

# N-Methyl-D-Aspartate Antagonists in Levodopa Induced Dyskinesia: A Meta-Analysis

Behzad Elahi, Nicolás Phielipp, Robert Chen

**ABSTRACT: Background:** Levodopa-induced dyskinesias (LID) are amongst the most disabling side-effects of levodopa therapy for Parkinson's disease (PD). It has been suggested that N-Methyl-D-Aspartate (NMDA)-receptor antagonist may reduce peak-dose dyskinesia in PD patients and may lead to motor improvement. In this study, we compared the efficacy of NMDA receptor antagonists versus placebo in the treatment of LID in PD through a meta-analysis of controlled trials. **Methods:** Electronic search of Pubmed (1990 - 2010), Medline (1966-2010), EMBASE (1974-2010) and other databases for relevant studies were performed. Controlled clinical trials of the effects of NMDA antagonists on LID that fulfill the study protocol were selected. Pooled data from included studies was then used to perform random and fixed effect models meta-analysis. **Results:** The search resulted in 11 randomized, placebo controlled clinical trials that involved a total of 253 PD patients with peak-dose LID. The outcome measures were various dyskinesia rating scales and the Unified Parkinson Disease Rating Scale (UPDRS) subscales III and IV. The analysis showed significant reduction in Standard Mean Difference (SMD) for UPDRS IV (SMD -1.45; 95% CI -2.28 to -0.63) and UPDRS III (SMD -0.41; 95% CI -0.69 to -0.12) after treatment with amantadine. Other included drugs did not show significant change in the outcomes measured. **Conclusion:** This meta-analysis provides an update on the clinical trials and confirms the short-term benefits of amantadine therapy in the treatment of dyskinesia. The effects of other NMDA receptor antagonists need to be evaluated further in clinical trials.

**RÉSUMÉ: Antagonistes de la N-méthyl-D-aspartate dans le traitement des dyskinésies induites par la lévodopa : une méta-analyse. Contexte :** Les dyskinésies induites par la lévodopa (DIL) sont parmi les effets secondaires du traitement de la maladie de Parkinson (MP) qui sont les plus invalidants. Selon certaines données, les antagonistes du récepteur de la N-méthyl-D-aspartate (NMDA) pourraient diminuer les dyskinésies lorsque l'effet de la dose de lévodopa est à son maximum chez les patients atteints de la MP et pourraient améliorer la motricité. Dans cette étude, nous avons comparé l'efficacité des antagonistes du récepteur NMDA à celle d'un placebo dans le traitement des DIL dans la MP au moyen d'une méta-analyse portant sur des essais cliniques à répartition aléatoire. **Méthode :** Nous avons effectué une recherche électronique PUBMED (1990-2010), Medline (1966-2010), EMBASE (1974-2010) ainsi que d'autres banques de données afin d'identifier les études pertinentes. Nous avons sélectionné les essais cliniques contrôlés portant sur les effets d'antagonistes de la NMDA sur les DIL qui rencontraient les critères de sélection de notre protocole. Nous avons effectué une méta-analyse selon un modèle à effets aléatoires et un modèle à effets fixes sur les données regroupées des différentes études. **Résultats :** Notre recherche a permis d'identifier 11 essais cliniques contrôlés par placebo et à répartition aléatoire, auxquels un total de 253 patients, atteints de la MP et présentant des DIL lorsque l'effet de la dose est à son maximum, ont participé. Différentes échelles d'évaluation et les sous-échelles III et IV de la United Parkinson Disease Rating Scale (UPDRS) ont été utilisées comme mesures des résultats. Cette analyse a montré une diminution significative de la différence moyenne standardisée (DMS) pour l'UPDRS IV (DMS -1,45; IC à 95% -2,28 à -0,63) et pour UPDRS III (DMS -0,41; IC à 95% -0,69 à -0,12) après le traitement par l'amantadine. Nous n'avons pas observé de changement significatif au niveau de la mesure des résultats en ce qui concerne les autres médicaments utilisés. **Conclusion :** Cette méta-analyse fournit une mise à jour sur les essais cliniques et confirme les bénéfices à court terme du traitement par l'amantadine dans le traitement des dyskinésies. Les effets d'autres antagonistes des récepteurs NMDA devront faire l'objet d'études cliniques supplémentaires.

