect dopamine neurons	Labour and time intensive, substantial mortality and morbidity	Locomotor dysfunction, loss of DA neurons in SN, alpha-synuclein-immunoreactive cytoplasmic inclusions similar to Lewy bodies, good response to DA receptor agonists	Variable individual susceptibility	Effective in Lewis rats
Transgenic alpha-synuclein	Reduced or abnormal motor activity	Alpha-synuclein-immunoreactive cytoplasmic inclusions, modest decrease in striatal TH-immunoreactivity in	Known pathogenic mutations	Screen drug therapies designed to protect dopamine cells	Expensive and time consuming; mice do not have characteristic PD pathology or phenotype	Locomotor dysfunction, loss of striatal dopamine terminals, cytoplasmic inclusions with alpha-synuclein	No loss of DA neurons in the SN	Results are inconsistent

Table 1: Features of various animal models of Parkinson's disease and comparison with those of human disease**.

1.4 – Aims of this study:

There is a belief that testing in animals increases the likelihood of identifying drugs that are sufficiently promising to justify the effort and expense of further clinical development. To date, very few meta-analyses have been carried out in order to determine which are the best PD studies to carry forward from animal trials to those in humans. This systematic review and meta-analysis aims to:

- establish the efficacy of different subclasses of dopamine receptor agonist in the treatment of animal models of PD.
- examine the relationship between details of the methods used in these studies, and how effective the drug is reported to be.
- determine whether the species of the animal used has a bearing on the efficacy of dopamine agonist.
- examine the concordance between animal and human studies into dopamine agonist treatment of PD.

2 – METHODS

2.1 – Search strategy:

Studies where PD was investigated using animal models of PD were identified from Pubmed (5012 to March 2007), Biosis (6779 to March 2007) and Embase (6212 to March 2007). The following search strategy was used: [Parkinson's disease] AND [1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine ORMPTP 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]. Foreign language reports were included only if an English abstract was published.

2.2 – Eligibility:

Studies were only included if they met the following criteria: they were a full publication, described the use of a dopamine agonist in an animal model of PD, and used a control group. The following outcome measures were included:

- Motor activity. This is measured using automated counters, an example of which is the microwave Doppler module. An effective drug hopes to increase activity in bradykinetic/akinetic PD animal models.

- Contralateral turning. When striatal tissue is unilaterally lesioned, and an animal is given a dopamine agonists, turning contralateral to the lesion is induced. The number of turns produced can then be used as a measure of the efficacy of that particular drug.

- Neurobehavioural score. This comprised data on Parkinson's disease score, akinesia score and bradykinesia score. Table 2 gives an example of the factors that make up neurobehavioural scores used in PD research.

Neurobehaviour:	**Score:**
Alertness	Normal = 0, reduced = 1, absent = 2
Head (checking movement)	Normal = 0, reduced = 1, absent = 2
Eye (attention, blinking, movement)	Normal = 0, reduced = 1, eye closed = 2
Posture	Normal = 0, abnormal trunk or limb = 2, abnormal trunk and limb = 3, grossly abnormal (fixed) = 3
Balance	Normal = 0, impaired = 1, no movement = 2
Motility (at rest)	Normal = 0, mildly slow = 1, moderate bradykinesia = 2, bradykinesia = 3, akinesia = 4
Motility (reaction to external stimuli)	Normal = 0, reduced = 1, slow = 2, absent = 3
Vocalisation	Normal = 0, absent = 1
Tremor (at rest)	Absent = 0, moderate = 1, severe = 2
Tremor (reaction to external stimuli)	Absent = 0, moderate = 1, severe = 2

Table 2: Rating scale to access neurobehavioural changes seen in animal models of PD**

The selection of publications to be included in this study was carried out by two individuals and then collated in order to reduce selection bias.

2.3 – Methodological quality:

The methodological quality of each study was rated according to the following criteria and one point was allocated for each attribute:

(1) Peer review publication
(2) Random allocation to group
(3) Sample size calculation
(4) Blinded assessment of outcome
(5) Statement of potential conflicts of interest
(6) Compliance with animal welfare regulations
(7) Anaesthetic without marked intrinsic neuroprotective activity (ketamine)
(8) Control of temperature

This scale was adapted from that used in previous meta-analyses***.

2.4 – Data extraction:

Where outcome was expressed graphically, raw data was requested from the author. Where no response was received, data was read from the bar charts.

