Efficacy of antidepressive medication for depression in Parkinson disease: a network meta-analysis

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Abstract

Background: Parkinson disease (PD) was considered as the 2nd most prevalent neurodegenerative disorder after Alzheimer disease, while depression is a prevailing nonmotor symptom of PD. Typically used antidepressive medication includes tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), monoamine-oxidase inhibitors (MAOI), and dopamine agonists (DA). Our study aimed at evaluating the efficacy of antidepressive medications for depression of PD.

Methods: Web of Science, PubMed, Embase, and the Cochrane library were searched for related articles. Traditional meta-analysis and network meta-analysis (NMA) were performed with outcomes including depression score, UPDRS-II, UPDRS-III, and adverse effects. Surface under the cumulative ranking curve (SUCRA) was also performed to illustrate the rank probabilities of different medications on various outcomes. The consistency of direct and indirect evidence was also assessed by node-splitting method.

Results: Results of traditional pairwise meta-analysis were performed. Concerning depression score, significant improvement was observed in AD, MAOI, SSRI, and SNRI compared with placebo. NMA was performed and more information could be obtained. DA was illustrated to be effective over placebo concerning UPDRS-III, MAOI, and SNRI. DA demonstrated a better prognosis in UPDRS-II scores compared with placebo and MAOI. However, DA and SSRI demonstrated a significant increase in adverse effects compared with placebo. The SUCRA value was calculated to evaluate the ranking probabilities of all medications on investigated outcomes, and the consistency between direct and indirect evidences was assessed by node-splitting method.

Conclusion: SSRI had a satisfying efficacy for the depression of PD patients and could improve activities of daily living and motor function of patient but the adverse effects are unneglectable. SNRI are the safest medication with high efficacy for depression as well while other outcomes are relatively poor.

Abbreviations: CrI = credible interval, DA = dopamine agonists, MAOI = monoamine-oxidase inhibitors, NMA = network meta-analysis, PD = Parkinson disease, SMD = standard mean deviation, SNRI = selective serotonin reuptake inhibitors, SUCRA = surface under the cumulative ranking curve, TCA = tricyclic antidepressants.

Keywords: adverse events, antidepressant, efficacy, meta-analysis, Parkinson disease
1. Introduction

Parkinson disease (PD) is considered as the 2nd most prevalent neurodegenerative disorder after Alzheimer disease. Age is the greatest risk factor of PD, the incidence rate of PD generally increases with it, peaking at 104.99 per 100,000 persons for female and 132.72 for male between the age of 70 to 79. The onset of PD is related to the degeneration of dopaminergic neurons in the substantia nigra as well as the development of Lewy bodies in dopaminergic neurons. Gradually in a long time of 2 decades or more, pathological changes in neurons may precede into both motor and nonmotor system manifestations. Lewy bodies in dopaminergic neurons. Gradually in a long time of 2 decades or more, pathological changes in neurons may precede into both motor and nonmotor system manifestations. The assessment of patients with 4 endpoints.

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In the motor system, PD is associated with rest tremor, bradykinesia, muscular rigidity, and postural instability. In the nonmotor system, cognitive changes, behavioral or neuropsychiatric changes, pain and fatigue, autonomic dysfunction, psychosis and hallucinations, sleep disorder, depression, and anxiety are also prevailing symptoms of PD patients.

The estimated prevalence of depression as a symptom of PD ranged from 7% to 76%, as a result of inconsistent sampling procedures, assessment techniques, and definitions of depression, and depression greatly eroded the lining quality of PD patients. There is evidence that depression is underrecognized and undertreated in clinical practice, so that the etiology of depression in PD has not been elucidated yet, but exogenously, being diagnosed with a disabling and incurable disease can be a shock for the patients and results in the state of depression, while depression may also be associated with the neurologists changes in the disease process. Currently, treatment for depression of PD includes antidepressive medications, behavioral interventions such as psychotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation, and deep brain stimulation.

