HHS Public Access

Author manuscript

*Mov Disord*. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

*Mov Disord*. 2015 October ; 30(12): 1696–1701. doi:10.1002/mds.26351.

# A Randomized, Double-Blind Phase I/IIa Study of Intranasal Glutathione in Parkinson's Disease

**Laurie K Mischley, ND, MPH, PhD(c)**[1,2,*], **James B Leverenz, MD**[3], **Richard C Lau, MPH**[1,4], **Nayak L Polissar, PhD**[5], **Moni B Neradilek, MS**[5], **Ali Samii, MD**[6], and **Leanna J Standish, ND, LAc, PhD**[1]

[1]Bastyr University Research Institute, Kenmore, WA

[2]University of Washington, Department of Nutritional Sciences, Seattle, WA

[3]Cleveland Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH

[4]Oregon State University, School of Biological and Population Health Sciences, Corvallis, OR

[5]The Mountain-Whisper Light, Seattle, WA

[6]University of Washington, Department of Neurology; Northwest PADRECC at the Seattle VA Medical Center

## Abstract

**Background—**Depletion of reduced glutathione is associated with Parkinson's disease (PD) and glutathione augmentation has been proposed as a disease-modifying strategy.

**Objectives—**The purpose of this study was to determine the safety and tolerability of intranasal reduced glutathione in individuals with PD.

**Methods—**30 individuals with PD were randomized to either placebo (saline), 300 mg/day or 600 mg/day intranasal glutathione in 3 divided daily doses. Follow-up visits included side effect screening of PD symptoms and cognition, blood chemistry, sinus irritation, and hyposmia. Tolerability was measured by frequency and severity of reported adverse events, compliance and withdrawals from the study.

**Results—**After 3 months, there were no substantial differences between groups in the number of adverse events reported or observed among all safety measures assessed. All groups met tolerability criteria.

[*]**Correspondence to:** Dr. Laurie K Mischley, Bastyr University, 14500 Juanita Dr NE, Kenmore WA 98028, Phone: +1-425-602-3417, lmischley@bastyr.edu; mischley@u.washington.edu.

**Conflict of Interest**: None of the authors have any conflicts of interest to disclose.

**Author Roles:**

Laurie Mischley: Research project conception and execution, manuscript preparation; James Leverenz: Research project organization, review and critique of final manuscript; Richard Lau: Research project organization and execution, execution of statistical analysis plan, manuscript preparation; Nayak Polissar and Moni Neradilek: Statistical analysis design, review, and critique, and manuscript review; Ali Sami: Research project conception, organization; Leanna Standish: Research project conception and organization, manuscript review and critique.

No clients have financial interest in this study; RC Lau and MB Neradilek: None.

**Conclusions—**These data support the safety and tolerability of intranasal glutathione in this population. Pharmacokinetic and dose-finding studies are warranted.

### Keywords

glutathione; antioxidant; nutrition; neuroprotection; deficiency

## Introduction

Glutathione is a well-established antioxidant, hydrogen peroxide reducing agent, essential for cellular detoxification, as a neuropeptide, and as a reservoir for cysteine, glycine, and glutamic acid. [1, 3] The loss of reduced glutathione (GSH) is the most consistently reported alteration in the antioxidant defense system in PD.[7–10] Where most individuals can synthesize enough GSH to maintain redox equilibrium, this is not the case in PD and other neurodegenerative disorders which have consistently been shown to be associated with GSH depletion,[10] defining GSH as a conditionally essential nutrient in PD.[11]

The value of exogenously administered GSH to patients with PD has been formally studied twice using intravenous GSH, (iv)GSH, based on the understanding that oral GSH is poorly absorbed.[14] Both studies concluded that further research was warranted on GSH as a neuroprotective agent in PD. [15, 16] (iv)GSH is limited by invasiveness, expense, and necessary clinic visits, which restrict therapeutic utility.