The quality score, the mean and standard deviation of the outcome measure were recorded for the control (lesioned animal + vehicle) and treatment (lesioned animal + dopamine agonist) groups, as well as the number of animals in each group, target receptor subtype, and species of animal model studied. Contralateral turning behaviour was taken as turns per hour, so that a meaningful comparison between studies could be made. The duration of lesioning, time to treatment (time of lesioning was taken as time = zero), duration of treatment and time of assessment (this was taken as the time from when the animal was both lesioned and given the dopamine agonist) were all included. Where a series of results were given over a set timeframe, the best result was taken and the time of this result noted as the time of assessment. Where multiple doses of a drug were given, the final cumulative result was taken, and the time of this result taken as the time of assessment.

The principle that no animal can contribute to more than one comparison in the meta-analysis was adhered to. Thus, where multiple outcome measures were measured on the same group of animals, the data was combined using meta-analysis to give an overall estimate of effect size with its standard deviation. If the same control group was used for multiple comparisons, the control group was divided by the number of experimental groups.

2.5 – Statistical analysis:

The effect size was calculated as the proportional difference between the treated and control groups and its standard error was calculated. Data was combined as follows; motor activity counts were analysed by standardised mean difference, contralateral turning data by weighted mean difference, and neurobehavioural scores by normalised mean difference.
A stratified meta-analysis was performed in order to determine the extent to prescribed study characteristics influence the estimated effect size. Experiments measuring the outcome of treatment with various dopamine agonists were grouped according to the quality score, the type of dopamine receptor agonised and the species of the animal model used. The significant difference between n groups was assessed using partitioning heterogeneity and the significance level was set to $p<0.001$ to allow for multiple comparisons.

3 – RESULTS

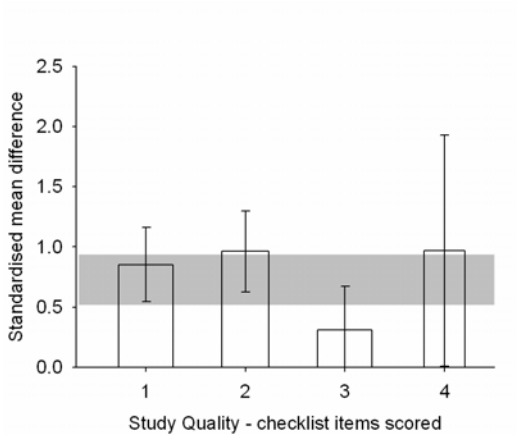
3.1 – Search results:

Of the 18006 articles found using Pubmed, Biosis and Embase, 11305 duplicates were removed by hand. Of the remaining articles, 276 contained information regarding dopamine agonists. Of these 41 were abstracts and not included in the study. A further 73 papers were requested, but did not arrive in time to be included in this report. 7 papers did not include variance values, and could thus not be included. A further 34 did not include relevant outcome measures. In total, this systematic review includes data from 114 articles (listed in Appendix 1), from which 600 comparisons were identified, using a total of 5687 animals.

3.2 – Methodological quality scores:

The median quality score achieved was 2 (range 1-4). No papers described a study sample size calculation or provided a statement of potential conflicts of interest. 19 papers blinded assessment of outcome. Individual scores are given in Appendix 2. Grouping by quality score accounted for between group heterogeneity for contralateral turning data and percentage improvement in neurobehavioural score ($p<0.0001$) (Figure 2 b and c respectively). This was not the case for motor activity data ($p=0.007$) (Figure 2 a).

(a)



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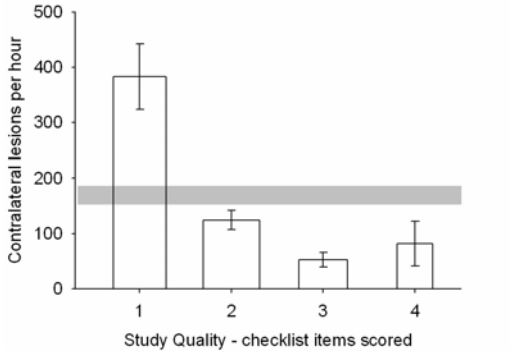