Typically used antidepressive medications include tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), monoamine-oxidase inhibitors (MAOI), and dopamine agonists (DA). Many clinical trials have been conducted to investigate their therapeutic effect on depression of PD. Barone et al[7] reported in their randomized trial that treatment with rasagiline, an MAOI, did not help to improve depressive symptoms in PD patients. Atomoxetine, an SNRI, was reported to be not efficacious for depression of PD, but might help to improve cognitive disorder and daytime sleepiness. Yet pramipexole, a DA was found to be able to improve depressive symptoms in patients with PD, through a direct antidepressant effect. A randomized clinical trial in the USA also found that nor- triptyline, a TCA, was efficacious in the treatment of depressive symptoms, but not paroxetine, an SSRI. However, sample sizes of previous studies were relatively limited. The assessment of depression and depression scale were not in consistence with each other. Thus, a large-sized meta-analysis was needed to help interpret data from previous trials. In the present study, we aimed at evaluating the efficacy of antidepressants on depression of PD patients with 4 endpoints.

2. Material and methods

2.1. Search strategy

Web of Science, PubMed, Embase, and the Cochrane library were searched for related articles concerning the therapeutic value of antidepressive drugs for PD. All typical antidepressive drugs were enrolled in the screening of relevant articles, including TCA, SSRI, SNRI, MAOI, and DA. Articles published between January 1, 1980 and September 1, 2016 were retrieved in the primary search. The following Mesh terms and their synonyms and abbreviations were used to find relevant studies in PubMed: “Parkinson Disease,” “antidepressive agents,” “tricyclic antidepressants,” “selective serotonin reuptake inhibitors,” “serotonin and norepinephrine reuptake inhibitors,” “dopamine agonists,” and “monoamine-oxidase inhibitors” (Table S1, http://links.lww.com/MD/B694). Two authors independently screened titles and abstracts of retrieved articles to evaluate their qualification according to the inclusion criteria. Reference list of enrolled articles were also reviewed manually to improve the integrity of this study. The analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

2.2. Evaluated outcomes and inclusion criteria

In the present study, a depression score was applied to evaluate the symptom of depression on patients. The depression score is based on Hamilton depression rating scale, Beck depression inventory, and Unified Parkinson Disease Rating Scale – Mental. Unified Parkinson Disease Rating Scale–Activities of daily living (UPDRS-II) for activities of daily living, Unified Parkinson Disease Rating Scale–Motor (UPDRS-III) for motor function, and adverse effect were evaluated as the secondary outcomes.

Inclusion criteria for retrieved studies was as follows: patients should be diagnosed with idiopathic PD; symptoms of depression were diagnosed clearly, with severity of depression evaluated by Hamilton depression rating scale, Beck Depression Inventory, or Unified Parkinson Disease Rating Scale – Mental; study should be performed with a randomized controlled design; sufficient data for further analysis should be provided in original articles; and patients should not receive irrelevant anti-Parkinson treatment in these studies.

2.3. Data extraction

Two authors extracted relevant data from eligible articles independently. In the current study, information as follows were extracted: last name of first author, year of publication, origin country, study design, number of subjects, time of follow-up (in weeks), age of subjects, duration of PD among the subjects (in years), average Hoehn and Yahr stage of subjects, treatments, and the evaluation scale of depression. A 3rd author would resolve discrepancies after discussion. Depression score was considered as the primary outcome in this study.

2.4. Statistical analysis

A traditional pair-wise meta-analysis was performed in order to evaluate the efficacy of different types of medication on depression. Standard mean deviation (SMD) and corresponding 95% credible interval (CrI) were calculated for depression score, UPDRS-II, and UPDRS-III. And for adverse effect, ORs and 95% CrI were calculated. The heterogeneity was evaluated by F test and Q statistics. Fixed-effect model was applied if significant heterogeneity was not observed in the ORs, while ORs with heterogeneity were calculated by random-effect model.

