Protocol Summary

Modulation of GABA-A Receptors in Parkinson Disease-Transdermal Flumazenil Arm

NCT03440112

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**TI:** Modulation of GABA-A Receptors in Parkinson Disease-Transdermal Flumazenil Arm

Axial motor impairments represent a significant cause of disability in Parkinson disease (PD). Dopaminergic treatments typically only provide limited or no relief of these symptoms (Bloem et al., 2003; Bohnen & Cham, 2006). Axial motor features are mediated by widespread neural networks that extend well beyond the nigrostriatal system. The role of γ-aminobutyric acid-A ($GABA_A$) has received limited attention in human PD research, despite the fact that main outflow structures of the basal ganglia largely employ inhibitory GABA to connect to areas outside the basal ganglia. Abnormally increased GABA activity from these nuclei has been demonstrated previously (Filion & Tremblay, 1991; M. Vila et al., 1997). We have preliminary in vivo [$^{11}$C]FMZ brain PET data that shows that reduced cerebral $GABA_A$ receptor availability (likely reflecting increased synaptic or extra-cellular GABA-ergic activity) is associated with more severe axial motor features in PD. These observations support the recent notion that excessive GABA-ergic inhibition of the basal ganglia outflow structures may be a critical mechanism underlying axial motor impairments in PD (Lewis & Shine, 2016). Flumazenil is a short-acting modulator of the $GABA_A$ receptor benzodiazepine binding site, which has shown to rapidly improve motor impairments in PD (Ondo & Hunter, 2003; Ondo & Silay, 2006). Flumazenil, however, can only be reliably given intravenously (Ondo & Silay, 2006). The overarching goal of this project is to perform $GABA_A$ receptor biomechanistic and target engagement studies to examine the effect of $GABA_A$ receptor modulation on axial motor features in PD. Our main hypothesis is that modulation of cerebral $GABA_A$ receptor activity improves dopamine-resistant axial motor features in PD, that can be predicted by [$^{11}$C]FMZ PET biomarker findings. The use of i.v. or t.d. flumazenil will allow direct testing of our hypothesis to provide biomechanistic proof of concept.

**Aim 1**: Detailed under NCT03462641.

Hypothesis 1: Detailed under NCT03462641.

**Aim 2**: To perform a $GABA_A$ receptor target engagement with detailed quantitative motor assessment and [$^{11}$C]FMZ PET imaging before and after 1 week of transdermal flumazenil (18 mg t.d. q3-4 hr while awake x 3d then if no side-effects - 36 mg t.d. q3-4 hr while awake, n=15 vs. placebo administration, n=15; total net recruitment, n=30) in PD subjects across a range of disease severity (Hoehn and Yahr stages 2-4 (Hoehn & Yahr, 1967)). No cream will be dispended within 4 hours of bedtime. Baseline [$^{11}$C]DTBZ brain PET imaging will be performed to assess for the integrity of nigrostriatal dopaminergic nerve terminals.

Hypothesis 2: Transdermal flumazenil administration results in improved overall motor severity of PD symptoms as assessed by MDS-UPDRS part III total score, and improved postural stability symptoms in particular as assessed by MiniBEST sensory subscore, with greater effects present in patients with lower pre-treatment [$^{11}$C]FMZ $GABA_A$ receptor availability.

**Research Strategy**

**A. Innovation**: Our approach and subject cohort are unique in several ways. To our knowledge, no other group has used [$^{11}$C]flumazenil $GABA_A$ receptor **biomechanistic and target engagement studies** and detailed quantitative gait and postural motor assessments in PD. Elucidation of the role of cerebral GABA-ergic receptors in dopamine-resistant motor impairments would be an entirely novel approach in PD. Prediction of motor treatment responsiveness to $GABA_A$ receptor *negative allosteric modulator* therapy in PD would also be entirely novel.