(in)GSH has been used as a potential route of central nervous system (CNS) glutathione augmentation since 2004, based on an acceptable safety and tolerability profile, [17, 18] biological plausibility that small, polar molecules may bypass the blood-brain barrier (BBB) via intranasal administration, and anecdotal case reports of improvement.[17, 19]

## Methods

This study was designed to evaluate the safety and tolerability of (in)GSH in a double-blind, placebo-controlled fashion in a cohort of individuals with PD. The study was approved by the Bastyr University IRB and conducted in accordance with The Code of Ethics of the World Medical Association for experiments involving humans. The FDA granted Investigational New Drug status. All clinical evaluations were conducted at Bastyr University Clinical Research Center, Kenmore, WA, USA. Only the data monitoring committee, the database manager and the compounding pharmacy were unblinded. The study was registered on ClinicalTrials.gov (#NCT01398748).

All participants were English-speaking residents of the Pacific Northwest, USA who reported having been diagnosed with idiopathic PD by a clinical neurologist within the previous 10 years, had a modified Hoehn & Yahr stage ≤ 3, were ≥ 21 years of age, and had been stable on medications, supplements, diet, and exercise for 30 days prior to study entry. Individuals were excluded if they had abnormal liver enzymes or kidney function, cognitive impairment (Montreal Cognitive Assessment (MoCA) score < 25), epilepsy, a history of stroke, a history of brain surgery, structural brain disease, diseases with features common to PD (e.g. essential tremor), chronic sinusitis, or a history of intranasal telangiectasia. All

individuals agreed to try to maintain stability of medications, diet, lifestyle, and alternative therapies throughout the study trial, although deviation from baseline routine throughout the trial did not disqualify them from continued participation.

Key Pharmacy (Kent, WA, USA) compounded the study medication for each participant enrolled according to a randomized schedule generated by the study statistician. Purity and potency of glutathione, both in powdered and compounded liquid form, was independently validated by Eagle Analytical (Houston, TX, USA) at the beginning and throughout the study. Liquid glutathione was assessed for potency and purity from both unissued medication and from medication returned by subjects after 30 days of storage. Mucosal Atomization Device (MAD) tips, used to turn the liquid glutathione into a mist for easier administration, were supplied by Wolfe-Tory Medical (Teleflex) and replaced monthly.

Study medication was dispensed as sterile, capped 1-ml syringes in a light-impermeable plastic bag shipped on ice and stored in the refrigerator. GSH has a sulfur smell; to limit risk of unblinding, study clinicians did not participate in dispensation, collection, counting, or disposal of study medication. Participants were instructed to store the study medication in the refrigerator and to rinse MAD tips with warm water and let air dry after each use.

The maximum dose, 4200 mg/ week, was chosen to match the dose used in a 2009 pilot study of intravenous GSH, 1400 mg three times weekly.[16] Subjects who passed screening were randomized into one of four groups: 600mg (in)GSH/day, 300mg (in)GSH/day, placebo (sterile saline) or watchful waiting using simple random allocation with uneven distribution (n= 10,10,10, and 4, respectively). In order to evaluate the impact of the saline spray on nasal symptoms, the study sponsor requested four additional individuals be enrolled to a watchful waiting arm, to provide a point of comparison for nasal irritation that could be caused by either the saline placebo or the active glutathione. Because these individuals did not receive placebo, they are excluded from all analyses other than those evaluating nasal irritation. Subjects randomized to intervention arms were instructed to spray one 1 ml syringe full of study medication three times daily for 3 months total. The medication was dispensed one month at a time, with instructions to return both used and unused syringes at the end of each month. Self-reported doses taken were confirmed through counts of returned syringes. Along with the medication, subjects were given a daily log and told to report medication use and any changes in symptoms and well-being.