Consequently, Bayesian network meta-analysis (NMA) was performed with a random-effects model using Markov chain Monte Carlo methods in WinBUGS (MRC Bio-statistics Unit, Cambridge, UK) to compare direct and indirect evidence. Depression score, UPDRS-II, and UPDRS-III were represented by SMD and 95% CrI, and adverse effect represented by ORs and 95% CrI.
Besides, surface under the cumulative ranking curve (SUCRA) was created to evaluate the ranking probabilities for different medications on various outcomes. Moreover, the consistency between direct and indirect evidence was assessed by node-splitting method; a \( P \) value less than .05 was deemed as inconsistent. STATA 12.0 (Stata Corp, College Station, TX) software was used in our analysis with a 2-side \( P \) less than .05 considered as significant.

### 3. Results

#### 3.1. Study characteristics

A total of 8890 subjects from 45 publications were involved to investigate the efficacy of TCA, SSRI, SNRI, DA, and MAOI in patients with PD. Flow chart in Fig. 1 illustrated the process of study selection. The following-up time of our enrolled studies ranged from 1 to 240 weeks with an average value of 31 weeks. Among the enrolled medications, nortriptyline, amitriptyline, and doxepin were categorized as TCA; fluoxetine, paroxetine, citalopram, sertraline, and desipramine were regarded as SSRI; venlafaxine, atomoxetine, and nefazodone were SNRI; MAOI included selegiline, rasagiline, and lazabemide; DA involved pramipexole, memantine, pergolide, ropinirole, pargyline, levodopa, bromocriptine, lisuride, piribedil, and cabergoline. Characteristics of enrolled articles were presented in Table 1. To clarify the comparisons involved in the NMA, a network plot was generated (Fig. 2). Numbers in the circles illustrated the number of subjects. The width of line is proportional to the total number of studies included. As indicated in the figure, MAOI and DA were investigated by large amount of studies, whereas TCA, SSRI, and SNRI obtained significantly fewer samples thus indicating a higher potential deviation in traditional meta-analysis.

#### 3.2. Pairwise meta-analysis results

Results of traditional pairwise meta-analysis were listed in Table 2. As illustrated in the table, compared with placebo, patients taking DA were observed to have improvement on depression score, UPDRS-II, and UPDRS-III (SMD = 0.52, 95% CrI: [0.08, 0.95]; SMD = 1.00, 95% CrI: [0.47, 1.53]; and SMD = 1.23, 95% CrI: [0.65, 1.81]). However, the issue of adverse effects remained to be resolved (OR = 1.41, 95% CrI: [1.17, 1.70]). Besides, concerning depression score, significant improvement was also observed in MAOI (SMD = 0.26, 95% CrI: [0.06, 0.46]), whereas TCA, SSRI, and SNRI obtained significantly effective in treating depression (DA: SMD = 0.38, 95% CrI: [0.2, 0.56]; MAOI: SMD = 1.35, 95% CrI: [1.00, 1.55]; SNRI: SMD = 1.5, 95% CrI: [2.16, 2.69]; DA vs MAOI: SMD = 4.09, 95% CrI: [2.69, 5.50]; DA vs SNRI: SMD = 3.24, 95% CrI: [1.18, 5.30]). However, DA and SSRI demonstrated a significant increase in adverse