**B. Significance**: Treatment approaches to reduce balance problems and falls have been recently identified as the number 1 research priority in PD (Deane et al., 2014). Excessive GABA-ergic inhibition by the main output structures of the basal ganglia has been proposed to be a critical mechanism in the etiology of dopamine-resistant motor features in PD (Lewis & Shine, 2016). $GABA_A$-ergic neurotransmission has also been implicated in postural control because of the well-known fall risk in elderly subjects taking benzodiazepine drugs (de Vries et al., 2013). Our preliminary findings show that reduced $GABA_A$ receptor availability (*likely* reflecting increased *synaptic or extra-cellular GABA-ergic activity*) associates selectively with more severe axial compared to other motor symptoms in PD. To the best of our knowledge, these are unique findings, which have not been reported previously and form the *scientific premise* of this proposal. Previous findings by Ondo and colleagues provide the basis for the proposed biomechanistic study using flumazenil (Ondo & Hunter, 2003; Ondo & Silay, 2006). Positive findings in this study will inform our understanding of the pathophysiology of dopamine-resistant motor disturbances in PD and may augur pharmacological modulation of excessive $GABA_A$-ergic activity as a novel non-dopaminergic treatment approach for disabling motor impairments in this disorder.

**i) Overview:** *The overarching goal of this project is to perform $GABA_A$ receptor biomechanistic and **target engagement studies** to examine the effects of $GABA_A$ receptor modulation on motor impairments in PD, including axial motor features. Our main hypothesis is that modulation of cerebral $GABA_A$ receptor activity improves axial motor impairments in PD.*

Timetable and landmark achievements: This study, to be conducted over a 4-year period, will include a net recruitment total of *60* subjects with PD (30 net subjects for each study).

**Table 1: Study enrollment per year**

| | Yr 01 | Yr 02 | Yr 03 | Yr 04 | Total |
|---|---|---|---|---|---|
| Baseline clinical test battery, *including quantitative postural and gait testing* | *17* | *17* | *17* | *17* | *68** |
| Brain MRI | *17* | *17* | *17* | *17* | *68** |
| [$^{11}$C]DTBZ | *17* | *17* | *17* | *17* | *68** |
| [$^{11}$C]flumazenil (64 baseline and 32 post-clarithromycin) | *24* | *24* | *24* | *24* | *96*** |
| i.v. flumazenil PET biomechanistic drug study (net target n=30) | *8* | *8* | *8* | *8* | *32*** |
| p.o. clarithromycin exploratory PET target engagement drug study (net target n=30) | *8* | *8* | *8* | *8* | *32*** |

**accounting for eligibility; **accounting for attrition*

**ii) Study Procedures**

After obtaining informed consent, study participants will undergo clinical testing, including detailed and quantitative mobility testing, [$^{11}$C]flumazenil and [$^{11}$C]DTBZ PET and brain MR imaging studies. Imaging will be done on separate days. Patients meeting eligibility criteria will be invited for the i.v. flumazenil/placebo and/or transdermal flumazenil studies. Qualified personnel who have been trained in the use of the instruments and have undergone inter-rater reliability evaluations will perform the assessments. To allow for *unbiased* assessments, these technicians will be blinded to the treatment status of the subjects. We will perform the motor assessments and the [$^{11}$C]DTBZ and [$^{11}$C]flumazenil brain PET studies in the dopaminergic "off" state.

Clinical Testing: Clinical assessment will consist of a general medical and neurological examination. The mobility and gait assessment will be performed in the dopaminergic "off" state in subjects on dopaminergic drugs. To allow for robust replication of results by other researchers we will use readily available motor assessments and standard procedures.

Outcome Measures:

1. *MDS-UPDRS part III total score*: We will use the total Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III - motor scale rating scores to assess general motor severity of PD. Scale from 0-132, higher scores indicate worse motor outcomes. Outcome measure will be collected during dopaminergic medication ON state on the first clinical visit (day 1) before treatment administration, after 7 days of treatment (day 7), and then after 7 days of treatment discontinuation (day 14).

