Assessing and Managing Problematic Anxiety in Patients with Parkinson's Disease

Parkinson Society BC AGM

Dr. Andrew Howard

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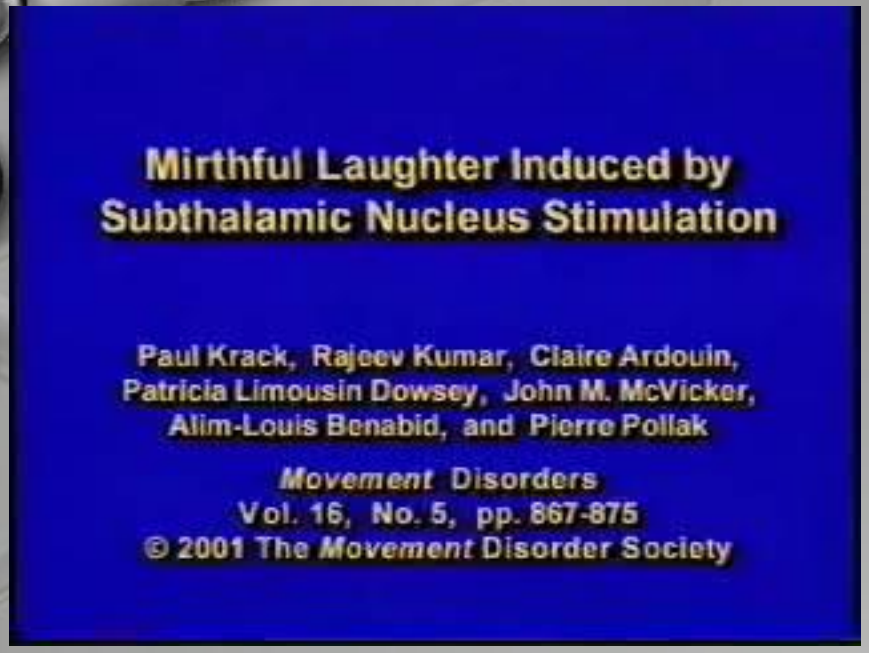
November 20th, 2021