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## BACKGROUND

Dopaminergic medications are effective treatments for Parkinson's Disease (PD), but over time therapeutic complications such as motor fluctuations and levodopa-induced dyskinesias (LID) frequently develops. Levodopa-induced dyskinesias are abnormal involuntary movements primarily affecting the extremities, trunk, or jaw. The underlying mechanism of LID is not completely known but it is associated with changes in dopamine receptors<sup>1</sup> and in the subunit phosphorylation pattern of co-expressed ionotropic N-Methyl-D-Aspartate (NMDA) glutamatergic receptors.<sup>2</sup> Sensitization of these receptors may augment cortical excitatory input to the spiny efferent striatal neurons, thus altering striatal output and

compromise motor functions.<sup>3</sup> N-Methyl-D-Aspartate antagonists monotherapy have been shown to reduce parkinsonian symptoms without induction of dyskinesia in animal models of PD.<sup>4</sup>

Current management guidelines for treatment of peak dose dyskinesia in PD encourage use of amantadine as an add-on

From Toronto Western Research Institute, Toronto Western Hospital; Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada.  
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Correspondence to: Behzad Elahi, MP13-314, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada.

medication, and reduction in the doses of levodopa and monoamine oxidase B (MAO-B) inhibitors or catechol-o-methyl transferase (COMT) inhibitors.<sup>5,6</sup> Other approaches including deep brain stimulation,<sup>7</sup> low frequency repetitive transcranial magnetic stimulation,<sup>8</sup> and new anti-dyskinetic drugs targeting non-dopaminergic receptors such as NMDA or metabotropic glutamate receptor (mGluR) subtypes<sup>9,10</sup> are promising alternative treatment options.

Meta-analysis is being used increasingly to combine results from multiple research studies to produce a summary estimate of the treatment effect. Meta-analysis is particularly useful when small number of subjects were enrolled in each of the trials to improve the analytic power of the studies by evaluating the collective body of evidence. This study evaluates published randomized, placebo controlled clinical trials which used drugs with NMDA receptor antagonistic properties to determine whether this group of medications is effective in management of LID in PD.

## METHODS

### Criteria for inclusion in this meta-analysis

All randomized, controlled trials comparing NMDA receptor antagonists (mainly amantadine and dextrometorphan) with placebo in the treatment of dyskinesia are included in this study. The patients recruited in these studies must have met standard

criteria for the diagnosis of PD<sup>11</sup> and have had experienced LID. Only prospective clinical studies with placebo control group were included in this study.

### Primary and secondary outcome measures

Our primary outcome was changes in dyskinesia rating scales used by the included studies. Secondary outcomes for this study were changes in the motor section (Part III) of the Unified Parkinson Disease Rating Scale (UPDRS) and changes in scale of complications of therapy, duration and severity of dyskinesias in UPDRS part IVa.

### Search methods for identification of studies

#### Electronic searches

Medline (1966-2010), Embase (1974-2010), CINAHL, Web of Science, Scopus bibliographic, and Google Scholar databases were searched for studies investigating the effect of NMDA receptor antagonists in treatment of LID in PD. Articles published between January 1985 and September 2010, were retrieved. Reference lists of the retrieved trials and review articles were manually inspected for cross-references. Conference abstracts and unpublished data were excluded. MeSH terms and text words were searched for NMDA antagonists (amantadine, dextrometorphan, dextrorphan,