2. *MiniBEST Sensory Subscore:* MiniBEST sensory subscore will be used as a measure of axial motor symptom severity. MiniBEST sensory subscore measures an individual's ability to maintain balance under conditions of sensory constrain and unstable/inclined standing surface. It is computed as a sum of MiniBEST items 7, 8, and 9. The score ranges from 0 to 6, with 0 indicating inability to balance under all of the condition, and 6 indicating no difficulty in maintaining balance under any of the conditions (lower score indicates worse balance). Outcome measure will be collected during dopaminergic medication ON state on the first clinical visit (day 1) before treatment administration, after 7 days of treatment (day 7), and then after 7 days of treatment discontinuation (day 14).

**Intravenous flumazenil study**: Detailed under NCT03462641.

**Transdermal flumazenil study:** There will be two groups of PD patients for a total of 30 patients (net recruitment): transdermal flumazenil (18 mg t.d. q3-4 hr while awake x 3d then - if no side-effects - 36 mg t.d. q3-4 hr while awake, n=15 vs. Lipoderm® based placebo cream 1 q3-4 hr while awake x 3d then placebo cream 2 t.d. q3-4 hr while awake, n=15; in PD subjects across a range of disease severity (Hoehn and Yahr stages 2-4 (Hoehn & Yahr, 1967)). No cream will be dispended within 4 hours of bedtime. Transdermal flumazenil will be applied to the forearms using a Topi-CLICK® 35

(DoseLogix, LLC) calibrated topical dosing applicator (0.25 ml calibrated dispense per click), where a dose of 18 mg will be 3 clicks (0.75 ml) and a dose of 36 mg 6 clicks (15 ml) of 24 mg/ml compounded cream. Subjects will be randomly assigned to one of these treatment groups by means of a computerized random number generator. Subjects randomized to transdermal flumazenil will take 18 mg t.d. q3-4 hr while awake x 3d and then -if no side-effects - 36 mg t.d. q3-4 hr while awake. If the clinician decides to keep the subject at the 18 mg dose or return to the 18 mg dose after a trial at 36 mg dose, the study assessments will be completed on this dose. Apart from the baseline visit for the overall study, there will be 3 separate visits for the sub-study: Day 1 pre-treatment testing followed by initiation of study drug (transdermal flumazenil/placebo), day 7 (maximum 10 days if needed for scheduling needs of scans or test) repeat testing on treatment with repeat optional [$^{11}$C]FMZ PET after completion of which the study drug will be discontinued, and a Day 14 follow-up visit to assess for possible persistent effects. If the patient cannot undergo a repeat optional [$^{11}$C]FMZ PET study by Day 7 of the treatment then the treatment will be continued for at least 1-3 additional day(s) to allow the repeat PET study as well as Visit 3.

**iii) Imaging Details:**

MR imaging**:** *MRI will obtained for anatomic volume-of-interest (VOI) definition and partial volume correction required for the PET analysis, and also to include unexpected pathology*. MR studies will be acquired in all subjects on a 3 Tesla Philips Achieva, a state-of-the-art 16-channel system running version R2x software. The "ISOVOX" exam card protocol primarily designed to yield isotropic spatial resolution at standard T1-weighted, proton-density-weighted, and T2-weighted settings. Following patient positioning and a sagittal survey, the following scans will be performed: *T1-weighted*: A 3D inversion recovery-prepared turbo-field-echo performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200x160slices reconstructed to 1mm isotropic resolution. *PD and T2-weighted*: A 2D dual-echo turbo-spin-echo is performed in the axial plane using TR/TE=6930/10&80ms; echo-train-length = 10; single average; FOV=380x260mm; acquired Matrix = 256x256 reconstructed to 256x256; 100 slices at 1.5mm. Testing time 45-60 minutes or less.

PET Imaging and analysis: This will be performed in 3D imaging mode using an Biograph 6 TruPoint PET/CT scanner (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum (FWHM) over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit will be attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view. Images will be corrected for scattered events also as implemented by the vendor. Images will be reconstructed using FORE rebinning followed by 2-D ordered-subsets expectation maximization (OSEM) using 4 iterations and 16 subsets (no smoothing) resulting in spatial resolution of approximately 5.5 mm full-width at half-maximum both in-plane and axially.