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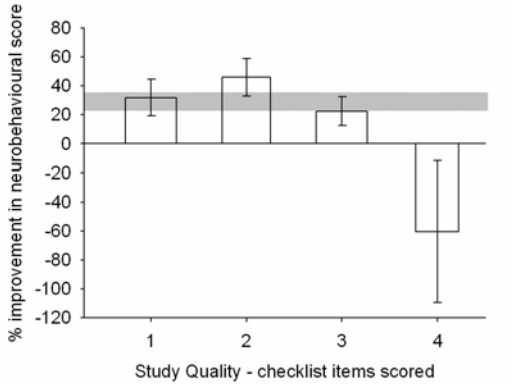
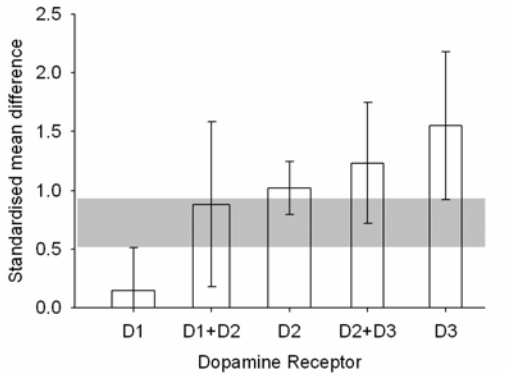


Figure 2: Study quality and the estimate of (a) motor activity, (b) contralateral turns per hour in unilateral lesioned animals and (c) percentage improvement in neurobehavioural score. Each result is the Qpe ± SEM of 9-100 comparisons. Grey band indicates global estimate and its 95% CI.

3.3 – Effect size and the type of dopamine receptor(s) agonised:

Grouping by dopamine receptor subtype significantly accounted for between group heterogeneity ($p<0.0000001$). Promotion of motor activity was greatest in response to D3 receptor agonists (1.552, 95% confidence interval (CI) 0.922-2.18), intermediate in D1+D2 (0.879, CI 0.177-1.580), D2 (1.021, CI 0.793-1.249) and D2+D3 (1.232, CI 0.719-1.745) receptor agonists and least in response to D1 receptor agonists (0.146, CI -0.22-0.510) (Figure 3 a). The greatest number of contralateral turns per hour were seen in D3 agonists (426.111, CI 275.088-577.134) and drugs that agonised D1+D2 (438.60, CI 359.929-517.279) receptors, with less marked effect seen in D1 (160.453, CI 127.807-193.098), D2 (87.129, CI 72.889-101.370) and D2+D3 (28.224, CI -0.668-57.117) agonists (Figure 3 b). Interestingly, the reverse was true for neurobehavioural scores, with the greatest improvement seen with D2 agonists (38.951, CI 27.916-49.987), and D3 receptors agonists producing detrimental effects (-13.700, CI -45.955-18.556). Dopamine agonists which agonised both D2 and D3 seemed to produce a synergistic effect (51.648, CI 39.462-63.834), with the best improvement of neurobehavioural score (Figure 3 c). D1 (19.205, CI 6.544-31.866) and D1+D2 (29.141, CI 10.107-48.176) produced an intermediate level of improvement in neurobehavioural score.

(a)



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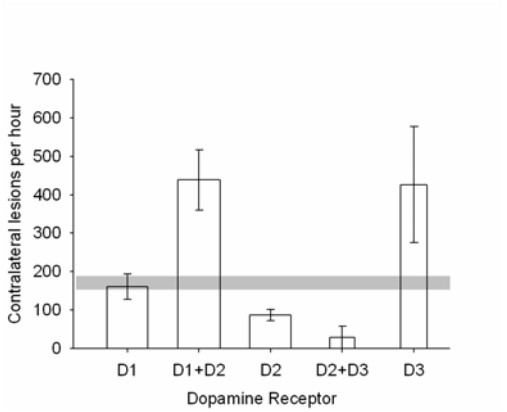

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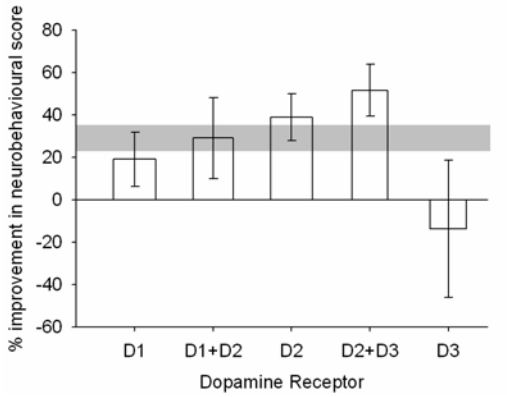

Figure 3: Effectiveness of different dopamine receptor in (a) promoting motor activity, (b) promoting contralateral turning behaviour in unilateral lesioned animals, and (c) improving neurobehavioural score. Each result is the Qpe ± SEM of 9-76 comparisons. Grey band indicates global estimate and its 95% CI.