**Table 1: Characteristics of the studies included in the meta-analysis**

Study	Design	Sample size	Age	Drug	Dosage	Duration of PD	H&Y	UPDRS IV		Dyskinesia		UPDRS III		follow-up*
								Drug	Placebo	Drug	Placebo	Drug	Placebo	
Silva-Junior 2005	P	18	60.6	Amantadine	100-200 mg/day	-	2.5±0.5	2.8±2.1 (IVa)	3.7±1.8 (IVa)	6.8±4.9 (CDRS)	13.0±11.5 (CDRS)	16.3±9.3	18.7±5.3	3w
Del Dotto 2001	P	9	59.7 ± 8	Amantadine	200 mg IV	8.4 ± 3	3 ± 0.5	-	-	4.1 ± 1.7 (AIMS)	8.3 ± 1.8 (AIMS)	21.6 ± 9.5	23.5 ± 9.7	3 hours after infusion
Luginger 2000	CO	11	63.5 ± 8.2	Amantadine	300mg/day	10.1 ± 5.1	2.8 ± 1.2	7.0 ± 8.2 (IVa)	14.5 ± 9.4 (Iva baseline)	9.1 ± 9.1 (Marconi)	19.3 ± 13.7 (Marconi)	~50 ± 20	~68 ± 20	2w
Merello 1999	CO	12	60.6 ± 3	Memantine	30 mg /day	14.5 ± 4.7	3-4	5.68±6.2 (IVa)	5.62±6 (IVa)	-	-	9.84±7.9	12.5 ± 9.1	2w
Parkinson study group 2001	P	39	64.3±8.4	Remacemide Hydrochloride	150-600 mg/day	13.3 ± 5.8	2.6 ± 0.6	-	-	1.61 ±0.6 (Goetz)	1.7 ±0.6 (Goetz)	26.7±14.4	26.3 ±13.4	2w
Snow 2000	CO	24	64.2 ± 8.90	Amantadine	100-200mg/d	10.6 ± 3.6	-	3.2±1.6(IVa)	4.3±1.5(IVa)	22 ± 13.2 (Goetz)	29.0 ± 12.6 (Goetz)	22.3 ±12.1	23.4 ±9.0	3w
Thomas 2004	P	40	62.7 ±5.2	Amantadine	300 mg/day	7.9 ±2.2	2.6 ± 0.2	6.1±2.8 (IVa)	6.7±2.6 (IVa)	10.5 ± 1.3 (DRS)	9.2 ±2.0 (DRS)	48.1 ±7.8 (I-III)	52.9 ±8.5	15 days
Verhagen Metman 1998c	CO	12	59 ±3.4	Dextromethorphan + quinidine 200 mg/day	180 mg/day	12 ± 0.7	3.5 ± 0.3 (off)	-	-	1.7 ± 0.7 (AIMS)	4.2 ±1.1 (AIMS)	-	-	3w
Verhagen Metman 1998b	CO	18	60 ± 2	Amantadine	350 ± 15 mg/day	13 ± 1.3	3.5 ± 2	1 (Items 32, 34, 39)	4 (Items 32, 34, 39)	3.6 ±0.6 (AIMS)	7.0 ± 0.9 (AIMS)	-	-	6w
Verhagen Metman 1998a	CO	18	62 ± 2.3	Dextromethorphan	60-120 mg/day	15 ±1.4	3.6 ±0.1	1.7 ± 0.3 (Items 32, 34)	3.4 ± 0.6 (Items 32, 34)	4.6 ± 1.3 (AIMS)	3.5 ± 1.0 (AIMS)	7.5±1.7	7.8±2	2 w
Wolf 2010	P	32	67±7.7	Amantadine	100mg/day	16.8±5.9	-	3.6±0.4 (items 32, 33)	4.4±0.4 (items 32, 33)	-	-	25.8±3.4	27.7±3.7	3w

AIMS: Abnormal Involuntary Movements Scale; CDRS: Clinical Dyskinesia Rating Scale; CO: Cross-over; DRS: Dyskinesia Rating Scale; H&Y: Hoehn and Yahr Parkinson's disease staging scale; P: Parallel design; PD: Parkinson's disease; RCT: Randomized Clinical Trial; UPDRS: Unified Parkinson Disease Rating Scale; item IVa, \*: follow-up indicates the most immediate evaluation time point after the end of treatment for each study. This is different from the maximum follow-up time for each study.

ibogaine, riluzole, memantine, remacemide, glycine and glutamate antagonists) with dyskinesia or Parkinson's disease and their related derivatives.

### Data collection and analysis

Three trained individuals (BE, NP, XS) independently reviewed the articles for the quality and validity of the trials. Data on the therapeutic regimen, sample size, trial duration and outcomes were extracted and results were summarized in a standard summary data sheet. Disagreements were resolved by discussion and consensus between reviewers. The characteristics of the included studies are shown in Table 1. All three reviewers also assessed the studies for risk of bias in blinding and allocation, and scored the quality of included studies using a critical appraisal toolkit.<sup>12</sup>

### Measures of treatment effect

#### Unit of analysis issues

The standardized mean difference (SMD) used in this systematic review is the effect size known in social science as Hedges' (adjusted) *g*. SMD is used as a summary statistic in meta-analysis when all studies assessed the same outcome, but measured it in a variety of ways (such as different scales). In this circumstance, it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study. Thus, studies in which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements.<sup>13</sup> In this study all the included scales point in the same direction; lower scores indicate improvement and higher scores represent deterioration of parkinsonism or dyskinesia.