[$^{11}$C]flumazenil and [$^{11}$C]DTBZ will be prepared as described previously (Holthoff et al., 1991; Scott et al., 2016). The binding of flumazenil to the central benzodiazepine receptor on the $GABA_A$-chloride ionophore complex will be determined as previously described (Holthoff et al., 1991). All [$^{11}$C]flumazenil sessions will be performed with the infusion equilibrium technique previously developed in our laboratory (Holthoff et al., 1993). Benzodiazepine receptor determination will begin after intravenous administration of a bolus injection containing 40% of the total administered 10 mCi [$^{11}$C]flumazenil dosage over 15 seconds, followed by continuous infusion of the remaining tracer at a constant rate for 62 minutes (at which time the infusion will be stopped) followed by delayed wash-out imaging 62-90 minutes. The tissue DV (calculated as milliliters of plasma per milliliter of brain tissue, proportional to benzodiazepine binding site density) will determined from the final 28 minutes of data (i.e., 62 to 90 minutes), and to be scaled to venous [$^{11}$C]flumazenil levels (following HPLC) at 50-60 min after injection to generate DV ratios (DVR) (Holthoff et al., 1993). A bolus/infusion protocol will be used for [$^{11}$C]DTBZ (15 mCi) in 60 minutes (Koeppe et al., 1999).

All dynamic PET image frames will be spatially co-registered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session (Jonides et al., 1993). We will use Neurostat software (University of Washington, Seattle, WA) for PET-MRI registration. The cropped MR volumetric SPGR image will be registered to the PET data. We will use Freesurfer software (http://surfer.nmr.mgh.harvard.edu) to define cortical and subcortical MR gray matter volumes. Time-activity curves will be generated for cortical and subcortical VOIs for the dynamic PET studies. MRI-based correction for partial volume effects due to cerebral atrophy will also be performed (Meltzer et al., 1996).

**iv) Human Subjects**

Description of subject populations: Subjects will include non-demented PD patients across a range of disease severity (Hoehn and Yahr stages 2-4 (Hoehn & Yahr, 1967)) As axial motor impairment are typically more prevalent with advancing disease we plan to recruit at least 24 subjects in each group who have at least 1 (or more) axial motor features, such as abnormal balance, slow gait or history of falls or freezing of gait based on our sample size calculations. During the course of the study we anticipate an ineligibility and attrition of approximately *12%*. Therefore we expect to recruit a gross total of *68* PD subjects for a net target enrollment of *60* PD subjects.

Recruitment: Subjects will be recruited from the UM and Ann Arbor VA movement disorders clinics. The UM movement disorders clinic follows a population of about 1,050 clinically well-defined patients with PD and will be the main source of recruitment of patients for this study. Dr. Frey, Co-Director of the Movement Disorders Division at UM, will be in charge of UM patient recruitment. In addition, subjects will be recruited from the Ann Arbor VA movement disorders clinic, directed by Dr. Bohnen, and currently follows 240 well-defined subjects with PD. At present, we recruit 6-8 subjects with PD for imaging studies per month at UM. Therefore, a recruitment requirement of about 1-2 per month for this study is not expected to be challenging. Additional sources of recruitment are the Michael J. Fox Trial Finders (https://foxtrialfinder.michaeljfox.org) and the University of Michigan centralized web-based recruitment initiative called MichR UM Clinical Studies (http://www.umclinicalstudies.org) that provides an online registry for interested volunteers. This online registry will provide a way for volunteers to let studies know that they are interested in participating in their research. It will also provide study staff with a preliminary screening tool to see who may be interested, and potentially, who is eligible for their study. Volunteers can enter their contact information, basic demographics, study preferences and some medical history. Additionally, volunteers who are UM patients may also grant access to their medical record for screening purposes only. In case of slower than expected recruitment we will increase the number of PD support group lectures in our region. We have found that PD support group lectures are a great tool to recruit subjects for research studies, maximize identification of the most appropriate subjects. Ann Arbor is close to Detroit (45 minutes) and its surrounding metropolitan areas, which host multiple PD support groups. We will also be able to utilize the infrastructure of the Michigan Parkinson Foundation (MPF; http://www.parkinsonsmi.org), the major lay organization supporting PD patients and caregivers in the state of Michigan. The MPF organizes and supports approximately 50 support groups in the state, organizes educational activities related to PD, and has a quarterly newsletter - The Messenger. The MPF mailing list comprises approximately 29,000 individuals, including individuals from northwestern Ohio and northern Indiana. The MPF is strongly supportive of clinical research on PD and related disorders. The MPF will permit us to advertise our research projects in The Messenger and will facilitate mailing of informational materials to MPF affiliated support groups.

