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# UPDATE ON TREATMENTS FOR NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE—AN EVIDENCE BASED MEDICINE REVIEW

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**Abstract:**

*Non-motor symptoms are one of the reasons that overload the morbidity of Parkinson, it affects 1-2/1000 persons at any time. Its prevalence rate depends upon age and PD affects 1% of the population above 60 years. Non-motor symptoms (NMS) are the key elements to determine the quality of life of a patient. The evidence base treatments of PD with non-motor symptoms are substantial, under considerations to meet the quality treatment in recent years. Although, with high prevalence and disease adverse effects and limited options for treatment given have become a top priority to develop and tests the new methods for treatment of non-motor symptoms in PD. This review based on pharmacological and surgical intervention to treat the NMS in PD and previously reported inclusion criteria was used. The data obtained from more than 33 studies did not meet the randomized controlled inclusion criteria for anxiety rapid eye movement sleep disorder, excessive sweating, impaired olfaction, or ophthalmologic dysfunction. Each trial showed the specific score based on specific quality, concluded criteria used like possibly useful, insufficient evidence, possibly, if statistically proved no-significant used term negative and for clinically implication used investigational.*

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## INTRODUCTION:

In this era, neurological abnormalities are the biggest reasons for disability worldwide, where Parkinson's disorder (PD) is the most prominent disease with greater numbers of affected people. According to international estimation in 2016, 6.1 million people got a diagnosis of Parkinson's disorder that was 2.4 times more than a diagnosis in 1990. However, in 2020 in the United State round, about 930,000 people are living with Parkinson's disease.[1] The most common Parkinsons' disease belongs to a term of neurological abnormalities knows as Parkinsonism including movement issues like slowness, twitching movements, and rigidity. This situation had increased the focused to bring the improvement in methods of detection and diagnosis of Parkinson disease, increase the awareness to the people, and to improve the quality of life of patient.[2]

Prakinson Disorder can be defined with neuropathologically, the existence of Lewy bodies with synuclein in the sustantia nigra portion of the brain, reduction or loss of dopamine producer cell (dopaminergic neurons) in the portion of substatia nigra, which is formed of dopaminergic neurons give rise to dysfunction of voluntary movement. Progression of the disease is due to assembling of a-synuclein widely in the brain[3] and from past 10-20 years considerable focused have been attained by non-motor symptoms in PD.[4]

However, its pathological reason not only related to motor symptoms, but the interconnected chain of non-motor symptoms (NMS) is also creating more severe problems.[5] The NMS is appeared before the motor symptoms and becomes the major risk to increased the numbers of patients with PD as the disease advances while its effect on a patient's life expectancy is observed to more than motor symptoms when compared to the relevancy of NMS. Therefore, early detection of PD is necessary as, diagnosis of NMS is a challenge due to overlapping of symptoms and feature of disease like depression, and fatigue.[6]

## METHOD:

In this review paper data collected from many previous and updated studies using the electronic database as a source of collection. Encompassing the intervention of surgery, and pharmacological studies for the treatment of non-motor-symptoms of Parkinson disease. Each trial consists of two groups with 20 numbers of patients and their trial duration was 4 weeks. Each trial showed the specific score based on specific quality, concluded criteria used like possibly useful, insufficient evidence, possibly, if statistically proved no-significant used term negative and for clinically implication used investigational.

**Pharmacological Treatment of non-motor symptoms.**

Non-motor symptoms of PD are treated in the same way as the treatment used to treat the symptoms of general patients of non-PD while the existence of evidence variability has been observed for Parkinson patient's treated with these treatments.[8] International Parkinson and Movement Disorder Society select the rivastigmine to treat the PD dementia patients during a clinical trial, where the efficacious response rate was recorded up to the 2.1 points improvement in 70 individuals receiving 3-12 mg daily rivastigmine. Limited evidence in support of PD for donepezil and galantamine therefore designated as possible useful whereas memantine did not have evidence.[7]

**Treatment of Depression**

- A review reported the antidepressants to use for adults to treat depressive disease thereby, amitriptyline considered more efficacious than other antidepressant.[9] Comparably, another study reported a substantial beneficial effect of sertraline and amitriptyline on a randomized trial base.[10] The use of Tricyclic Antidepressants (TCAs) for the treatment of depression is possibly useful because of changes in practice implications.[9]