#### Assessment of heterogeneity

The Cochran Q and I square inconsistency tests were used to examine heterogeneity. A statistically significant Cochran Q may indicate a problem with heterogeneity although heterogeneity cannot be excluded with a non-significant result.

Sensitivity analysis, subgroup analysis for the different drugs and assessment methods was performed to examine methodological variations among studies. Both random and fixed effect models were used to arrive at conclusions. RevMan version 5.0.25 (Cochrane Information Management System) was used for analysis.

## RESULTS

### Description of included studies

Eleven studies were included in analysis with a total of 233 participants (Table 1). Two studies used dextromethorphan,<sup>14,15</sup> one study used remacemide,<sup>16</sup> one study used memantine<sup>17</sup> and amantadine was used in the remaining studies.<sup>18-24</sup> The quality of the studies was assessed by all three reviewers and all the included studies had moderate to high quality scores.<sup>12</sup>

We excluded seven studies<sup>12,25-30</sup> due to lack of control group and one study due to comparison of their data with a historical control group.<sup>31</sup> The design of trials varied between randomized,

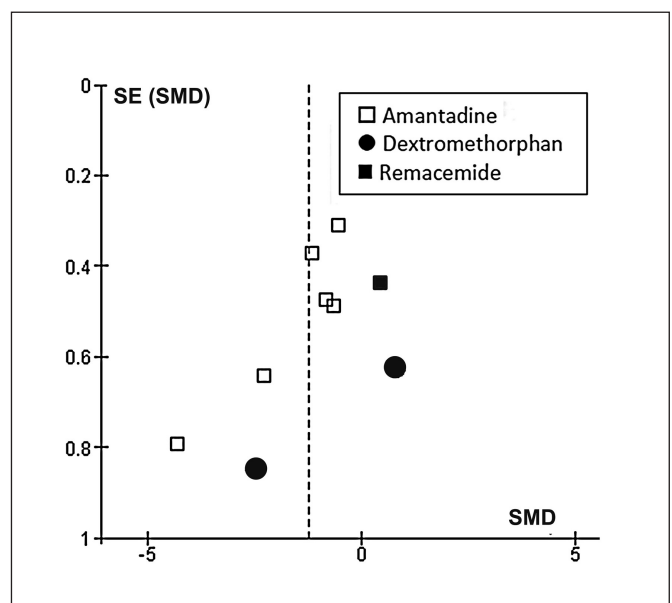
parallel groups design in four studies<sup>16,20,22,24</sup> and cross-over design in the remaining studies.<sup>14,15,17,19,21,23</sup> The participants in all the included studies were diagnosed with PD and had peak dose LID. The majority of the included patients had moderate to advanced PD with Hoehn and Yahr stage ranged from 2 to 4, and the mean age ranged from 59 to 67.7 years old.

The route of drug administration was oral tablets or capsules except in one study which used intravenous amantadine.<sup>18</sup> Since the duration of follow-up varied among the included studies (range 0-12 months), we only considered the immediate measurements of LID after the last dose of medication used in each study. Various regimen and dose were used in each study (Table 1) and the duration of drug administration ranged from one day to six weeks. In most of the studies, the measurements of LID were performed after an oral<sup>17-21</sup> or intravenous levodopa challenge test.<sup>15,23</sup> However, in four studies LID measurements were recorded in both "On" and "Off" drug states and a levodopa challenge test was not performed.<sup>14,16,22,24</sup> In these studies, results from "On" state were used in the analysis.

### Risk of bias in the included studies

#### Allocation concealment

Most studies used computer generated or random number tables to allocate study subjects to treatment and placebo groups. Allocation method is not stated in one study<sup>14</sup> and was done manually by a neurologist not involved in patient evaluations in another study.<sup>15</sup>



**Figure 1:** Bias indicator for NMDA antagonist effect on peak dose levodopa induced dyskinesia. The horizontal axis shows the standard mean difference (SMD). The vertical axis shows the standard error of SMD effect size, which is an indicator of the sample size. Larger studies have smaller standard errors and are located in the upper part of the graph; smaller studies are in the lower part of the graph. The vertical line represents the pooled effect size for random-effect model of meta-analysis.

