

Critical Review: Does levodopa medication have an impact on perceptual ratings of the speech and voice of individuals with Parkinson's disease?

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Abstract: This critical review examines the evidence regarding the effect of levodopa medication on perceptual ratings of the speech and voice of individuals with Parkinson's disease. While levodopa has long been the standard of care for mitigating gross motor symptoms in Parkinson's disease, its effect on the dysarthric speech and voice symptoms have long been debated. Some studies included in this review used a nonrandomized within group pre-posttest design while others included an additional nonequivalent control group in their pre-posttest design. The results were mixed, with most studies suggesting no benefit of levodopa on speech and voice ratings and one suggesting a speech severity effect.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease and the second most common in its class, affecting 1 to 2% of the population (Lill & Klein, 2017). It is characterized by advancing loss of dopaminergic neurons causing a deficiency of dopamine in the basal ganglia. This loss of dopamine in the brain leads to several motor and non-motor symptoms in PD, including resting tremor, bradykinesia (slowness of movement), rigidity of movements, postural instability and gait abnormalities, among others (Obeso et al., 2010). Also common for individuals with Parkinson's disease (IWPd) are speech and voice problems, including hypokinetic dysarthria. Features of hypokinetic dysarthria include low speech intensity (hypophonia), reduced pitch variation and stress patterns, imprecise articulation, abnormal voice quality, and abnormal speech rates (Adams & Dykstra, 2008).

While there is no cure for Parkinson's disease, most IWPd can manage their gross motor symptoms through the administration of levodopa (along with other dopamine agonists), a dopamine synthesis therapy developed in the early 1960s and still used today as the standard treatment for this disease (Tolosa et al., 1998). Speech and voice symptoms, however, have not consistently been found to improve on levodopa treatment. Early perceptual studies found improvements in speech intelligibility (Nakano et al., 1973) and pitch variation (Wolfe et al., 1975), while later studies looking at speech acoustic measures (jitter, shimmer, etc.) have shown mixed results using an array of study designs.

Whether focused on acoustic measures, perceptual ratings or both, these studies are carried out using an "ON/OFF levodopa challenge." Language samples are taken in the "OFF" state (at least 12 hours after the last

levodopa dose) and again during the "ON" state, after a standard or individualized dose of medication. Samples are then analyzed using acoustic analysis software or rated perceptually on a variety of speech characteristics, voice quality or overall speech intelligibility using blinded listeners (usually speech-language pathologists). In this analysis of the literature, only recent studies including perceptual ratings will be reviewed with the purpose of determining the real-life impact of levodopa medication on speech and voice symptoms in PD. While objective acoustic measures can be useful, it is this writer's view that improvements in speech and voice quality as well as overall speech intelligibility as determined by listener perception is of more value to individuals living with Parkinson's disease.

Objectives

The objective of this paper is to critically evaluate the existing literature regarding the impact of levodopa treatment on perceptual ratings of speech symptoms in individuals with Parkinson's disease (IWPd).

Methods

Search Strategy

Computerized databases including PubMed, Medline and Google Scholar were searched using the following search strategy: [(speech) or (voice) and (Parkinson's) and (levodopa)]. As the number of studies looking at levodopa and its effects on symptoms in PD are limited and also cover a variety of speech and voice characteristics, this necessitated using broad search terms. The search was limited to articles written in English, published between 2004 and 2019.

Selection Criteria

The search criteria yielded studies that included both acoustic and perceptual measures. Studies selected for inclusion in the review included only those reporting

perceptual evaluations of speech and voice after levodopa treatment for IWPDP.

Data Collection

The results of the literature search revealed six articles consistent with the selection criteria. Four studies used a nonrandomized within group pre-posttest design and two studies used a nonrandomized between groups (nonequivalent control) pre-posttest design.

Results

De Letter et al. (2005) sought to investigate the effects of levodopa medication on speech intelligibility in IWPDP. The study included 10 participants between the ages of 63 and 80 years, evaluated during a hospital stay with the purpose of receiving adjustments to their medication plan.