Appendix 3 lists the effect sizes seen for motor activity, contralateral turning, and neurobehavioural scale for each dopamine agonist included in this study.

3.5 – Effect size and species of PD model:

Grouping by species significantly accounted for between group heterogeneity ($p<0.0000001$). The mouse produced the largest number of contralateral turns (401.57, CI 264.994-538.59), with an intermediate number seen in the rat (213.357, CI 189.785-236.929) and the fewest in the monkey (62.071, CI 47.191-76.950) (Figure 4).

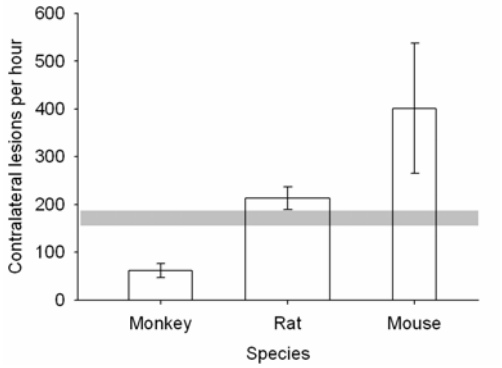

Figure 4: Induced contralateral rotations in different species. Each result is the Qpe ± SEM of 2-151 comparisons. Grey band indicates global estimate and its 95% CI.

4 – DISCUSSION

4.1 – Quality score has a bearing on outcome when outcome is measured by subjective observation:

Quality score had a significant effect on contralateral turning data and neurobehavioural score, whereas this was not the case for motor activity counts. Interestingly, activity is measured by an automated counter, whereas the former outcome measures are determined by subjective observation. Only 19 of the 114 papers were blinded for assessment of outcome. One could therefore postulate that blinded outcome assessment may have significant bearing on how effective a drug is reported to be in studies using subjective measurement of outcome.

4.2 – Effect size is dependent on the type of dopamine receptor(s) agonised:

This meta-analysis found a variance in effect size which was dependent on the subtype of dopamine receptor agonised. The type of outcome measure used also altered how effective the drug was reported to be. Taking motor activity and contralateral turns per hour, D3 receptor agonists showed the greatest effect size. However, percentage improvement in neurobehavioural score was greatest when D2+D3 were agonised, with a marked decrease in score seen if D3 was agonised alone. Neurobehavioural score takes into account a broader number of factors, and is perhaps more relevant to human clinical trials. Also, a drug's suitability for PD treatment is not merely based on whether it can stimulate movement, but rather its affect on a patient's ability to carry out their Activities of Daily Living, which turn relies on such 'neurobehavioural' factors as balance and tremor. Stimulating D3 receptors may increase movement, but a 'side effect' of this movement may be a decrease in balance, tremor, or other such factors which make up the neurobehavioural score. In both rat and human brain, D3 receptors are enriched in the ventral striatum (nucleus accumbens) and other limbic areas (Sokoloff et al., 1990; Landwehrmeyer et al., 1993; Herroelen et al., 1994), implicating a possible role in mental and emotional functions. Psychotic manifestations in humans are dose-related, and it may be possible that the activation of D3 receptors contributes to the psychiatric side effects of dopamine agonist treatment. On the other hand, further studies have found that in human striatum, D3 receptors are not restricted to the nucleus accumbens, but show a widespread distribution throughout the whole striatum similar to that of the D1 and D2 receptors, implicating a possible role in motor function as well (Herroelen et al., 1994). This meta-analysis supports this finding, with marked increases in motor activity seen upon D3 stimulation. It has also been suggested that D3 receptor activation is associated with the genesis of dyskinesia in clinical trials, but also that combination D2+D3 agonists, such as pramipexole, have significant antiparkinsonian effects. This correlates with our finding that agonising both their receptor subtypes produced a marked improvement in neurobehavioural score.