#### 3.3. NMA results

In additional to traditional meta-analysis, NMA was performed to promote result validity by merging direct and indirect evidences. Corresponding results were presented in Table 3 and plotted in Fig. 3 and Figure S1, http://links.lww.com/MD/B694. In the assessment of depression score, all medication other than MAOI were observed to be significantly effective in treating depression (DA: SMD = −0.56, 95% CrI: [−0.93, −0.2]; MAOI: SMD = −0.38, 95% CrI: [−0.81, 0.06]; SNRI: SMD = −1.55, 95% CrI: [−2.65, −0.45]; SSRI: SMD = −1.56, 95% CrI: [−2.16, −0.96]); and TCA: SMD = −1.5, 95% CrI: [−2.31, −0.7]). Interestingly, both SSRI and TCA were more significant than DA and MAOI in NMA, while traditional comparisons were not available as a result of limited sample size. Concerning UPDRS-III that represents improvement of motor function, DA were illustrated to be effective over placebo, MAOI, and SNRI (placebo vs DA: SMD = −4.09, 95% CrI: [−5.6, −2.69]; DA vs MAOI: SMD = 3.32, 95% CrI: [1.18, 5.30]; DA vs SNRI: SMD = 4.29, 95% CrI: [0.46, 8.40]). DA were also observed to be the only medication that demonstrated a better prognosis in UPDRS-II scores for activities of daily living compared with placebo and MAOI (placebo vs DA: SMD = −1.53, 95% CrI: [−2.15, −0.93]; DA vs MAOI: SMD = 1.46, 95% CrI: [0.46, 2.49]). However, DA and SSRI demonstrated a significant increase in adverse
effects compared with placebo (OR = 2.29, 95% CrI: [1.67, 3.17]; OR = 2.58, 95% CrI: [1.00, 6.77], respectively).

### 3.4. Ranking probability

To better understand the results, the SUCRA value was calculated to evaluate the ranking probabilities of all medications on investigated outcomes. Results were presented in Fig. 4 and Table 4. As suggested by ranking probabilities, SSRI were the most effective medication for depression in patients with PD (0.800), SNRI and TCA were also among the best (0.746 and 0.740 independently). Regarding to the improvement in UPDRS-II and UPDRS-III, DA was the most helpful one (0.873 for UPDRS-II and 0.958 for UPDRS-III) while MAOI ranked the 3rd (0.492 for UPDRS-III) and MAOI (0.533 for UPDRS-II and 0.518 for UPDRS-III) and MAOI ranked the 3rd (0.492 for UPDRS-II and 0.492 for UPDRS-III). In the aspect of adverse effect, SNRI were the safest (0.714), whereas patients taking SSRI and TCA were more likely to suffer from