Mirthful Laughter Induced by STN Stimulation

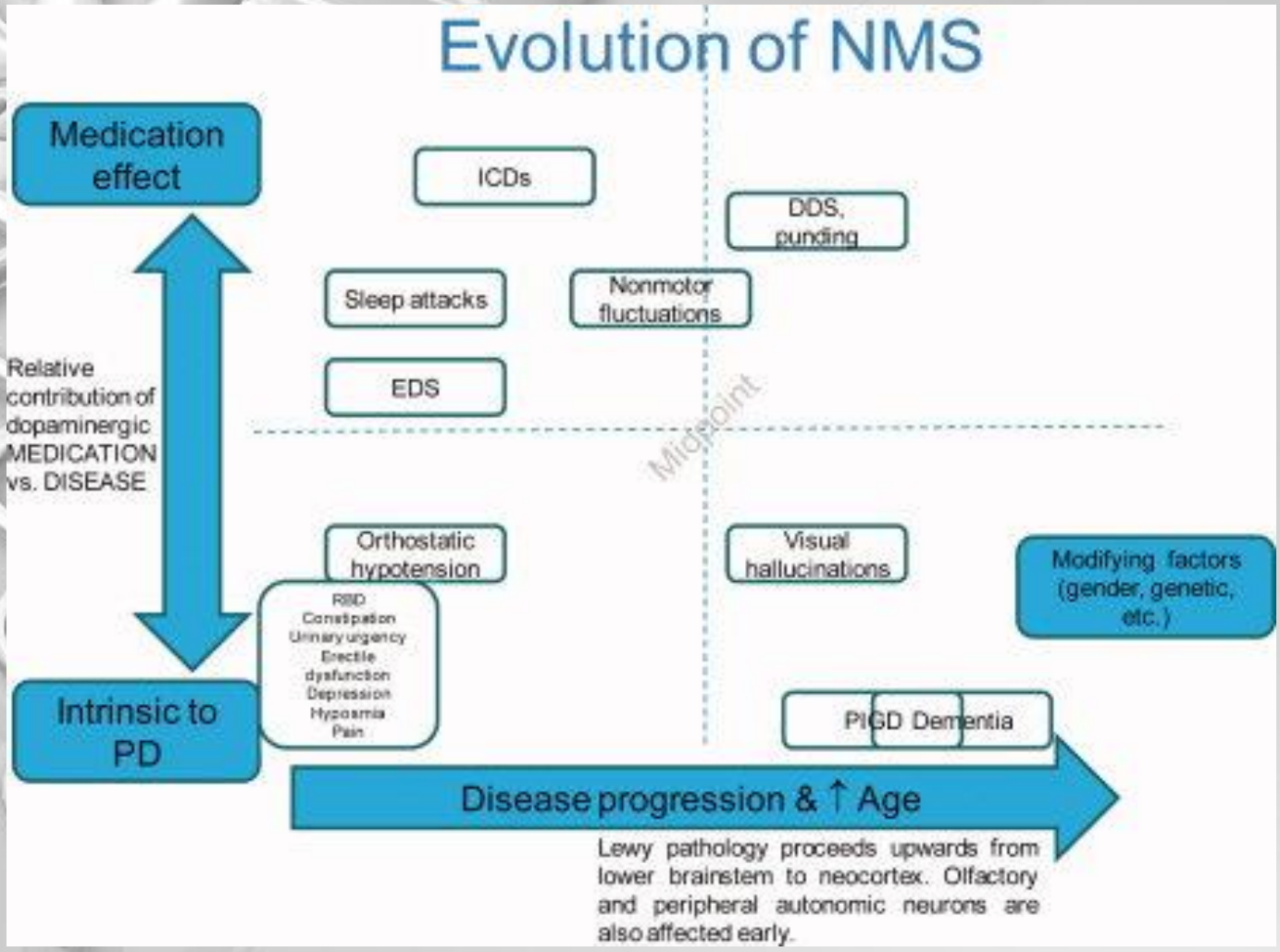


Krack P, Kumar R, Ardouin C et al. Movement Disorders 2001; 16(5): 867-75.

Non-Motor Symptoms (NMS)

Neuropsychiatric	Other
Cognitive Dysfunction	Autonomic dysfunction
Dementia	Sexual dysfunction
Depression	Olfactory dysfunction
Psychosis	Pain syndromes
Impulse control disorders	Sensory disturbance
Anxiety	Dermatologic findings
Apathy/Abulia	
REM/sleep disturbances	
Fatigue	

Clinical Attributions of Nonmotor symptoms



Lim SY, Lang AE. Movement Disorders 2010

	Never	Sometimes	Often	Always
Problems with thinking, concentration and/or memory	18.04%	48.63%	22.55%	10.78%
Loss of independence	36.44%	36.83%	13.66%	13.07%
Frustration and/or anger	19.68%	61.83%	16.10%	2.39%
Depression	30.25%	50.20%	16.53%	3.02%
Apathy	25.88%	53.42%	18.22%	2.48%
Isolation	42.68%	39.02%	14.05%	4.27%
Embarrassment in public	49.90%	40.49%	8.18%	1.43%
Impulsive behaviours	64.67%	29.74%	4.99%	0.60%
Hallucinations and/or delusions	68.26%	23.95%	6.79%	1.00%
Anxiety	16.67%	53.14%	24.12%	6.08%

Courtesy of Jean Blake, CEO, Parkinson Society British Columbia

Anxiety in Parkinson's: Unmet Needs

World Parkinson Congress in Portland, Oregon in 2016

Survey of patients and care partners re unmet needs. 33 choices given and respondees ranked top 3.

1026 responses:

141 (13.7%) ranked anxiety as top unmet need

434 (42.3%) ranked anxiety as one of top 3 unmet needs

Anxiety in Parkinson's: Unmet Needs

Parkinson's UK Priority-Setting

1000 individuals (patients, caregivers, health care and social service professionals) developed a list of unmet research needs.

Of the top 10 management research priorities, stress and anxiety ranked second after balance and falls.

Anxiety in Parkinson's: Impact

One of the strongest predictors of Parkinson's disease caregiver stress.