It has been hypothesised that the antiparkinsonian effect of dopamine agonists is mediated primarily by D2 receptors. A recent systematic review of PD treatment in humans noted that there is no evidence that different DA agonists varied in treatment effects***. Other studies report that drugs such as pergolide, which acts on both D1 and D2 receptors, are more effective than those which act on D2 receptors alone, such as bromocriptine. Simply recommending that D1+D2 receptor agonists be brought forward into clinical trials based on their superior efficacy in terms of contralateral turning behaviour would be an

oversimplification. It is important to understand the effect of chronic treatment, as PD is a protracted disease; D2 receptor agonists have a lower incidence of dyskinesias in human in comparison with D1+D2 agonists. Our results also show that D1+D2 receptor agonists were not shown to be more efficacious in terms of motor activity and neurobehavioural score. Very little is known about the role of D1 receptors in the human brain. However, experiments in rats and primate models of Parkinson's disease suggest that selective D1 agonism may potentiate the antiparkinsonian efficacy of D2 agonists (Walters et al, 1987; Gomez-Mancilla et al., 1992). Drugs which act on D1 and D2 receptors are especially effective in advanced PD, and do not lead to the same level of complications observed when D2 receptors are agonised alone. However, D2 agonists decrease motor fluctuations significantly in early disease.

4.3 – For contralateral turning data, effect size is dependent on the species of PD model used:

That treatment with dopamine agonists produces a greater number of contralateral turns is perhaps to be expected, given that a bulkier animal will take more time to complete a turn. This hypothesis is supported by the finding that there was no such variance between species seen for neurobehavioural score or motor activity counts. Control of movement and coordination is more complex in the monkey**, and therefore more comparable to the human, and this may also influence the number of rotations achieved. It is important to emphasise that differences in agonist affinities for dopamine receptors exist between species. To obtain a more accurate insight into the functional properties of dopamine agonists in different species, further pharmacodynamic evaluations are required.

4.4 – The pros and cons of meta-analysis and animal models of PD – scope for further study:

It is important to note that the majority of the time only positive findings are published, and this creates an intrinsic bias. A large amount of research also occurs within pharmaceutical companies that is out-with the public domain for patenting reasons. A number of the studies included in this meta-analysis may also have been carried out in order to explain negative clinical findings. Another problem with meta-analysis is that averaging across all results may mask the potential utility of a treatment within a particular subclass of patients.

Research standards for testing drug efficacy have changed considerably over the past two decades, as our understanding of the development of PD has evolved. It would be reasonable to suggest that blinding assessment of outcome could have a bearing on effect size, although there may be some other factor involved, out-with our quality score which has an influence on our results. Our scoring system may also underestimate the actual quality of the study, as it is purely based on data presented in the final publication. Due to space limitations, these may not include all data on methodological quality.

Another factor which may alter outcome is the level of lesioning in a PD model. Animals show variable sensitivity to lesioning drugs, and a broad range of doses of these substances were used throughout all the studies in this analysis. An interesting area of further study would be to determine if the method of lesioning has a bearing on effect size. This may also bear a relation to the aetiology of PD in humans, be it genetically linked, or triggered by an environmental factor. A good animal model should be reliable and produce consistent, replicable outcomes, and have the ability to predict the effect of an intervention on clinical outcome.

The results of human and animal trials need to be compared, to determine how well one predicts the other. Translating animal research into clinical trials can pose problems. Animal studies often rely heavily on motor effects because of difficulties in quantifying responses to more complex tasks. This contrasts with clinical trials where far broader aspects are analysed, including the affect of a particular drug on psychiatric health, or induction of more subtle side-effects. Conditions in clinical trials also often do not replicate the conditions under which drugs have been shown to work in animals. This is especially the case with regard to the time of administration of drugs and the extent of dopamine neuron deficit at this time. The duration of lesioning, time to treatment and time of assessment was input into our database for later analysis. This data is not presented here, owing to the word limit of this report, but may provide information that could go on to inform further research.

A large number of studies into the side-effects of dopamine agonists have been carried out. A study that shows efficacy in an animal initially, may go on to produce significant dyskinesias as a side-effect when administered chronically**. It would be fascinating to research this further and marry results with our findings in order to determine the most effective treatment with the fewest detrimental side-effects when taken over extended periods of time.