### Table 1. Characteristics of studies included in the network meta-analysis.

| First author, year | Country | Design | Subjects | Duration of PD, y | Hoehn stage (mean) | Treatment 1 | Treatment 2 |
|---------------------|---------|--------|----------|------------------|-------------------|-------------|-------------|
| Aihin, 1993         | France  | RCT    | 93       | 12               | 64.9              | NA          | MAOI        |
| Amsterdam, 2003     | Philadelphia | RCT | 289    | 8               | 42.4              | NA          | MAOI        |
| Antonini, 2006      | Italy   | RCT    | 81      | 12               | 70.2              | 7.3          | MAOI        |
| Antonini, 2015      | Italy   | RCT    | 349     | 12               | 67.5              | 2.2          | DA          |
| Barone, 2006        | Italy   | RCT    | 67      | 12               | 66.5              | 2            | MAOI        |
| Barone, 2010        | Italy   | RCT    | 206     | 14               | 67                | 4.1          | DA          |
| Barone, 2015        | Italy   | RCT    | 123     | 66.1             | 3.7               | 1.9          | MAOI        |
| Bodkin, 2002        | USA     | RCT    | 177     | 42.3             | NA                | NA          | MAOI        |
| Bronzova, 2010      | Netherlands | RCT | 139   | 9               | 59.5              | NA          | MAOI        |
| Dalrymple-Alford, 1995 | New Zealand | RCT | 20    | 6               | 65.7              | 1.3          | MAOI        |
| Devos, 2008         | France  | RCT    | 48      | 61.8             | 8.1               | 2            | SSRI        |
| Feiger, 2006        | USA     | RCT    | 265     | 42               | NA                | NA          | MAOI        |
| Hauser, 2014        | USA     | RCT    | 321     | 62.6             | 2.1               | NA          | MAOI        |
| Larsen, 1997        | Norway  | RCT    | 163     | 64.3             | 2                 | 1.9          | MAOI        |
| Pogarell, 2002      | Germany | RCT    | 84      | 63.6             | 6                 | 2            | SSRI        |
| Pinter, 1999        | Austria | RCT    | 78      | 60.1             | 8.5               | 2.96         | DA          |
| Parkinsson Study Group, 1989 | USA | RCT    | 800    | 68.1             | 2.43              | 1.7          | MAOI        |
| Rascol, 2005        | Italy   | RCT    | 354     | 64               | 7.9               | 2.43         | DA          |
| Navan, 2003         | UK      | RCT    | 30      | 54.8             | 3                 | 2            | DA          |
| Nomoto, 2013        | Japan   | RCT    | 172     | 66.9             | 5.4               | 2.7          | DA          |
| Onda, 2010          | USA     | RCT    | 40      | 69.1             | NA                | 2.33         | DA          |
| Pahwa, 2007         | USA     | RCT    | 391     | 66.2             | 8.6               | 2.7          | DA          |
| Parkinson Study Group, 1993 | USA | RCT    | 201    | 62.9             | 2.17              | 1.79         | MAOI        |
| Parkinson Study Group, 1994 | USA | RCT    | 137     | 67               | 4.19              | 2            | MAOI        |
| Parkinson Study Group, 1996 | USA | RCT    | 321     | 64.1             | 1.7                | MAOI        |
| Parkinson Study Group, 1997 | USA | RCT    | 264     | 61.7             | 1.7                | 1.8          | MAOI        |
| Parkinson Study Group, 2009 | USA | RCT    | 222    | 60.2             | 1.7                | 1.85         | DA          |
| Pinto, 1999         | Austria | RCT    | 78      | 60.1             | 8.5               | 2.96         | DA          |
| Pogarell, 2002      | Germany | RCT    | 84      | 63.6             | 6                 | 2            | DA          |
| Rascol, 2015        | Germany | RCT    | 68      | 65.9             | 5.6               | 2.55         | DA          |
| Richard, 2012       | UK      | RCT    | 115     | 63.5             | 7                 | 2.33         | SSRI        |
| Rico Romenets, 2013 | Canada  | RCT    | 12      | 64.5–69.5        | 5.2               | NA          | TCA         |
| Sampaio, 2011       | Portugal | RCT  | 457    | 62.1             | 0.8               | 1.95         | DA          |
| Serrano-Duenas, 2002 | Ecuador | RCT  | 77     | 68.2             | 6.9               | 2            | SSRI        |
| Shoulton, 2002      | USA     | RCT    | 368     | 67               | NA                | 2.11         | MAOI        |
| Stern, 2004         | USA     | RCT    | 56      | 61.5             | 0.8               | 1.5          | MAOI        |
| Pardoprunox         | Placebo |
| Italian Parkinson Study Group, 1992 | Italy | RCT    | 475     | 63.5             | 1.43              | MAOI        |
| Tremblay, 2011      | Germany | RCT    | 287     | 64.7             | 4.9               | NA          | DA          |
| Watts, 2007         | USA     | RCT    | 277     | 62.87            | 1.4               | 2.1          | DA          |
| Weintraub, 2010     | Denmark | RCT    | 55      | 64.3             | 5.7               | NA          | SNRI        |
| Weintraub, 2016     | Denmark | RCT    | 162     | 67.7             | NA                | 2            | MAOI        |
| Wermuth, 1998       | Denmark | RCT    | 37      | 64               | NA                | NA          | SSRI        |
| Zhang, 2013         | China   | RCT    | 345     | 63.9             | 8                 | NA          | DA          |
| Ziegler, 2002       | France  | RCT    | 115     | 64.1             | 4                 | 2.07         | DA          |