Inclusion Criteria:

1. Parkinson's disease (PD): PD diagnosis will follow the UK Parkinson's Disease Society Brain Bank Research Center (UKPDSBRC) clinical diagnostic criteria for PD.
2. Hoehn and Yahr stages 2-4
3. Absence of dementia confirmed by cognitive testing.
4. Abnormal [$^{11}$C]-Dihydrotetrabenazine ([$^{11}$C]-DTBZ) PET study to demonstrate nigrostriatal dopaminergic denervation

Exclusion Criteria:

1. PD with Dementia (PDD) or dementia with Lewy bodies (DLB).
2. Other disorders which may resemble PD, such as vascular dementia, normal pressure hydrocephalus, multiple system atrophy, corticobasal ganglionic degeneration, or toxic causes of parkinsonism. Prototypical cases have distinctive clinical profiles, like early and severe dysautonomia or appendicular apraxia, which may differentiate them from idiopathic PD. The use of the UKPDSBRC clinical diagnostic criteria for PD will mitigate the inclusion of subjects with atypical parkinsonism.
3. Subjects currently on benzodiazepine, $GABA_B$-ergic medications (baclofen, tizanidine), modafinil, neuroleptic, anticholinergic (trihexyphenidyl, benztropine), or cholinesterase inhibitor drugs.
4. Evidence of a mass lesion on structural brain imaging (MRI).

5. Participants in whom MRI is contraindicated including, but not limited to, those with a pacemaker, presence of metallic fragments near the eyes or spinal cord, chest, or cochlear implant.
6. Severe claustrophobia precluding MR or PET imaging.
7. Subjects limited by participation in research procedures involving ionizing radiation.
8. Pregnancy (urine or serum pregnancy test within 48 hours of each PET session) or breastfeeding.
9. History of seizures
10. Significant anxiety or history of panic disorder.
11. History of recent suicide attempt or overdose of tricyclic antidepressants or other medications.
12. History of transient ischemic attack (TIA) or stroke within the last year.
13. History of systemic lupus erythematosis.
14. Abnormal liver enzymes (AST or ALT) > 3 times upper limit of normal.
15. History of atrial fibrillation.
16. History of retinal branch artery occlusion.
17. Active dermatitis inner forearms.
18. Any other medical history determined by investigators to preclude safe participation.

Additional Exclusion Criteria for Flumazenil sub-studies:

1. Allergy to flumazenil
2. Significant liver disease
3. History of alcohol or other substance abuse within past two years.
4. Subjects currently taking benzodiazepines

**v) Data safety and monitoring board (DSMB)**

As this study will be performed with FDA approved drugs (i.e., flumazenil) IND-exempt status will be requested. *This request is submitted by the University of Michigan MICHR IND/IDE Investigator Assistance Program (MIAP)*. IND-exempt reporting and study monitoring will be performed by MIAP in accordance with FDA guidelines and procedures. In addition, University of Michigan neurologists (Dr. Vikas Kotagal and Peter Todd) who are not involved with any of the research procedures will serve as chairs for the DSMB for this study. They will review outcomes with the PI on an annual basis. Review of study procedures and adverse effects will be performed on a monthly basis. The PI will be responsible for the day-to-day monitoring any potential breach of confidentiality and for reporting any adverse events (AE) following University of Michigan IRB guidelines. For purposes of this study, an AE is defined as any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with participation in this study, whether or not a causal relationship with the study has been established. Breaches of confidentiality will be considered related to the research whenever they occur and will be reported. Withdrawals from the study and the reason for these withdrawals will also be reported. The PI will be in daily contact with the study research staff. The research staff will test the participants, score and enter the data and will monitor their procedures to ensure that confidentiality is maintained. Research staff will be responsible for reporting any significant events to the PI. The PI will ensure that the IRB is notified of any adverse event following the IRB guidelines. Expected and unexpected serious (including fatal) adverse reactions and major unresolved disputes between the research investigator(s) and the research participant or between research investigator(s) will be expeditiously reported to the IRB of the University of Michigan. At the time of renewal, the IRB will be provided with a summary indicating the frequency of the monitoring, cumulative adverse event data, information regarding participant safety or ethics changes, confidentiality issues, benefit-to-risk changes and recommendations on continuing, changing or terminating the study.