**Table 2: Effects of NMDA antagonists on levodopa-induced dyskinesia measured by various scales and subgroup analysis**

Outcome or Subgroup	No. of studies	No. of participants	Effect size estimate [95% confidence interval]	P-value
<b>Dyskinesia various scales*</b>	9	203	<b>-1.10 [-1.88, -0.32]</b>	<b>0.0006</b>
Amantadine	6	159	<b>-1.45 [-2.28, -0.63]</b>	<b>0.0006</b>
Other drugs	3	44	<b>-0.85 [-2.45, 0.74]</b>	<b>0.29</b>
<b>UPDRS IV</b>	8	195	<b>-0.98 [-1.66, -0.30]</b>	<b>0.005</b>
Amantadine	6	159	<b>-1.10 [-1.92, -0.28]</b>	<b>0.009</b>
Other drugs	2	36	<b>-1.52 [-4.76, 1.72]</b>	<b>0.39</b>
<b>UPDRS III</b>	9	258	<b>-0.35 [-0.60, -0.09]</b>	<b>0.007</b>
Amantadine	7	195	<b>-0.41 [-0.69, -0.12]</b>	<b>0.005</b>
Other drugs	2	63	<b>-0.13 [-0.66, 0.41]</b>	<b>0.64</b>

Random-effect model and inverse variance was used to calculate effect size estimate; \* The dyskinesia scales used include the Abnormal Involuntary Movements Scale (AIMS), the Clinical Dyskinesia Rating Scale (CDRS), the Dyskinesia Rating Scale (DRS), the Goetz Dyskinesia Rating Scale and the Marconi Scale.

### Blinding

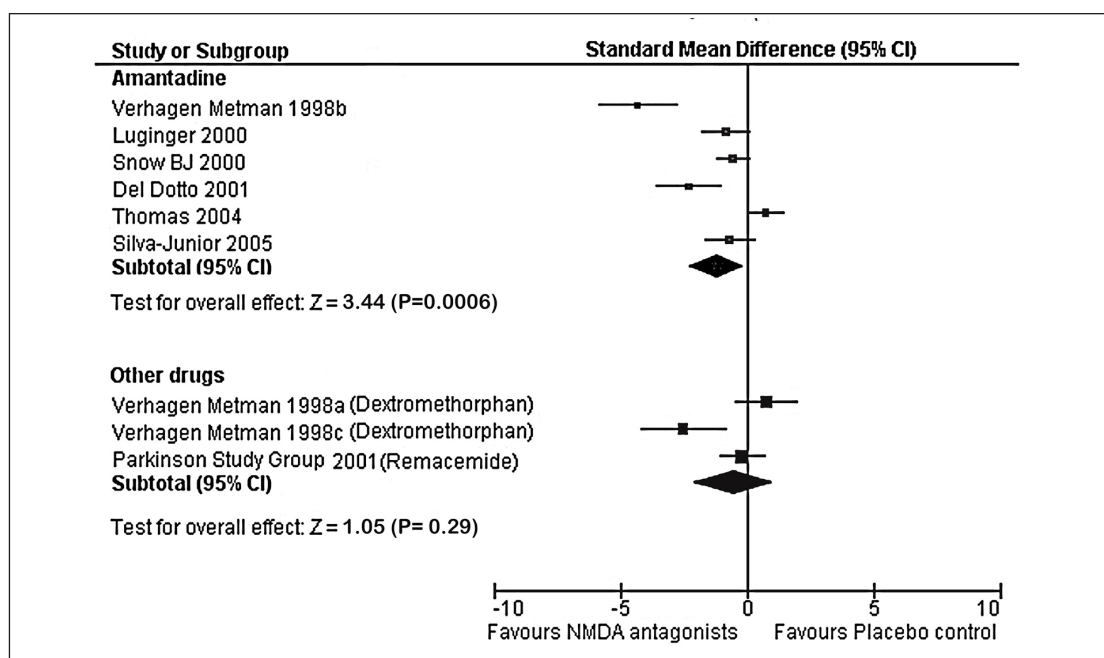
All the included studies were double blind, although proper blinding of the raters was not clearly stated in one study.<sup>17</sup>