One of the strongest predictors of lowered quality of life in individuals living with Parkinson's disease.

One of the most effectively treated symptoms by mental health professionals.

Best Clinician Reference

REVIEW ARTICLE **OPEN**

Report from a multidisciplinary meeting on anxiety as a non-motor manifestation of Parkinson's disease

Gregory M. Pontone[1,2*], Nadeeka Dissanayaka[3,4,5], Liana Apostolova[6], Richard G. Brown[7,8], Roseanne Dobkin[9], Kathy Dujardin[10], Joseph H. Friedman[11], Albert F. G. Leentjens[12], Eric J. Lenze[13], Laura Marsh[14,15], Lynda Mari[16], Oury Monchi[17], Irene H. Richard[18], Anette Schrag[19], Antonio P. Strafella[20], Beth Vernaleo[21], Daniel Weintraub[22,23] and Zoltan Mari[24]

Anxiety is a severe problem for at least one-third of people living with Parkinson's disease (PD). Anxiety appears to have a greater adverse impact on quality of life than motor impairment. Despite its high prevalence and impact on daily life, anxiety is often undiagnosed and untreated. To better address anxiety in PD, future research must improve knowledge about the mechanism of anxiety in PD and address the lack of empirical evidence from clinical trials. In response to these challenges, the Parkinson's Foundation sponsored an expert meeting on anxiety on June 13th and 14th 2018. This paper summarizes the findings from that meeting informed by a review of the existing literature and discussions among patients, caregivers, and an international, clinician-scientist, expert panel working group. The goal is to provide recommendations to improve our understanding and treatment of anxiety in PD.

npj Parkinson's Disease (2019)5:30 ; https://doi.org/10.1038/s41531-019-0102-8

Patient Report

"I was diagnosed with Parkinson's 15 years ago when I was 43 years old. Before my diagnosis, I was a very active husband, father, son, trial lawyer, and musician. I was easygoing and not anxious about anything! Anxiety makes me feel indecisive and worsens my PD symptoms, particularly slowness and rigidity, tremor, dyskinesia, and body temperature. Anxiety produces unwarranted fear of simple things in life such as how to walk through a room, enter an elevator, airplane or train, choose a meal from the refrigerator, or select my clothing... I think it is essential for the PD community to consider anxiety and emotional needs at the same level as the motor functions since they are so intertwined and not addressing one can interfere with other interventions that might work otherwise."

Len Schwartz, person with Parkinson's

Caregiver Report

"Anxiety has pervaded every aspect of our lives, even more so than the physical manifestations of PD. It has limited our ability to interact with family and friends, entertain, shop, travel, visit public spaces and try new things. While the physical symptoms can be bad enough on their own, anxiety exacerbates them exponentially."

-Sharon Aldouby, wife and care partner

Anxiety vs Depression in Parkinson's

- PROMS-PD
  - 513 PWP assessed annually for 4 years
  - At each time point 41-46% reported clinical levels of psychological distress
  - Those with anxiety alone: 22%
  - Those with depression and anxiety: 8.6%
  - Those with depression alone: 8.9%
  - Less than 20% movement between psychologically distressed groups and no distress group over 4 years
  - Movement between anxiety alone and mixed group

Richard G Brown, Sabine Landau, John V Hindle, Jeremy R Playfer, Michael Samuel, et al.. Depression and anxiety subtypes in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry, BMJ Publishing Group, 2011, 82 (7), pp.803. 10.1136/jnnp.2010.213652 . hal-00607143

Rates of Anxiety in Parkinson's

- Up to 31% point prevalence of Parkinson's sufferers report clinically meaningful anxiety symptoms (45 studies)
- Up to 49% (min 20% reported) of patients - higher than MS and illnesses with similar physical disability
- Higher rates of social anxiety and panic disorder compared to MS, type 1 diabetes, rheumatoid arthritis with similar physical disability
- Exact rates unclear as anxiety often precedes motor onset (sometimes by as many as 20 years)