- The selective serotonin re-uptake inhibitor, venlafaxine, and paroxetine both were used as a placebo in a research study for depression treatment in PD. Venlafaxine trial response is positive "clinically useful" to treat the depression patient's of PD while for the paroxetine not enough evidence present, results were negative for treatment of depression.[9]

- The dopamine agonists primary efficacy study on rotigotine was concluded the practical implication is investigational to use it for depression treatment.[11]

**Treatment of Apathy**

- An acetylcholinesterase inhibitor, rivastigmine was assessed in a study of small size and its end conclusion is efficacious apathy treatment of Patients with PD. Due to its small size, its application is possible useful.[12]

- Dopamine Agonists, piribedil was assessed in a small group of study and the obtained outcomes are likely efficacious and its treatment application is possible useful.[13] Moreover, for rotigotine "investigational"

outcomes was derived from a study of one high quality group.[14]

**Treatment of Psychosis**

- One study demonstrated the use of olanzapine to treat the psychosis and concluded that "not useful".[15] Antipsychotic, pimavanserin is considered clinically useful as updated analysis of FDA has not found any new risk related with its use to treat the patients of psychosis with PD.[16]
- Commonly, ensured use of anti-psychotics with great attention in lunatic patients with Parkinson disease psychosis due to multiple risk factor including cognitive impairments, pneumonia, CVD effects leads to stroke and ultimate death of patient.[17]

**Treatment of Disorders of Sleep and Wakefulness**

- The medicine modafinil used for treating sleep disorders have not enough evidence concluded from an efficacy study treatment of drowsiness with Parkinson's disease[7]. In another review, the substantial reduction in sleepiness was evaluated through questionnaire know as Epworth Sleepiness Scale in three trials evaluation.[18]
- The day time sleepiness disorder with PD has insufficient study results obtained from caffeine evaluation. On the other hand, placebo comparison shows some substantial effects on caffeine. Many people use caffeine without specific monitoring and with risk acceptability, because of its high consumption and easy availability in several countries.[19]
- Piribedil investigation through trial studies has not sufficient evidence which supports the efficacy to ameliorate caution and mental health specifically for those suffering from day time sleepiness.[20]

**Treatment of Fatigue**

- A trial based study on the use of oxycodone-naloxone prolonged-release had shown a negative effect, where trail did not meet the results and concluded to insufficient evidence.[21] As the oxycodone-naloxone prolonged release is used in adults to treat the severe pain therefore it can be used for pain treatment of patients with PD. The available data of oxycodone-naloxone is not enough to ensure the safety aspects, but general population base data can be considered for its, with acceptable risk without specialized monitoring. The evaluated adverse events are headache, dizziness, cognitive impairments, nausea, vomiting, and constipation. Although by increasing the severity of constipation in PD may lead to the more complicated situation sigmoid volvulus. [22]
- Dopaminergic agents, rotigotine based study trial did not meet the end response rate and concluded results are negative with insufficient evidence to treat the patients with PD.[23]

## DISCUSSION:

Non-motor symptoms are one of the reasons that overloading the morbidity of Parkinson, specifically of those patients who are surviving with advanced stages. The clinical treatment of this disease is possible by reviewing the updated management schedule for disease, critically assessment of all factors, and current drugs using to minimize the risk factors. These all having the supreme value for the treatment of psychosis, sleep disorder, cognitive dysfunction, and autonomic dysfunction. Although the two randomized controlled cholinesterase inhibitor studies in Parkinson's disease dementia had published their results, the first one in favor of rivastigmine while second study results were imprecise for donepezil. The statistically substantial effects were recorded of this study in PD dementia that rivastigmine can be used clinically for treatment.[27\]

In routine consultation and randomized controlled trials for the treatment of PD, common NMS are less considered or missed and according to the data collected from different studies, only 60% of trials met the criteria of quality evaluation.[25] On the other hand, insufficient inclusion criteria of randomized controlled treatments to treat anxiety, excessive sweating, olfactory and ophthalmologic dysfunctions.[26] Thus, lack of evidences was found during this study.

## CONCLUSION:

The data obtained for Parkinson's disease with non-motor symptoms from the multiple reviews base on randomized control trial is a lack of evidence-based studies. Because of the insufficiency of clinical trials practice and implications. Therefore, more need to focus on changing methodology, upgrading of assessment tools along the continual updating clinicians and investigators, to make ease in decision-making process.[24]

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