Participants were evaluated using the classic levodopa challenge protocol, with samples taken during the “OFF” state after at least 12 hours after their evening dose. Word intelligibility measures were taken using the Dutch version of a word subtest from the Yorkston and Beukelman Assessment of Intelligibility of Dysarthric Speech. The same testing protocol was then used one hour after levodopa administration. All testing was video-taped to later be evaluated by a group of five speech-language pathologists with at least five years of experience working in the treatment of patients with dysarthria. Instead of using a rating scale, evaluators transcribed what was heard in order to provide a percentage of word intelligibility that was averaged across the five raters.

Appropriate statistical analyses were performed using Wilcoxon’s signed-ranks test. Results of the study revealed a significant improvement of intelligibility in the “ON” state at the single-word level, with a mean group improvement score of 5.6%. However, the results showed some variability, with two participants showing lower intelligibility scores in the “ON” state.

Strengths of this study include clear methodology and rationale for choosing to include auditory-visual data for evaluation. Weaknesses of the study include a high variability in levodopa dose across participants, a lack of a control group, a small sample size and the choice of evaluating speech intelligibility at the single-word level. Additionally, the inclusion of participants seeking alterations to their levodopa medication program suggest a lack of medication stability in this group of patients.

Given the small sample size and inconsistent medication dose and stabilization across patients, the results of this

study provide equivocal evidence that speech intelligibility is improved by levodopa medication in PD.

Plowman-Prine et al. (2009) conducted a study that aimed to define the perceptual speech characteristics of idiopathic Parkinson’s disease (IPD) and examine the effects of levodopa on 35 perceptual speech dimensions and to compare the effectiveness of levodopa on global motor functioning vs. speech production. For the purpose of this review, we will examine only the methodology and results of the second purpose.

Included in this study were sixteen IWPDP recruited at a movement disorders clinic who displayed evidence of idiopathic “tremor-predominate” PD, as diagnosed by a movement disorders neurologist. Participants ranged from 43 to 81 years of age, with a duration of disease following diagnosis ranging from 1 to 15 years. All subjects were screened for cognitive, visual and hearing impairments, depression and former speech therapy.

Participant speech sample recordings were taken for the “OFF” state after a minimum of 12 hours after their last dose. “ON” state recordings were taken at 60 minutes after each patient received their individual standard dose of levodopa, ranging from 600-1500mg. The speech task included a reading of the Grandfather Passage, recorded at a consistent distance of 4 cm. Perceptual ratings were completed by three speech language pathologists who attended two training sessions aimed at improving intra and inter-rater reliability. Each of the 35 perceptual dimensions as well as overall intelligibility were rated on a 7-point rating scale, with raters blinded to participant and medication status.

Appropriate statistical analyses were employed, including Wilcoxon Signed-Rank tests and a Bonferroni correction. Intra-rater reliability was excellent (0.84), while inter-rater reliability across the three raters was fair-good (0.65). Results of the analysis showed no significant differences between the “ON” and “OFF” states on any of the 35 perceptual speech dimensions.

Strengths of this study include clear methodology and inclusion criteria, the exhaustive evaluation of speech dimensions as well as robust attempts at improving intra-rater reliability. Weaknesses of this study include a small sample size, lack of control group, poor inter-rater reliability and the inclusion of only participants with mild dysarthria. The omission of subjects with more severe speech symptoms resulting from Parkinson’s disease excludes the potential for evaluating a severity-effect.

In this study, Plowman-Prine et al. (2009) provided suggestive evidence that levodopa has no significant effect on the speech symptoms of IWPDP suffering from mild dysarthria. Further studies using a larger sample with individuals displaying varying degrees of speech symptom severities would have to be conducted to generalize this conclusion to all IWPDP.