Common Types of Anxiety in Parkinson's

- Panic attacks unrelated to timing of medications
- Episodic anxiety associated with wearing off of anti-parkinsonian (dopaminomimetic) medication
- Generalized anxiety/worry
- Social anxiety (embarrassment fear)
- Simple phobias (e.g. fear of freezing, falling, choking)
- Avoidance behaviour (e.g. in anticipation of events)

Common Symptoms of Anxiety in Parkinson's Disease

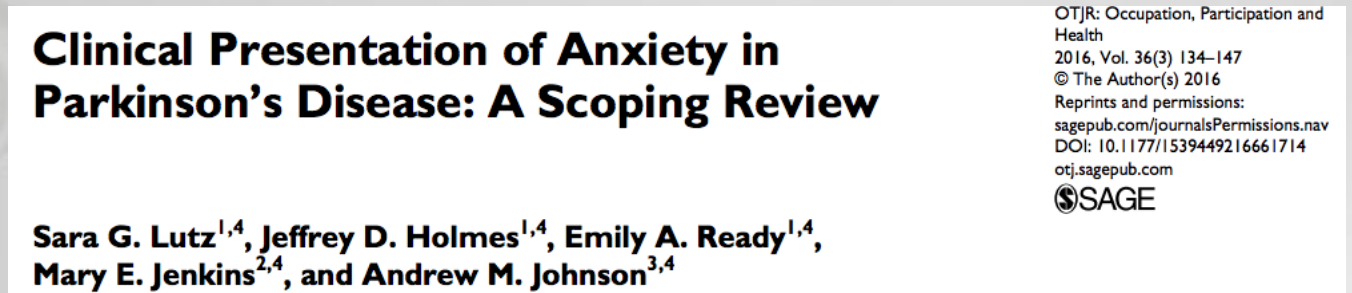
- Tension
- Restlessness
- Worry
- Generalized anxiety
- Panic
- Irritability
- Fatigue
- Slow thinking
- Poor concentration

Important Historical Data in Anxiety in Parkinson's Disease

- Personal and family history of anxiety
- Onset and course
  - Anxiety symptoms in the prodrome (preceding motor onset)
  - Anxiety symptoms arising immediately following diagnosis
  - Anxiety symptoms correlating with progressive disability
- Provoking and alleviating factors (e.g. situations)
- Associated psychiatric symptoms (e.g. depression, fatigue, insomnia, psychosis, cognitive dysfunction, ICDs)

Clinical Presentation of Anxiety in Parkinson's

- Internal tremor: distressing, subjective, and often painful sensation
- More likely to have marked bradykinesia and painful spasms/cramps and freezing of gait and motor symptom severity
- Anxiety higher in off states and in dyskinetic states
- Motor fluctuations higher in those with panic attacks and generalized anxiety
- Disturbed sleep (frequent arousals and lack of subjective restfulness)
- Fatigue, cognitive impairment, and depression all more common



Clinical Presentation of Anxiety in Parkinson's Disease: A Scoping Review

Sara G. Lutz[1,4], Jeffrey D. Holmes[1,4], Emily A. Ready[1,4], Mary E. Jenkins[2,4], and Andrew M. Johnson[3,4]

OTJR: Occupation, Participation and Health
2016, Vol. 36(3) 134–147

DOI: 10.1177/1539449216661714
otj.sagepub.com
SAGE

Risk Factors for Anxiety in Parkinson's

- Female
- History of anxiety and depression and family history of psychiatric conditions

  (NONSPECIFIC FOR PD)

- Younger age of onset for PD
- Motor fluctuations

  (ASSOCIATIONS NOT RISK FACTORS)

Risk Factors for Anxiety in Parkinson's

- Faster rate of progression
- Greater disease severity
- Postural instability gait disorder subtype
  (WORSE DISEASE)

- Dysautonomic features
- REM sleep behaviour disorder
- Larger echogenic areas in the substantia nigra
  (WORSE DISEASE IN THE BRAINSTEM)

Risk Factors for Anxiety in Parkinson's

- Psychological risk factors
  - reliance on emotion-focused coping skills (vs problem-focused)
  - perception of loss of internal and external control over disease symptoms
  - less social support
  - avoidant personality traits

Anxiety and Motor Fluctuations in PD: Chicken or Egg?