Subjects returned at weeks 2, 4, 8, 12, and 16 for assessments of complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and a urinalysis. Monitoring of Side Effects Scale (MOSES) is a standardized questionnaire designed to assess 83 potential symptoms across 8 body systems, and was used to screen for side effects. The SNOT-20, a validated measure of rhinosinusitis [20], was employed in this study because sinus irritation was anticipated. For our purposes, questions 1–10, specific to sinusitis (e.g. runny nose, sneezing, cough), were used to screen for sinus-specific AEs. The UPDRS was used to monitor PD symptoms, and the Sensonics Smell ID Test was used to test olfactory function. AEs were predefined to reflect clinically relevant worsening or occurrence of all outcomes evaluated. According to protocol, study clinicians were blinded and required to have successfully completed the

MDS UPDRS Training Program. Each participant was asked to select a time of day when they were most likely to be 'on'; once that time was selected, all subsequent evaluations were scheduled at the same time to minimize the impact of circadian fluctuations of PD symptoms.

All comparisons presented are between the active arms of the study and placebo; data from the no-intervention arm (n=4) was eliminated from all analyses except sinus irritation, which was anticipated in all arms. Individuals who did not make the three month study visit were dropped from the analysis. Descriptive statistics were the primary outcome measure, and thresholds for reporting were determined *a priori*. Clinical side events were defined as a 2-point change on the MOSES or a rating of 3 or 4 (severe) on the 0–4 MOSES scale; Laboratory adverse events were predefined as a deviation from accepted reference ranges, e.g. ALT > 50 IU/L. Tolerability was defined as 80% of the group taking 80% of the prescribed dose of study medication.

## Results

Of the 30 participants assigned to a treatment arm, 28 completed the study intervention; one participant withdrew due to schedule conflicts and the other withdrew due to an adverse event (AE) attributed to the study medication. The AE necessitating withdrawal from the study was a "ringing in her head" following the first use of study medication exacerbation of chronic pruritus that had been several months quiescent prior to the screening visit. The participant reported the ringing sensation resolved over 4–6 hours and the dermal inflammation resolved within two weeks. Across study arms, the predominately Caucasian (96%) participants were evenly distributed for gender (50%/50% male/female) and HY (median 2).

Subject compliance with study medication use met criteria for tolerability in all cohorts. GSH retained 89% of its potency after over 30 days of home storage. As expected, individuals in all intervention arms reported an increase in sinus symptoms, and this was approximately equivalent across arms. There were no statistically significant differences in the frequency of laboratory events as defined by CBC, WBC with differential, ALT, AST, creatinine, blood urea nitrogen, uric acid or urinalysis. UPDRS scores, included as a safety measure, improved in both treatment arms over placebo. In *post hoc* analysis, UPDRS trends remained consistent after excluding all individuals (n=10) who changed medications throughout the study. Side effects, deviations from laboratory reference ranges, and change from baseline clinical scores are listed in Table 1.

To evaluate whether individuals were unblinded by the smell, participant feedback was evaluated. Qualitative interviews generated 189 total comments; two comments referenced the salty taste, one mentioned the smell of sulfur in nose and stool. Of the six participants who expressed confidence in knowing their group assignment, two were correct.

## Discussion

In this phase I/IIa clinical trial, (in)GSH was well-tolerated. A naturally occurring molecule, exogenously administered GSH has an excellent record of safety. The few studies that have evaluated exogenous administration of GSH to humans with PD have been reassuring. [16, 18]

Mild clinical improvement in UPDRS symptoms came as a bit of a surprise for this non-dopaminergic therapy, although exogenous GSH has been shown to increase dopamine transporters.[22] The benefit measured may be explained by regression toward the mean, although anecdotal reports suggest at least some individuals do experience an acute improvement in clinical symptoms following administration of exogenously supplied gluathione.[19] While the study was double blind with a placebo control, GSH has a distinct smell that unblinded at least one participant.

The clinical response, while fortunate for patients, suggests delayed-start trial (or similar) design should be utilized when attempting to determine the neuroprotective capacity of (in)GSH over time. Symptomatic improvement with (in)GSH should be verified in a larger study powered for detecting differences between groups.

Overall, this study supports the safety and tolerability of (in)GSH in a sample of patients who are within 10 years of PD diagnosis. The identification of a non-dopaminergic strategy capable of improving UPDRS scores may herald a new generation of therapeutics. GSH perturbations have been documented in numerous other disorders of the CNS, such as schizophrenia, dementia, Huntington's disease, and autism and thus the therapeutic potential of (in)GSH may not be limited to PD.