### Effects of interventions

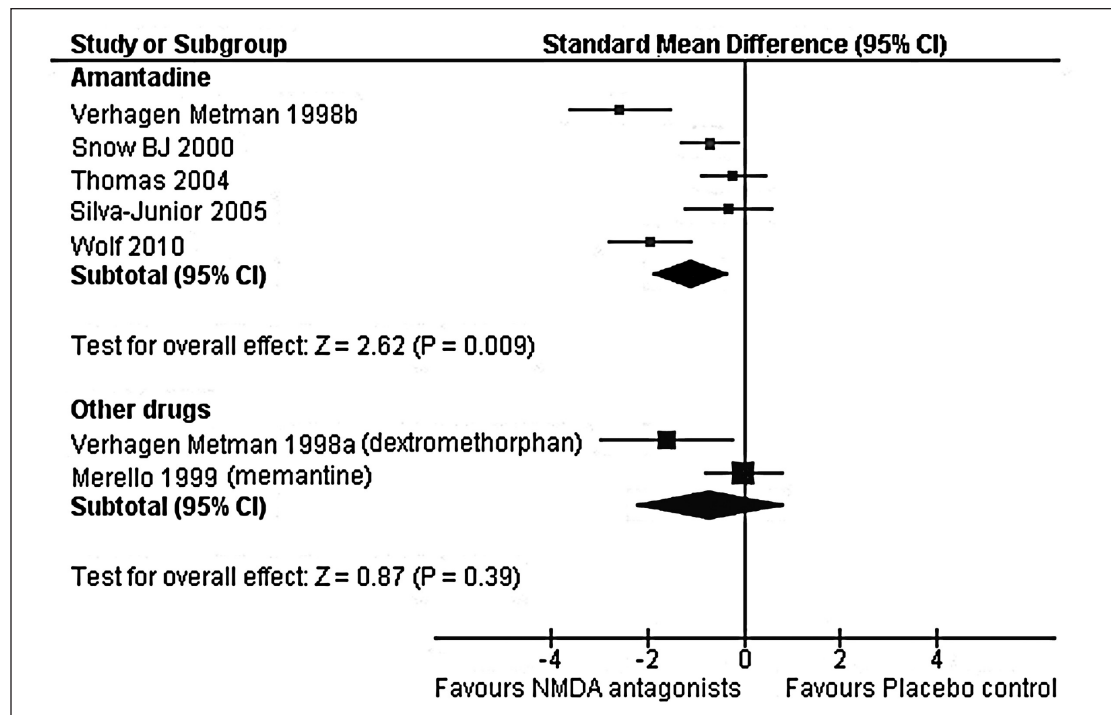
The pooled SMD effect size was calculated by pooled intervention-specific standard deviations for each study/stratum

(see Table 2 for estimate of effect size for subgroup analyses).

We pooled all the studies with dyskinesia as their primary outcome which used dyskinesia scales other than UPDRS IV (9 studies, 203 participants). This analysis showed a significant improvement in favor of the experimental drug (SMD -1.10; 95% CI -1.88 to -0.32,  $P < 0.001$ ) in both the random-effect model with the DerSimonian and Laird method and the fixed-



**Figure 2:** Individual and random-effect model of pooled standardized mean difference (SMD) for various dyskinesia rating scales in PD patients treated with amantadine and other drugs. The size of the squares increases with increasing sample size. Significant improvement in dyskinesia rating scales was observed for amantadine but not for other drugs.



**Figure 3:** Individual and random-effect model of pooled standardized mean difference (SMD) for UPDRS-IV subscale in PD patients treated with amantadine and other drugs. The size of the squares increases with increasing sample size. Amantadine resulted in significant reduction in UPDRS-IV scores no significant effect was observed for other drugs.

effect model. Test of variation, or heterogeneity, among the intervention effects indicates a heterogeneous data with  $\text{Tau}^2 = 1.11$  ( $P < 0.0001$ ) and I square test for inconsistency of 82%.

Funnel plot for these studies shows that studies showing greater improvement in dyskinesia scores after NMDA receptor antagonists therapy tend to have larger Standard Error (SE) of SMDs. Visual inspection of the funnel plot shows few studies with negative results and high SE (lower right side of the plot), suggesting that no study has been published with small sample size and negative results, possibly due to a publication bias against negative results. However, firm conclusion cannot be made because of the small number of studies included and the low power for analysis of asymmetry in the funnel plots (Figure 1).