Skodda et al. (2009) investigated the effects of short and long-term administration of dopaminergic treatment (levodopa + dopamine agonists) on speech in individuals in the early stages of Parkinson's disease. Participants included 23 IWPDP ranging from 42 to 78 years old, with an average time since diagnosis of 2.41 years. A confirmation of diagnosis was performed using the UK Parkinson's Disease Society Brain Bank Criteria (Hughes et al., 1992). Ten participants were newly diagnosed with PD and were not yet receiving levodopa treatment. The remaining thirteen participants were on dopaminergic therapies consisting of levodopa and other dopamine agonists. A group of twenty-four healthy volunteers with a similar age-range were tested once as a control group (for baseline age-equivalent comparison) without levodopa. Both a perceptual rating of "global speech performance" and an acoustic analysis were conducted on each participant, with the former being of interest for this review.

Participants were evaluated in the "OFF" state (t0) at 10am, after at least 12h since their last levodopa dosage, and in the "ON" state (t1) after 30-45 minutes after the administration of 200mg of a levodopa preparation. Each patient was then tested again using the same procedures after being stable for at least 3 weeks, 12-14 weeks later (t2). All testing included an evaluation of motor performance using the UPDRS III, as well as a speech task consisting of a free monologue of at least thirty seconds and a standard reading passage of four complex sentences, recorded in a quiet room. A perceptual rating of global speech impairment using these speech samples was conducted by a blind rater.

Appropriate statistical analyses were performed. Results of the study revealed no significant differences between neither the baseline "OFF" condition (t0), the immediate "ON" condition (t1) nor the stable dopaminergic condition (t2).

Strengths of this study involve the inclusion of a control group and the comparison of results across states of levodopa intake (t0, t1, t2), standardized administration procedures as well as well-defined exclusion criteria. Weaknesses of this study include the use of only 1 perceptual rater, the absence of rating-procedure methodology and vague presentation of perceptual results. While detailed results of acoustic analysis were

provided in the form of clear tables, only a brief statement on the results of perceptual impression were given.

Given the ambiguous reporting of perceptual measures and results, this study provides equivocal evidence regarding the effect of levodopa medication on perceptual ratings of speech in individuals with idiopathic Parkinson's disease.

Spencer et al. (2009) sought to improve on previous perceptual rating studies of intelligibility, naturalness and vocal quality following levodopa use in IWPDPs. Their study included fifteen participants all receiving a stable course of levodopa, ranging from 47 to 79 years old, with an average of 7.61 years since diagnosis. Participants were not required to exhibit symptoms of dysarthria, however those who did were given a severity rating (mild, moderate or severe) by two experienced SLPs. Individuals scoring beyond predetermined cutoffs on evaluations of dementia, language comprehension, phonological encoding difficulties and moderate-severe depression were excluded from the study.

Speech samples of IWPDPs reading the standard Grandfather Passage and reciting a 1-minute monologue in a quiet room (at a distance of 2 inches) were recorded in both "OFF" and "ON" levodopa states. The "OFF" state for each participant involved a minimum of 15 hours without taking their levodopa medication. The last 4 sentences of the reading passage as well as the last thirty seconds of the monologue were then evaluated by ten experienced SLP raters who were blinded to the medication condition of each sample. The raters evaluated each sample on three dimensions (understandability, naturalness and voice quality) using a Visual Analogue Scale (VAS) with numerical values between 1 and 100.

Statistical analysis procedures were appropriate. The results of this study revealed no significant group differences between medication states on any of the three measures (understandability, naturalness or voice quality). When analyzed individually, 6 of 15 participants were shown to have measurable differences on at least one of the perceptual dimensions assessed. A breakdown of change on the three measures revealed mixed results, with some participants seeing improvements on 1 or more measures in the "ON" state, and some receiving higher ratings in the "OFF" state.

Spencer et al. (2009) attempted to improve on the methodologic design seen in other similar studies by providing clear exclusion criteria, strict procedural guidelines and a larger group of blind raters. While these were all strengths of their study, a significant

limitation of the investigation design was the inclusion of participants displaying no symptoms of dysarthria. The overall mild range of speech symptom severity of the participants could have potentially limited the potential to see change in their speech quality between the “ON” and “OFF” states. The sample is therefore not representative of the population of individuals with Parkinson’s disease or their speech symptoms. Additionally, this study similarly suffered from a small sample size and lack of control group.