## Acknowledgements

We gratefully acknowledge the participation of all individuals in this study. We thank Key Pharmacy for collaborating with the research team and their willingness to provide additional product purity and potency data throughout the study. We wish to acknowledge the donation of Mucosal Atomization Device tips by Wolfe-Tory Medical (Teleflex). The SNOT-20 and MoCA were used with permission from J. Piccirillo and Z. Nasreddine, respectively.

**Financial Disclosures**

LK Mischley: Research funding from NIH NCCAM, Charles and Barbara Wright, Bastyr University Research Institute, honoraria from Kadlec Neurological Resource Center, Union Hospital, Indiana State University, Northwest Parkinson's Disease Foundation; A Samii: Honoraria from Teva Pharmaceuticals, UCB, and US WorldMeds; LJ Standish: NIH NCCAM, The John and Lotte Hecht Memorial Foundation, Bastyr University School of Naturopathic Medicine; NL Polissar: Fee-for service statistical consulting. JB Leverenz: Consulting Boehringer-Ingelheim, Navidea Biopharmaceuticals, Piramal Healthcare;

**Funding:** NIH NCCAM K01 AT04404, Bernard Osher Foundation, Veterans Affairs P50 NS062684

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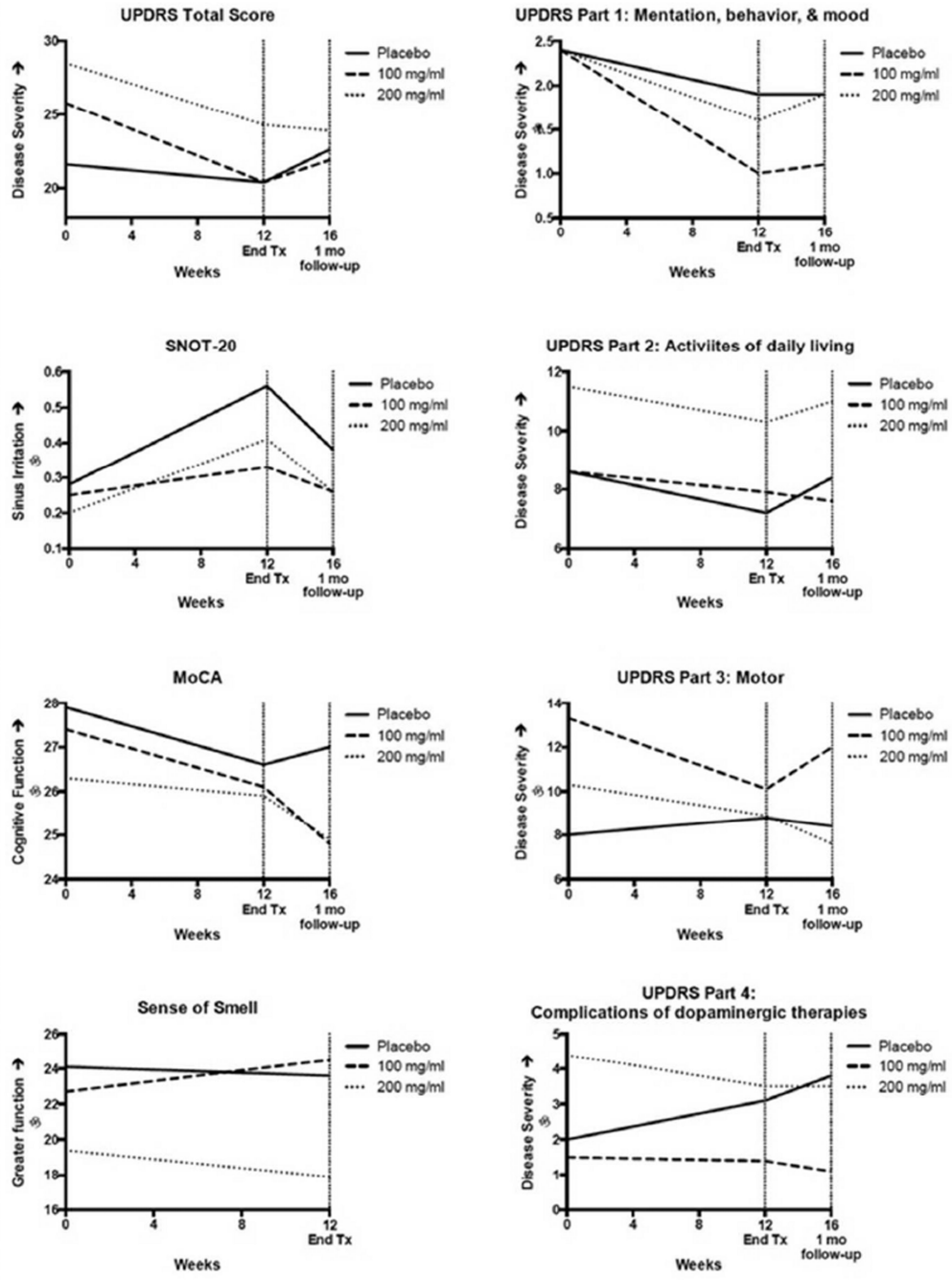
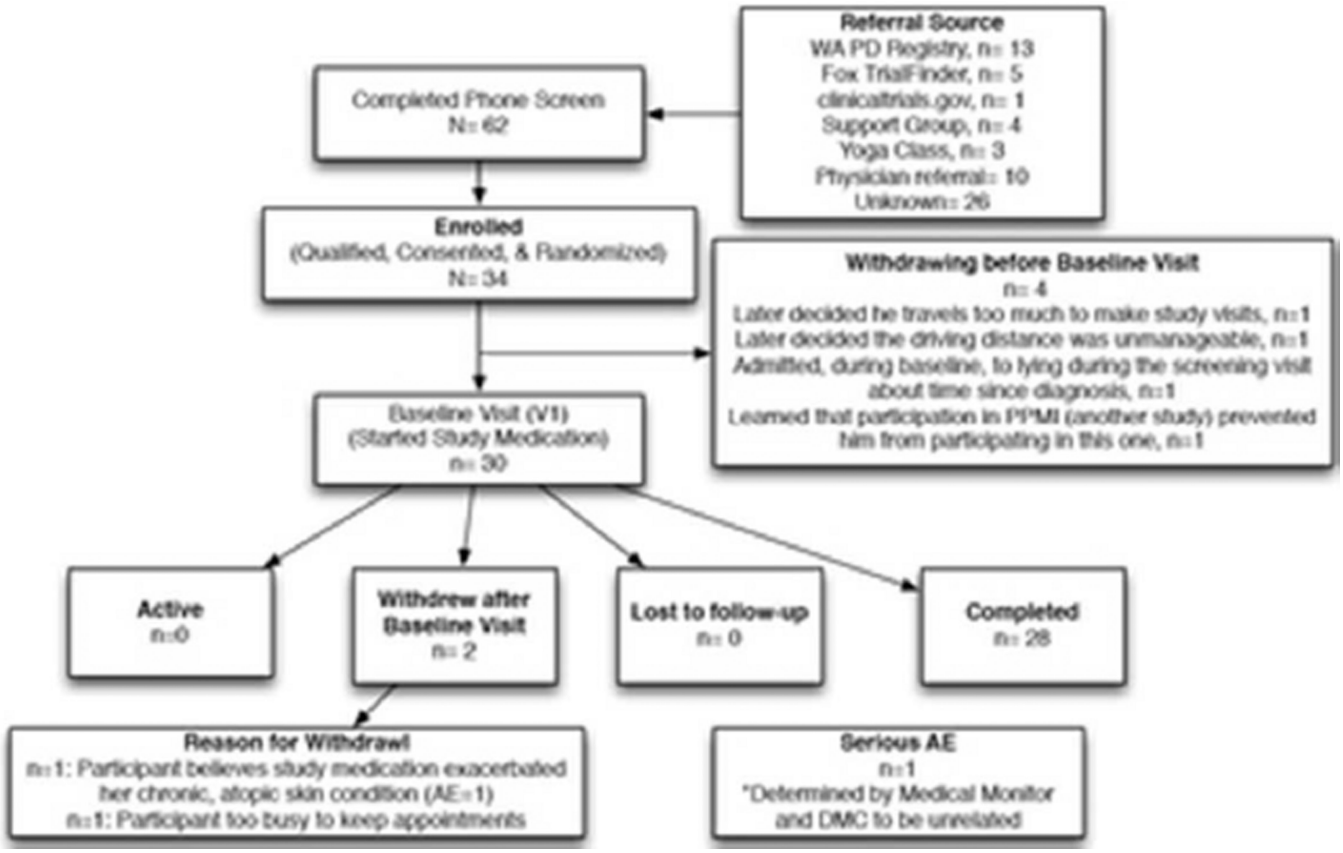