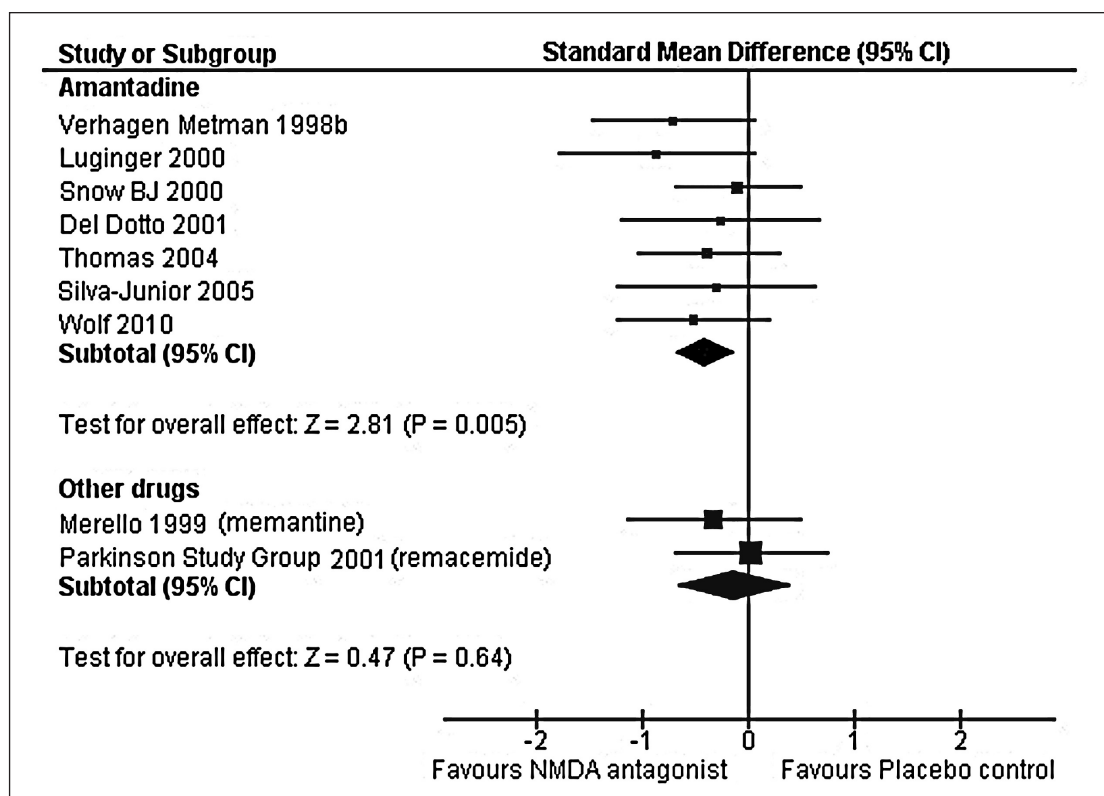
In the next step, the same statistical models were used for subgroup analysis of different drugs. There was a significant improvement in dyskinesia scales used in favor of amantadine (SMD -1.45; 95% CI -2.28 to -0.63) with overall effect of  $Z = 3.44$  ( $P < 0.001$ ) for the random effect model and  $Z = 6.01$  ( $P < 0.001$ ) for the fixed-effect model (six studies, 159 participants). Subgroup analysis for amantadine showed significant heterogeneity with  $I^2 = 79\%$ . Subgroup analysis for other drugs (dextromethorphan and remacemide, three studies, 44 subjects) did not show significant effect of drug treatment on dyskinesia (Figure 2).

UPDRS sub-scale IV for dyskinesia was an outcome measure in eight studies (195 patients). Luginer et al.<sup>19</sup> was excluded from this calculation because UPDRS IV score after placebo

therapy was not available. Meta-analysis shows SMD (95% confidence interval) of -0.98 [-1.66, -0.30] with the random effect model, which indicates a significant improvement in favor of NMDA antagonist ( $Z = 2.83$ ;  $P = 0.005$ ) (Figure 3). Test for heterogeneity showed heterogeneous data with  $\text{Tau}^2 = 0.95$  and  $I^2 = 74\%$ . Subgroup analysis for amantadine showed significant improvement after amantadine therapy compared to the placebo group in both random and fixed-effect models ( $P < 0.01$ ) (Figure 3). These findings translate to approximately 1.33 point reduction in UPDRS-IV sub-scale for amantadine. The findings for memantine and dextromethorphan (other drugs) were not significant for UPDRS IV scale (Table 2 for details).