Finally, it was striking that 7 peer-reviewed studies were found to contain no data on variance. Two of these papers were published as late as 1995. Further attention to appropriate and sufficient statistical analysis is paramount.

5 – Conclusion

In conclusion, the methodological quality score achieved by a particular paper has a marked influence on reported effect size. The treatment of PD is complex. It involves a delicate balance between direct and indirect pathways involving the basal ganglia. Stimulation of different dopamine receptor subtypes has a variable effect on the level of motor activity, contralateral turning, and percentage improvement in neurobehavioural score. It is important to balance the improvement in outcome with the potential side-effects of these PD treatments. The species of the animal also has an influence on effect size, depending on the outcome measure used. Further study is required in order to determine which outcome measure is most informative in terms of human clinical trials, and which species of animal model behaves most like the human in response to dopamine agonist treatment.

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7 – Appendix

Appendix 1 – Reference list for papers used in this systematic review and stratified meta-analysis:

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Appendix 2 – PD Quality Score Table:

Name	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*Quality Score*
Akai,T [1]	1995	+			+					2
Anderson,R [2]	2001	+					+			2
Asin,K [3]	1997	+					+			2
Atsumi,M [4]	2003	+					+			2
Battaglia,G [5]	2002	+								1
Belluzzi,J [6]	1994	+					+			2
Blanchet,P [7]	1997	+					+			2
Boeckler,F [8]	2003	+					+		+	3
Boldry,R [9]	1993	+								1
Brucke,t [10]	1988	+								1
Casas,M [11]	2000	+					+		+	3
Close,S [12]	1990	+	+		+					3
Close,S [12]	1990	+			+					2
de Yebenes,J [13]	1988	+								1
Dethy,S [14]	1999	+								1
Dhanasekaran,M [15]	2001	+							+	2
Domino,E [16]	1997	+			+		+			3
Duty,S [17]	1997	+								1
Eden,R [18]	1991	+								1
Euvrard,C [19]	1979	+							+	2

Name	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Quality Score
Falardeau,P [20]	1988	+								1
Fang,D [21]	2005	+			+		+		+	4
Fleming,S [22]	2006	+			+		+			3
Fornaguera,J [23]	1995	+	+				+			3
Fox,S [24]	1996	+								1
Fox,S [25]	2000	+	+						+	3
Fukuda,T [26]	1996	+								1
Fukuzaki,K [27]	2000	+					+		+	3
Fukuzaki,K [28]	2000	+					+		+	3
Gancher,S [29]	1994	+								1
Gassen,M [30]	1998	+								1
Gille,G [31]	2005	+								1
Gille,G [32]	2002	+								1
Gille,G [33]	2002	+								1
Gnanalingham,K [34]	1995	+					+			2
Gnanalingham,K [35]	1995	+	+				+			3
Goulet,M [36]	1997	+					+			2
Goulet,M [37]	2000	+			+		+			3
Goulet,M [38]	2000	+					+			2
Grunblatt,E [39]	1999	+								1
Grunblatt,E [40]	2001	+	+				+		+	4

Name	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Quality Score
Gulwadi,A [41]	2001	+					+			2
Hara,H [42]	2006	+								1
Hayakawa,T [43]	1999	+							+	2
Heinrich,J [44]	2006	+	+							2
Henry,B [45]	1999	+			+				+	3
Hill,M [46]	2006	+								1
Hinzen,D [47]	1986	+								1
Hsu,A [48]	2004	+			+		+		+	4
Hudson,J [49]	1994	+	+							2
Iida,M [50]	1999	+					+		+	3
Irifune,M [51]	1993	+								1
Irifune,M [51]	1993	+								1
Irifune,M [52]	1994	+							+	2
Ismayilova,N [53]	2004	+					+		+	3
Jenkins,O [54]	1985	+							+	2
Jenner,P [55]	1992	+								1
Jiang,H [56]	1993	+							+	2
Johnson,B [57]	1995	+	+							2
Joyce,J [58]	2004	+			+			+		3
Kashihara,K [59]	1996	+							+	2
Kaur,S [60]	1994	+							+	2