The results of this study provide suggestive evidence that speech symptoms are not improved by levodopa medication in individuals with mild dysarthric symptoms caused by Parkinson’s disease. However, the strength of the evidence presented does not indicate that similar conclusions may be generalized to individuals with Parkinson’s disease who display more severe speech and voice symptoms.

Lechien et al. (2018) investigated the usefulness of levodopa challenge tests evaluating voice quality and orofacial strength for the diagnosis of Parkinson’s disease. To measure voice quality, the study included subjective ratings using both the Voice Handicap Index (VHI) and a perceptual evaluation using the GRBAS (grade, roughness, breathiness, asthenia and strain), as well as objective acoustic measures. Only methods and data concerning the perceptual ratings are relevant to the present review.

Twenty participants newly diagnosed with idiopathic Parkinson’s disease were recruited from 2014 to 2017 at Neurology Departments of Epicura Hospitals. Patients with comorbidities that would impact speech and voice quality were excluded from the study, after examination by an otolaryngologist. Qualifying participants were administered a standardized dose of 375mg of levodopa after assessment at baseline in the “OFF” state (t0). Patients were subsequently assessed at 45 minutes after L-dopa intake (t1) and at 3-9 months postdiagnosis (t2), once stabilized (as confirmed by the Hoehn & Yahr scale).

Appropriate statistical analyses using Wilcoxon Rank Tests (paired t-test) were employed to evaluate the data. Analysis of perceptual scores using the GRBAS revealed no significant improvements in voice quality from baseline (t0) to t1 and from baseline (t0) to stabilization at t2.

A strength of this study was the use of variable measures, including acoustic, perceptual and a self-questionnaire (VHI) to evaluate voice quality. Additional strengths were the inclusion of a third evaluation after medication stabilization (t2) and the use

of a blinded rater with good intra-rater reliability for the perceptual rating. However, the inclusion of only 1 rater was a significant weakness of the study design. Additionally, the lack of demographic data for participants, a small sample size, the inclusion of only newly diagnosed IPDs, the omission of speech sample procedures and the absence of a control group are all limitations of this study.

The results of this report suggest equivocal evidence that there is no benefit of levodopa medication on perceptual voice quality in individuals with Parkinson’s disease. The weaknesses in data reporting and study design significantly reduce the strength of the study.

Cushnie-Sparrow et al. (2018) completed a nonrandomized between groups pre-posttest study that investigated the effect of levodopa medication on both perceptual and acoustic measures of voice quality in individuals with Parkinson’s Disease (IWPD). For the purpose of this review, only methods and results pertaining to perceptual measures will be discussed.

Participants included fifty-one IWPD and eleven controls, recruited from the Movement Disorders Centre at University Hospital in London, Ontario. Inclusion criteria involved a diagnosis of Parkinson’s disease for at least 2 years, being within the age range of 45 to 85 years, having been on a stable dose of a levodopa-based anti-Parkinson medication for at least 6 months and the ability to give informed consent. The motor symptoms of each participant were assessed using the standard UPDRS-III rating scale. IWPDs were evaluated “OFF” levodopa after a minimum of a 12-hour overnight cessation period and “ON” levodopa 1-hour after receiving a dose of 300mg (300/75 levodopa/carbidopa). The speech samples were rated by 3 graduate speech-language pathology students using a 10 cm visual-analogue scale (VAS).

Appropriate statistical analyses were conducted. Results of initial analyses revealed no significant differences in perceived voice quality while on medication when the IWPDs were examined as a group. However, when grouped by voice quality severity (as determined by perceptual ratings in the “OFF” state), IWPDs with “poor voice quality” showed significantly improved perceived voice quality ($p < .001$) in the “ON” state. Interestingly, IWPDs with “better voice quality” were rated as having significantly poorer voice quality in the “ON” state.

The strengths of this study include the large sample size (in comparison to other similar studies) and use of a control group. Both the procedural methods and inclusion/exclusion criteria were well-defined and

justified. Additionally, the in-depth statistical analysis was particularly robust. While the perceptual ratings showed good inter-rater reliability (ICC = .826) and moderate intra-rater reliability (ICC = .754), the use of only 3 perceptual raters is a relative weakness of the study. Another weakness of this study was the collection of only a sustained vowel in lieu of more natural, connected speech.