**BDI = Beck depression inventory, DA = dopamine agonists, HDRS = Hamilton depression rating scale, MAOI = monoamine-oxidase inhibitors, NA = not available, RCT = randomized controlled trials, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, UPDRS-I = Unified Parkinson Disease Rating Scale – Motor; UPDRS-II = Unified Parkinson Disease Rating Scale – Intellectual; UPDRS-III = Unified Parkinson Disease Rating Scale – Mental.**
3.5. Consistency analysis

The consistency between direct and indirect evidences was evaluated by node-splitting method. As listed in Table 5 and Fig. S2, http://links.lww.com/MD/B694, significant difference between evidences was observed in the comparison on depression score between placebo and SNRI, as well as the comparison between SSRI and SNRI (both $P < .001$). DA and MAOI also presented significant inconsistency with respect to UPDRS-II. To further clarify the source of inconsistency, the net heat plot was generated and presented in Fig. 6.

4. Discussion

A total of 8890 subjects from 45 studies were enrolled in the analysis, and the therapeutic efficacy of common used antidepressive medication on PD was investigated. And all of the adverse effects. A clustered ranking plot based on SUCRA values was also generated and presented NMA results visually in Fig. 5.
Table 3  
Network meta-analysis results according to depression score represented by SMD and 95% CrI, UPDRS-II and UPDRS-III represented by MD and 95% CrI, and adverse effect represented by ORs and 95% CrI.

| Depression score | Placebo | DA | MAOI | SNRI | SSRI | TCA |
|------------------|---------|----|------|------|------|-----|
| Placebo          | 2.29 (1.67, 3.17) | 1.49 (0.98, 2.29) | 0.65 (0.38, 1.10) | 0.51 (0.13, 2.04) | 1.12 (0.43, 3.01) | 2.58 (1.80, 6.77) |
| -0.56 (-0.93, -0.2) | -0.38 (-0.81, 0.06) | 0.19 (-0.36, 0.73) | -0.99 (-2.13, 0.16) | -1.17 (-2.35, 0.01) | -1.12 (-2.04, -0.21) | 0.05 (-1.22, 1.32) |
| -1.55 (-2.65, -0.45) | -1.56 (-2.16, -0.96) | -0.99 (-1.66, -0.33) | -1.18 (-1.92, -0.44) | -0.01 (-1.1, 1.09) | -1.03 (-1.90, 0.76) | 0.44 (-0.68, 0.79) |
| -1.5 (-2.31, -0.7) | -0.57 (-7.06, 6.12) | 3.53 (-2.99, 10.26) | 0.18 (-6.48, 7.14) | -0.80 (-7.80, 6.56) | -1.23 (-5.63, 3.30) | 2.47 (-9.11, 13.60) |

| UPDRS-II | Placebo | 3.22 (2.31, 4.13) | 1.66 (1.06, 2.69) | 0.95 (-0.08, 1.98) | -0.26 (-4.21, 3.93) | 3.38 (1.18, 5.50) |
| UPDRS-III | Placebo | -1.53 (-2.15, -0.93) | -0.07 (-0.93, 0.78) | 1.46 (0.46, 2.49) | 0.99 (-1.80, 3.71) | -1.12 (-1.50, -0.74) |
| Placebo | 3.22 (2.31, 4.13) | 1.66 (1.06, 2.69) | 0.95 (-0.08, 1.98) | -0.26 (-4.21, 3.93) | 3.38 (1.18, 5.50) |
| Placebo | -1.53 (-2.15, -0.93) | -0.07 (-0.93, 0.78) | 1.46 (0.46, 2.49) | 0.99 (-1.80, 3.71) | -1.12 (-1.50, -0.74) |
| Placebo | 3.22 (2.31, 4.13) | 1.66 (1.06, 2.69) | 0.95 (-0.08, 1.98) | -0.26 (-4.21, 3.93) | 3.38 (1.18, 5.50) |

In lower half of the table, row treatments are compared against column treatments, whereas in the upper half, column treatments are compared against row treatments. CI = credible interval, DA = dopamine agonists, MAOI = monoamine-oxidase inhibitors, MD = mean difference, OR = odds ratio, SMD = standard mean deviation, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, UPDRS-II = Unified Parkinson Disease Rating Scale-Motor, UPDRS-III = Unified Parkinson Disease Rating Scale-Activities of daily living.
significant as other medication, but great improvement in activities of daily living and motor function was observed.