**Inclusion of Women and Minorities:**

Inclusion of Women:

Women will be included in this research project. Males and females will be given equal priority in recruitment. However, because PD affects males more than women, the PI will monitor recruitment of women to this project throughout the study, and institute procedures to enhance enrollment of women, if numbers are not adequate. See the Targeted/Planned Enrollment Table.

Inclusion of Minorities:

See the Targeted/Planned Enrollment table for this project. Enrollment targets are based on population estimates of the 2000 US consensus for the state of Michigan. Estimates are < 1-2% (or N <1) for American Indian/Alaska natives, Native Hawaiian or Other Pacific Islander, and Asian Americans for Michigan. The PI will monitor recruitment of minorities to this project throughout the study, and institute procedures to enhance enrollment of minorities, if numbers are not adequate.

**Target/Planned Enrollment**

See Table 1.

Enrollment targets of minorities are based on population estimates of the 2010 US consensus for the State of Michigan. Estimates are 4.4% for Hispanic or Latino population, 14.2% for Black or African Americans, 2.4% for Asian Americans, 0.6% for American Indians and Alaska Natives, and <0.1% for Native Hawaiians or Pacific Islanders.

**Inclusion of Children**

No children will be included. PD occurs predominantly in late-life and, indeed, the risk of developing PD increases with increasing age. In rare cases with clear familial inheritance, the onset of the disease may occur in the 30's and 40's, but there is no evidence of clinical PD in children. Therefore, the research topic to be studied is not relevant to children.

Costs and Payments: Subjects will not be charged for their participation in this study. Subjects will receive $200 for the completion of DTBZ and flumazenil PET scans. Payments for the mobility and postural testing will be $100. Lodging and meals (including meals for the caretaker) will be provided for subjects outside the immediate Ann Arbor region ($300). Reimbursements for transportation (based on average trip of 50 miles one-way, $15) and hospital parking costs ($8).

Note: This is a protocol summary that do not contain language that will be used for peer-reviewed publications based on this project.

**Substantive Amendments to the Protocol**

1) *AME00099120* (Approved 4/9/2020) – Initial study protocol included clarithromycin capsule as one of the active treatments. Around the time of this amendment, FDA issued a warning about increased mortality in older people taking this antibiotic even with a short course treatment. For that reason, clarithromycin arm of the study was dropped in favor of the safer transdermal flumazenil alternative.

2) *AME00101365* (Approved 5/28/2020) – Due to COVID19 pandemic, an option was added to perform applicable assessments over zoom and to sign the consent form remotely via electronic system. Imaging assessments that would require individuals to attend the hospital in-person were made optional in case the participant was not comfortable. Electrocardiogram, which was initially included in the clarithromycin arm is removed from the protocol since that arm of the study was dropped previously.

**References**

Bloem, B. R., Steijns, J. A. G., & Smits-Engelsman, B. C. (2003). An update on falls. *Current Opinion in Neurology*, *16*(1), 15–26. https://doi.org/10.1097/01.wco.0000053580.70044.70

Bohnen, N. I., & Cham, R. (2006). Postural Control, Gait, and Dopamine Functions in Parkinsonian Movement Disorders. *Clinics in Geriatric Medicine*, *22*(4), 797–812. https://doi.org/10.1016/j.cger.2006.06.009

de Vries, O. J., Peeters, G., Elders, P. J. M., Elders, P. J. M., Sonnenberg, C. M., Muller, M., Deeg, D. J. H., & Lips, P. (2013). The elimination half-life of benzodiazepines and fall risk: Two prospective observational studies. *Age and Ageing*, *42*(6), 764–770. https://doi.org/10.1093/ageing/aft089