Name	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Quality Score
Kitamura,Y [61]	1998	+							+	2
Koller,W [62]	1987	+							+	2
Koller,W [63]	1986	+							+	2
Koller,W [64]	1980	+								1
Kuno,S [65]	1998	+								1
LaHoste,G [66]	1990	+							+	2
Lorenc-Koci,E [67]	1999	+					+			2
Loschmann,P [68]	1992	+							+	2
Maneuf,Y [69]	1997	+							+	2
McCall,R [70]	2005	+					+		+	3
McElroy,J [71]	1995	+							+	2
Mierau,J [72]	1992	+								1
Mohanasundari,M [73]	2006	+					+			2
Morelli,M [74]	1991	+								1
Neisewander,J [75]	1991	+	+							2
Nomoto,M [76]	1998	+			+		+		+	4
Nomoto,M [77]	1987	+								1
Nomoto,M [78]	1988	+								1
Ogawa,N [79]	1994	+								1
Pearce,R [80]	1999	+					+		+	3
Pollack,A [81]	1997	+					+			2

Name	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Quality Score
Pollack,A [82]	2001	+					+			2
Prat,G [83]	2000	+					+		+	3
Ramirez,A [84]	2003	+					+		+	3
Richard,M [85]	1994	+					+			2
Robertson,H [86]	1992	+								1
Rouillard,C [87]	1990	+								1
Scheller,D [88]	2007	+	+		+		+			4
Schneider,A [89]	1994	+								1
Schneider,J [90]	1994	+								1
Schneider,M [91]	1984	+								1
Shiosaki,K [92]	1996	+								1
Silverdale,M [93]	2004	+			+		+			3
Silverdale,M [93]	2004	+					+			2
Sit,S [94]	2002	+								1
Smith,L [95]	2002	+					+		+	3
Smith,L [96]	2000	+					+		+	3
Smith,L [97]	1996	+			+				+	3
Smith,L [98]	2002	+					+		+	3
Spooren,W [99]	1999	+	+						+	3
Starr,M [100]	1994	+							+	2
Stephenson,D [101]	2005	+					+			2

Name	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*Quality Score*
Tanaka,K [102]	7988	+					+		+	3
Temlett,J [103]	1989	+								1
TurleLorenzo,N [104]	2006	+				+	+			3
Van Diep,D [105]	1999	+								1
Van Kampen,J [106]	2006	+					+		+	3
Van Kampen,J [106]	2006	+			+		+		+	4
Vermeulen,R [107]	1994	+	+		+				+	4
Vermeulen,R [108]	1994	+	+		+				+	4
Vermeulen,R [109]	1993	+	+		+				+	4
Wachtel,H [110]	1992	+							+	2
Woiciechowsky,C [111]	1995	+								1
Yoshioka,M [112]	2002	+					+		+	3
Zivin,J [113]	1998	+							+	2
Zou,L [114]	2000	+								1

Appendix 3 – Table of results for individuals dopamine agonist drugs:

Activity			
Drug	**Qpe**	**lower 95%CI**	**Upper 95%CI**
(+)-PHNO	1.35683104	0.38188477	2.331777
A77636	0.70693263	0.053995931	1.359869
A86929	0.86042644	0.040238525	1.680614
Apomorphine	2.43321412	1.271857326	3.594571
AY27110	-0.66105307	-1.223395537	-0.098711
Bromocriptine	0.72762228	0.249438033	1.205807
C1-APB	1.44565278	0.534143699	2.357162
Cabergoline	0.97027704	0.009030889	1.931523
CY208-243	1.26431817	0.405894635	2.122742
dihydrexidine	-2.51483096	-4.178956192	-0.850706
Dopamine	0.62648835	-0.209442514	1.462419
Lisuride	4.49489506	0.860944283	8.128846
LY-171555	0.57632477	-2.471498098	3.624148
PD128,907	3.16619605	1.599212316	4.73318
Pergolide	0.58433636	-0.993351035	2.162024
Piribedil	1.45185693	0.839808653	2.063905
Quinpirole	1.64274308	1.002170747	2.283315
Ropinirole	1.26215504	0.615522282	1.908788
RU24213	0.66772926	-0.091592252	1.427051
S32504	0.71195135	-0.230109688	1.654012
SFK83959	0.48228505	-0.392033745	1.356604
SKF 81297	-1.15847274	-2.193892723	-0.123053
SKF38393	-0.28694927	-0.957385552	0.383487
SKF75670	-2.75440595	-4.722985848	-0.785826
SKF80723	0.69544473	-0.715036136	2.105926
SKF82958 chloro-APB	1.32173556	-0.167080776	2.810552
Sumanirole	-0.12798149	-1.214249202	0.958286
Talipexole	1.28815434	0.780290223	1.796018