TCA exerts symptomatic benefits in depression score but was reported to be associated with a delay in reaching the end point of need to start dopaminergic therapy,\cite{55} which also resulted in a higher adverse effect in our NMA. DA is proved to function through Nurr1, which plays an essential role in midbrain dopaminergic neurons development and survival, thus being a potential target for PD,\cite{4} and our NMA also demonstrated an excellent performance in improving UPDRS-II and UPDRS-III scores. However, our NMA also suggests DA had a poor efficacy in our primary outcome and could result in a high adverse effect, it has been reported by Kataoka et al\cite{1} that an increased dose of DA could trigger tactile hallucinations.

SSRI exhibited outstanding efficacy in our NMA, not only illustrated an outstanding performance in daily living as well as motor function, but also presented a high curative effect in depression score. It is confirmed by Kostic et al\cite{4} that fluoxetine (SSRI) significantly reduced depression in PD patients while no motor performances were impaired. However, unlike other antidepressants, the use of SSRI was associated with greater apathy,\cite{5} which is agreed by our study that SSRI also presented a high adverse effect. It is demonstrated that prolonged SSRI could provide enduring antidyskinetic effects through 5-HT (1A) receptors and enhance striatal dopamine levels to maintain L-DOPAs anti-Parkinsonian efficacy,\cite{56} which could possibly share the cause of adverse events with DA. Due to their promising performances, SSRI and TCA were the 2 most traditionally

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**Table 4**

SUCRA results of depression score, UPDRS-II, UPDRS-III, and adverse effect.

|                     | Depression score | UPDRS-II | UPDRS-III | Adverse effect |
|---------------------|------------------|----------|-----------|----------------|
| Placebo             | 0.034            | 0.358    | 0.292     | 0.898          |
| DA                  | 0.393            | 0.873    | 0.958     | 0.296          |
| MAOI                | 0.296            | 0.400    | 0.492     | 0.614          |
| SNRI                | 0.746            | –        | 0.298     | 0.714          |
| SSRI                | 0.800            | 0.533    | 0.518     | 0.258          |
| TCA                 | 0.740            | 0.335    | 0.450     | 0.234          |

DA = dopamine agonists, MAOI = monoamine-oxidase inhibitors, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, SUCRA = surface under the cumulative ranking curve, TCA = tricyclic antidepressants, UPDRS-II = Unified Parkinson Disease Rating Scale-Activities of daily living, UPDRS-III = Unified Parkinson Disease Rating Scale-Motor.

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**Figure 4.** SUCRA of depression score, UPDRS-II, UPDRS-III, and adverse effect. SUCRA = surface under the cumulative ranking curve, UPDRS-II = Unified Parkinson Disease Rating Scale-Activities of daily living, UPDRS-III = Unified Parkinson Disease Rating Scale-Motor.
administered psychiatric medications for depression and anxiety in PD.

SNRI also presented a good performance in depression score and had no obvious side effects, but its results regarding UPDRS are poor. However, there are cases suggested that SNRI may act as substitution therapy for depression in PD that had inadequate response to SSRIs.[3] Accordingly, the latest NMA by Liu et al.[57] based on 11 trials concluded that SNRI and TCA had favorable balance between benefits and acceptability, which is concurred with our results. Moreover, MAOI was identified as one of the safest medications, which concur with Frisina et al.[58] that selegeline (MAOI) does not produce a risk of substantial side effects or mortality for patients with PD.