Outcomes associated with study arms. The mean change, by treatment arm, in clinical outcomes assessed over the course of the three-month study intervention and after a one-month wash out period. UPDRS: Unified Parkinson's Disease Rating Scale; SNOT-20: SinoNasal Outcomes Test; MoCA: Montreal Cognitive Assessment; Sense of Smell was determined by Sensonics Smell Identification Test.




Enrollment algorithm according to CONSORT guidelines.

## Table 1

Side effects by cohort. The table reports the number of individuals meeting criteria for adverse events and includes only those symptoms reported by two or more participants in any cohort. Sinusitis and UPDRS reported as mean change in absolute score from baseline, by cohort.

**Table of Side Effects**

| | Placebo (n=9) | 300 mg/d (n=8) | 600 mg/d (n=8) |
|---|---|---|---|
| *Number of individuals reporting symptom:* | | | |
| **Negative Side Effects** | | | |
| Labored breathing | 0 | 0 | 2 |
| Sore throat/redness | 0 | 0 | 2 |
| Flatulence | 2 | 0 | 1 |
| Increased thirst | 0 | 0 | 2 |
| Contortions/neck-back arching | 0 | 2 | 0 |
| Chills | 2 | 0 | 0 |
| **Positive Side Effects** | | | |
| Improved blink rate | 1 | 5 | 0 |
| Improved arm swing | 1 | 1 | 2 |
| Fewer muscle pains or aches | 2 | 1 | 2 |
| Reduced edema | 0 | 0 | 2 |
| Improved incontinence/Nocturnal enuresis | 0 | 2 | 0 |
| Reduced urinary frequency | 3 | 0 | 0 |
| Reduced agitation | 0 | 3 | 0 |
| Improved drowsiness/lethargy/sedation | 2 | 1 | 2 |
| Improved insomnia | 1 | 0 | 2 |
| Less crying/feelings of sadness | 2 | 0 | 0 |
| **Deviation from laboratory normal reference ranges** | | | |
| Hemoglobin | 0 | 0 | 2 |
| Hematocrit | 0 | 0 | 2 |
| Creatine | 1 | 1 | 2 |
| Uric acid | 0 | 0 | 2 |
| *Change from baseline, Mean (SD):* | | | |
| **Sinusitis** (SNOT-20 Score 0–1) | 0.275 | 0.185 | 0.213 |
| **Change in Parkinson's Symptoms** | | | |
| UPDRS total (0–199) | −1.1 (4.1) | −5.3 (4.8) | −4.3 (7.5) |
| UPDRS Part 1: Mentation, behavior, & mood | −0.6(1.2) | −1.4(2.0) | −0.8(1.7) |
| UPDRS Part 2: Activities of daily living | −1.3(3.5) | −0.8 (2.3) | −1.3(3.5) |
| UPDRS Part 3: Motor score | 0.8 (3.7) | −3.1 (2.9) | −1.4(3.7) |
| UPRDS Part 4: Complications of dopaminergic therapy | 1.0(1.5) | −0.1 (1.0) | −0.9 (2.4) |