Contralateral turning			
Drug	**Qpe**	**lower 95%CI**	**Upper 95%CI**
(+)Dinapsoline	518.7931	243.6009	793.9853
(+-)Dinapsoline	316.8966	34.92547	598.8676
(+)-PHNO	191.8643	59.76986	323.9588
18Dinapsoline	211.129	-73.7268	495.9848
7-OH-DPAT	400.4566	182.9674	617.9457
A86929	192.5163	89.33914	295.6934
Apilindore DAB 452	227.3748	45.06645	409.6831
Apomorphine	526.8493	427.3885	626.3101
AY27110	186.6	2.052266	371.1477
Bromocriptine	114.2593	53.5281	174.9905

dihydrexidine	354.4038	22.72347	686.0841
Dinapsoline	101.6374	-6.65759	209.9325
Dopamine	77.00099	-209.543	363.5455
Lisuride	17.96706	-79.6704	115.6045
LY-171555	130.3196	19.92879	240.7104
N-0923	358.4955	158.8842	558.1068
Pergolide	636.7819	-119.962	1393.525
Pramipexole	28.22431	-0.66834	57.11697
quinelorane	393.27	103.7919	682.7481
Quinpirole	97.826	59.92137	135.7306
Ropinirole	450	240.1282	659.8718
SKF83959	321.2554	68.86076	573.65
SKF 81297	48.24915	-4.92301	101.4213
SKF38393	111.2166	83.52307	138.9101
SKF75670	61.51883	19.43318	103.6045
SKF80723	197.2465	74.45603	320.0369
SKF82958 chloro-APB	120.367	59.08493	181.6491
Sumanirole	468.6	380.6332	556.5668
Talipexole	1.557193	-0.8499	3.964289
Terguride	36	-74.5253	146.5253

Neurobehavioural score			
Drug	**Qpe**	**lower 95%CI**	**Upper 95%CI**
(+)-PHNO	41.72794	-41.5568	125.0127
7-OH-DPAT	59.2	23.10259	95.29741
A77636	44.99092	29.68238	60.29945
A86929	31.59243	0.111072	63.07379
Alpha-DHEC	-5.24189	-15.9333	5.449475
Apomorphine	26.85978	22.13903	31.58054
Apomorphine	-1.26616	-29.9702	27.4379
BAM-1110	71.33164	53.79801	88.86527
BP897	-154.513	-265.4	-43.626
Bromocriptine	-35.9965	-55.7723	-16.2206
Bromocriptine	28.00278	16.22933	39.77624
Cabergoline	8.47865	3.664297	13.293
Cabergoline	84.375	67.0512	101.6988
dihydrexidine	49.7504	27.82967	71.67113
Dopamine	283.9389	14.44605	553.4318
FAUC 329	9.809924	0.413744	19.2061
lisuride	17.75315	2.806364	32.69993
LY-171555	29.34971	-59.209	117.9084
pergolide	43.47529	-20.0992	107.0498
Piribedil	51.64832	39.46219	63.83446
Pramipexole	40.95874	30.44862	51.46886
Quinpirole	14.67012	3.846221	25.49402
Quinpirole	43.93309	32.17907	55.68712
Rapomorphine	19.2729	-4.4187	42.96449
Ropinirole	248.8664	37.37746	460.3554
Ropinirole	28.57435	0.365489	56.78322
Rotigotine	27.87893	-15.9829	71.74078

RU24213	37.81343	23.17501	52.45185
RU24926	32.45429	25.43914	39.46944
SKF83959	-4.26754	-61.9122	53.37716
SKF 81297	35.50493	5.021709	65.98816
SKF38393	-1.01694	-4.99602	2.962135
SKF38393	-33.0898	-71.8979	5.718294
SKF75670	-113.161	-161.448	-64.8745
SKF80723	20.96946	-55.9869	97.92587
SKF82958 chloro-APB	-14.1224	-32.9927	4.747804
Sumanirole	67.34114	60.84326	73.83902
Talipexole	23.40945	7.880567	38.93833
Talipexole	49.54684	31.38281	67.71086
Terguride	22.01199	17.91769	26.10629
U91356A	-0.8662	-1.48762	-0.24478