Apart from previous results, inconsistency was widely observed among studies. Although uncertainty on SSRI efficacy in depression is reported,[59] this uncertainty was not observed in our consistency analysis. Besides, different studies could draw contradictory conclusions. For example, Bomasang-Layno et al.[60] concluded from 13 trials that SSRI could significantly improve depression of PD with high efficacy, which is consistent with our results. Yet Troeung et al.[61] observed in their study that the pooled effects of antidepressive medication in PD were insignificant, which involved 9 clinical trials. Rocha et al.[62] also found that the results about antidepressant efficacy on depression of PD were unstable, and Frisina et al.[58] stated that the SSRI literature in their study might have suffered from sampling error. Although there existed such deviations, with a distinctively larger sample size of 45 trials, our results guaranteed a more robust conclusion, and the accumulation of evidence from randomized clinical trials could lead to a more precise conclusion on the efficacy of antidepressants on PD.

The primary limitation of this analysis relates to the limited sample size of involved drugs and subjects, especially for TCA and SNRI. Also, the average duration of follow-up was 31 weeks, whereas the follow-up time in more than half of the enrolled studies was less than 15 weeks, which is possibly not long enough to show complete effects, thus a longer follow-up time is demanded. Fortunately, short follow-up time in Bodkin and Devos studies is unlikely to influence the accuracy of the conclusion, because there is other evidence of comparison between involved treatments in our current study. In addition, it has been suggested that a more unified depression diagnostic criteria should established to assess depression accurately and indicates an internal inconsistency.[61] Larger and well-designed clinical trials on the efficacy of antidepressant on patients with PD are needed for further investigation.

In conclusion, we observed in our meta-analysis that SSRI had a satisfying efficacy for depression of PD patients. They can also help to improve activities of daily living and motor function of patients, yet the adverse effects were also distinctive. SNRI are the safest medication with high efficacy for depression as well. SNRI and TCA are also good at improving depression scores while DA and MAOI tended to have better performance in other symptoms in PD. Larger clinical trials on the efficacy of antidepressant on patients with PD are needed for further investigation.

Table 5

Results of direct and indirect comparisons according to depression score.

| Treatment 1 | Treatment 2 | SMD (95% CI) | Direct comparison | Indirect comparison | Difference | P |
|-------------|-------------|--------------|-------------------|--------------------|------------|---|
| Placebo     | DA          | 0.51 (−0.01, 1.03) | 0.91 (−0.57, 2.39) | −0.39 (−1.96, 1.17) | .622       |
| Placebo     | MAOI        | 0.35 (−0.27, 0.97) | 0.84 (−1.14, 2.82) | −0.49 (−2.56, 1.59) | .645       |
| Placebo     | SNRI        | 3.14 (1.53, 4.75)  | −4.76 (−7.95, −1.57) | 7.9 (4.24, 11.56) | <.001      |
| Placebo     | SSRI        | 1.83 (0.85, 2.81)  | 0.24 (−1.28, 1.77) | 1.59 (−0.22, 3.4) | .086       |
| Placebo     | TCA         | 0.73 (−0.75, 2.22) | 2.08 (0.36, 3.77)  | −1.35 (−3.6, 0.91) | .242       |
| DA          | MAOI        | 0.26 (−1.66, 2.18) | −0.23 (−1.03, 0.56) | 0.49 (−1.58, 2.57) | .640       |
| DA          | SSRI        | −0.26 (−2.18, 1.66) | 1.13 (0.09, 2.18)  | −1.39 (−3.58, 0.8) | .213       |
| SNRI        | SSRI        | 1.49 (−0.07, 3.06) | −6.41 (−9.66, −3.15) | 7.9 (4.24, 11.56) | <.001      |
| SSRI        | TCA         | 0.35 (−0.77, 1.47) | −1.61 (−3.83, 0.6) | 1.96 (−0.52, 4.44) | .122       |

CI = confidence interval, DA = dopamine agonists, MAOI = monoamine oxidase inhibitors, SMD = standard mean deviation, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants.
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