Given the suggestive results of this study, Cushnie-Sparrow et al. (2018) propose a “speech severity responsiveness hypothesis,” wherein the level of levodopa response increases with increasing perceptual voice quality severity. When individuals with more severe voice quality symptoms were grouped separately from those with mild symptoms, greater medication effects became clear. This suggests that early studies did not see this severity-effect because of increased variation in severity across participants.

Discussion

Overall, the results of this review revealed suggestive evidence that levodopa medication does not lead to improvements in mild speech and voice symptoms resulting from Parkinson’s disease. However, the evidence provided in these studies should be approached with caution, given the small sample sizes, the lack of clear demographic data as well as poor statistical reporting in some instances. Some studies also showed poor inter-rater reliability and the use of very few perceptual raters, decreasing the strength of the evidence provided.

When a larger sample size was included (Cushnie-Sparrow et al (2018)), researchers were able to control for severity of dysarthric symptoms, which revealed significant effects. Similarly, De Letter et al. (2005) noted that participants in their study with lower overall intelligibility showed greater differences between the “ON” and “OFF” states. This suggests that as the severity of symptoms increases, so does the perceptual impact of levodopa medication. Had the former investigators included measures of connected speech (mimicking real-world context), their results would have proved compelling.

In addition to the weaknesses found in all studies examined, limitations of this present review also impact the conclusions that can be drawn about the effects of levodopa. Namely, there was considerable variability in the specific speech and voice characteristics evaluated in each report. This limited the strength of corroboration between studies, as direct comparisons could not be made. This was largely due to the small pool of studies that met selection criteria, as only those including

perceptual measures were accepted. A much larger group of studies looking at more similar measures could have been evaluated if acoustic measures were considered. However, despite the considerable subjectivity of this type of measure, this writer maintains that perceptual ratings are the gold standard for drawing conclusions about the real-life implications of results, if good inter and intra-rater reliability is maintained.

Future Research Considerations

The evidence in this review ranged from equivocal to suggestive, based on study designs that limited their real-world confirmation of results. In future studies looking at the impact of levodopa treatment on perceptual measures of speech and voice symptoms in PD, the following recommendations should be considered to strengthen the level of evidence:

- a) Researchers should collaborate with other centres to include much larger sample sizes to increase the validity of results. This will allow studies to control for severity of symptoms, age and time since disease onset.
- b) Samples should include larger numbers of individuals with mild, moderate and severe dysarthric symptoms to compare results.
- c) Speech samples should always include connected speech to mimic real-life context.
- d) Variables such as previous behavioural speech therapy should be controlled for.
- e) Researchers should conduct repeat-trials with patients receiving standard doses of levodopa as well as their physician-prescribed dosages in order to compare effects.
- f) Studies should look at a wider range of perceptual characteristics (ie. voice quality, overall intelligibility, prosodic features, etc). Particular attention should be paid to speech intensity, as hypophonia (low speech intensity) is a chief voice symptom for many individuals with Parkinson’s disease.
- g) Perceptual ratings should be conducted by larger groups of raters with evidence of good inter and intra-rater reliability to limit the effects of subjectivity in results.

- h) Raters should include untrained listeners as well as SLP and SLP students to evaluate the real-world impact of treatments

Clinical Implications

While this review highlighted some potential benefits of levodopa treatment for individuals with severe speech and voice symptoms resulting from Parkinson's disease, additional pharmacological studies are required to determine effective dosage requirements for maximal impact in these areas.

For speech-language pathologists working with these individuals, it is clear that there is a role to play in the traditional therapy context, as many individuals do not appear to benefit from the standard treatment. As a person's quality of life can be greatly impacted by their ability to communicate effectively, SLPs need to be continually striving to create successful behavioural therapies to mitigate these symptoms. Peer-reviewed studies looking at the benefits of the prevailing Lee Silverman Voice Treatment (LSVT) will also be necessary to determine its validity and to pave the way for other possible programs that could prove beneficial for those suffering PD-induced dysarthria.

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