Deane, K. H. O., Flaherty, H., Daley, D. J., Pascoe, R., Penhale, B., Clarke, C. E., Sackley, C., & Storey, S. (2014). Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease. *BMJ Open*, *4*(12). https://doi.org/10.1136/bmjopen-2014-006434

Filion, M., & Tremblay, L. (1991). Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Research*, *547*(1), 142–151. https://doi.org/10.1016/0006-8993(91)90585-j

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology*, *17*(5), 427–442. https://doi.org/10.1212/wnl.17.5.427

Holthoff, V. A., Koeppe, R. A., Frey, K. A., Paradise, A. H., & Kuhl, D. E. (1991). Differentiation of radioligand delivery and binding in the brain: Validation of a two-compartment model for [11C]flumazenil. *Journal of Cerebral Blood Flow and Metabolism*, *11*(5), 745–752. https://doi.org/10.1038/jcbfm.1991.131

Holthoff, V. A., Koeppe, R. A., Frey, K. A., Penney, J. B., Markel, D. S., Kuhl, D. E., & Young, A. B. (1993). Positron emission tomography measures of benzodiazepine receptors in Huntington's disease. *Annals of Neurology*, *34*(1), 76–81. https://doi.org/10.1002/ana.410340114

Jonides, J., Smith, E. E., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature*, *363*(6430). https://doi.org/10.1038/363623a0

Koeppe, R. A., Frey, K. A., Kuhl, D. E., & Kilbourn, M. R. (1999). Assessment of extrastriatal vesicular monoamine transporter binding site density using stereoisomers of [11C]dihydrotetrabenazine. *Journal of Cerebral Blood Flow and Metabolism*, *19*(12), 1376–1384. https://doi.org/10.1097/00004647-199912000-00011

Lewis, S. J. G., & Shine, J. M. (2016). The Next Step A Common Neural Mechanism for Freezing of Gait. *The Neuroscientist*, *22*(1), 72–82. https://doi.org/10.1177/1073858414559101

M. Vila, Vila, M., Levy, R., Herrero, M. T., Ruberg, M., Faucheux, B., Obeso, J. A., Agid, Y., & Hirsch, E. C. (1997). Consequences of Nigrostriatal Denervation on the Functioning of the Basal Ganglia in Human and Nonhuman Primates: An In Situ Hybridization Study of Cytochrome Oxidase Subunit I mRNA. *The Journal of Neuroscience*, *17*(2), 765–773. https://doi.org/10.1523/jneurosci.17-02-00765.1997

Meltzer, C. C., Zubieta, J., Jon Kar Zubieta, Jon Kar Zubieta, Zubieta, J. K., Brandt, J., Tune, L. E., Tune, L. E., Mayberg, H. S., & Frost, J. J. (1996). Regional hypometabolism in Alzheimer's disease as measured by positron emission tomography after correction for effects of partial volume averaging. *Neurology*, *47*(2), 454–461. https://doi.org/10.1212/wnl.47.2.454

Ondo, W. G., & Hunter, C. (2003). Flumazenil, a GABA antagonist, may improve features of Parkinson's disease. *Movement Disorders*, *18*(6), 683–685. https://doi.org/10.1002/mds.10426

Ondo, W. G., & Silay, Y. S. (2006). Intravenous flumazenil for Parkinson's disease: A single dose, double blind, placebo controlled, cross-over trial. *Movement Disorders*, *21*(10), 1614–1617. https://doi.org/10.1002/mds.21022

Scott, P., Scott, P., Shao, X., Desmond, T. J., Hockley, B. G., Sherman, P., Quesada, C. A., Frey, K. A., Koeppe, R. A., Kilbourn, M. R., & Bohnen, N. I. (2016). Investigation of Proposed Activity of Clarithromycin at GABAA Receptors Using [11C]Flumazenil PET. *ACS Medicinal Chemistry Letters*, *7*(8), 746–750. https://doi.org/10.1021/acsmedchemlett.5b00435