Finally, analysis for changes in motor sub-scale of UPDRS (Part III) from nine studies and 258 patients indicates a significant reduction in UPDRS III after NMDA antagonist therapy in both random and fixed-effect model ( $P < 0.01$ ) with pooled effect size SMD = -0.35 [CI: -0.60, -0.09] (Figure 4). This finding indicates an approximately 1.28 point reduction in UPDRS III. Details for subgroup analyses are shown in Table 2. Number of patients in this analysis was larger than total number of participants (233) for all studies. This is mainly because of the crossover design of some of the studies. Patients in each arm were counted separately and therefore the majority of patients in crossover design studies were counted twice. For the fixed effect model, Cochran Q test for non-combinability of studies was not significant (Cochran  $Q = 7.4$  ( $df = 8$ )  $P = 0.49$ ,  $I^2$  (inconsistency) = 0%).

None of the included studies reported any severe adverse



**Figure 4:** Individual and fixed-effect model of pooled standardized mean difference (SMD) for UPDRS-III subscale in PD patients treated with amantadine and other drugs. The size of the squares increases with increasing sample size. Treatment with amantadine resulted in mild but significant improvement in UPDRS-III score no such effect was observed for other medications.

event. Some of the studies reported side effects such as confusion and worsening of hallucination. Because these minor side effects were not systematically reported in the studies, they were not analyzed further.

## DISCUSSION

Our results indicate amantadine can be effective in treatment of peak dose LID in PD. Treatment with amantadine resulted in large effect size ( $>0.8$ )<sup>32</sup> in favor of improvement in UPDRS-IV, other dyskinesia rating scales and in UPDRS-III subscale for PD motor symptoms. The effects of other medications such as dextrometorphan and remacemide on LID were not significant. Since the majority of studies used amantadine, the statistical power for the effects of “other medications” was much less than that for amantadine.

There is only one published systematic reviews on treatment of LID and only amantadine was studied<sup>33</sup>. The current study has a larger scope and evaluated other NMDA receptor antagonists. This review also includes more studies than the previous one<sup>33</sup> and confirms the efficacy of amantadine as a short-term treatment for LID. Our study also highlights the importance of using validated scales to assess the severity of the dyskinesia, include longer follow-up periods and in case of crossover studies, and sufficient washout period. The effects of novel

NMDA receptor antagonists on LID need to be evaluated in proper clinical trials.

A major concern in interpretation of results is that several different dyskinesia rating scales were used to assess the primary outcome in the included studies. Several rating scales have been used in clinical studies since the 1970s for the assessment of dyskinesia in PD. Some were specifically developed for dyskinesia in PD, whereas others were part of global scales that measure motor disability in PD such as UPDRS-IV. Some scales were originally developed for use in other syndromes with dyskinesia, but were adapted to score PD dyskinesia<sup>34</sup>. An example is abnormal involuntary movement scale (AIMS) which was originally developed for assessment of tardive dyskinesia.<sup>35</sup> In this meta-analysis, the majority of the studies used either UPDRS-IV or AIMS for evaluation of dyskinesia. Although UPDRS-IV is widely being used in practice, the items covering dyskinesia have not been independently studied from a clinimetric perspective. On the other hand, AIMS has high inter and intra rater reliability<sup>36,37</sup> but cannot differentiate between different movement abnormalities. Considering these limitations, both of these tools and especially the AIMS are among the recommended scales for use in assessment of dyskinesia in PD.<sup>36</sup>

Another limitation of this study is that no study examined the long-term results of NMDA receptor antagonist treatment on

LID and therefore only short-term results are reported here. However, in one study<sup>24</sup> patients on stable doses of amantadine were randomized to receive placebo or continue taking amantadine. This study reported worsening of symptoms after amantadine cessation and demonstrated longer term effects of amantadine therapy. There may be potential publication bias for negative studies (Figure 1). Registration of future clinical trials may reduce publication bias. The different study regimen, route of drug administration, and different dyskinesia scales used can potentially reduce the precision of our findings. Four of the included studies used a parallel group design and six studies used a cross-over design. Cross-over design offers several advantages over parallel group design. Each participant acts as his or her own control and this reduces variation among participants. It also increases the study power as every participant receives both interventions. However, there is a possibility of inadequate washout and may be more prone to unblinding due to beneficial or adverse effects. Sensitivity analysis between parallel and cross over studies was not significant but we observed a larger effect size for studies with cross-over design.

We only analyzed published data and we did not search the unindexed or unpublished data, academic theses and conference abstracts which may result in a publication bias for favorable results. We imposed no language limitation in our search, nevertheless all the included studies were in English.

## CONCLUSIONS

Amantadine appeared to be safe and effective for reducing of LID. However, further studies are needed to examine the long-term effects of NMDA antagonist therapy.

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