- CHICKEN (ANXIETY IS THE CAUSE)
  - On functional imaging PD patient with more anxiety demonstrate more striatum-frontal dysconnection and greater disruption of serotonin pathways.
  - Virtual reality threat paradigms can induce freezing of gait.
  - Clinically, increased anxiety and sleep disturbance precedes the subacute onset of motor fluctuations which are atypical (prolonged and more severe and sudden).

Anxiety in Parkinson's Disease: A Systematic Review of Neuroimaging Studies

Kate Perepezko, M.S.P.H., Farah Naaz, Ph.D., Carrie Wagandt, Nadeeka N. Dissanayaka, Ph.D., Zoltan Mari, M.D., Julie Nanavati, M.L.S., M.A., Arnold Bakker, Ph.D., Gregory M. Pontone, M.D., M.H.S.

J Neuropsychiatry Clin Neurosci 2021; 33:280–294;
doi: 10.1176/appi.neuropsych.20110272

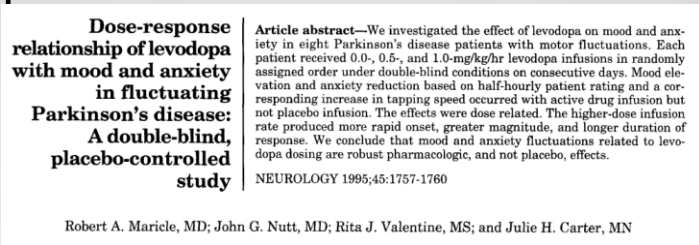
Anxiety and Motor Fluctuations in PD: Chicken or Egg?

- EGG (LOSS OF MOTOR CONTROL IS THE CAUSE)

- More severe trait anxiety linked to decreased DA uptake in the caudate at diagnose in drug naïve patients; in functional imaging studies, medication status affects task-based and resting-state amygdala-striatal connectivity.

- Dose-response relationships with levodopa infusions on mood and anxiety have been observed and compared with placebo.

- Lesions in rats that cause dopamine decrease provoke anxiety-like behaviours (however these lesions also disrupt serotonin modulation of the amygdala).



Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: A double-blind, placebo-controlled study

Article abstract—We investigated the effect of levodopa on mood and anxiety in eight Parkinson's disease patients with motor fluctuations. Each patient received 0.0-, 0.5-, and 1.0-mg/kg/hr levodopa infusions in randomly assigned order under double-blind conditions on consecutive days. Mood elevation and anxiety reduction based on half-hourly patient rating and a corresponding increase in tapping speed occurred with active drug infusion but not placebo infusion. The effects were dose related. The higher-dose infusion rate produced more rapid onset, greater magnitude, and longer duration of response. We conclude that mood and anxiety fluctuations related to levodopa dosing are robust pharmacologic, and not placebo, effects.

NEUROLOGY 1995;45:1757-1760

Robert A. Maricle, MD; John G. Nutt, MD; Rita J. Valentine, MS; and Julie H. Carter, MN

Measuring Anxiety in Parkinson's

- Assessment
  - Geriatric Anxiety Inventory
  - Parkinson Anxiety Scale (3 sections: episodic anxiety, persistent anxiety, avoidance behaviour)
  - No scales validated in dementia
  - Most other scales cannot separate depression/anxiety
  - PD Specific Anxiety Inventory under study looking at specific presentations such as anxiety during wearing off, anxiety during off, situational anxiety (with falling risk, etc)

Measuring Anxiety in Parkinson's

The Parkinson Anxiety Scale (PAS); English Version

A. Persistent Anxiety

Please mark one circle for each item below

In the past four weeks, to what extent did you experience the following symptoms

A.1. Feeling anxious or nervous

- O Not at all, or never
- O Very mild, or rarely
- O Mild, or sometimes
- O Moderate, or often
- O Severe, or (nearly) always

A.2. Feeling Tense or stressed

- O Not at all, or never
- O Very mild, or rarely
- O Mild, or sometimes
- O Moderate, or often
- O Severe, or (nearly) always

A.3. Being unable to relax

- O Not at all, or never
- O Very mild, or rarely
- O Mild, or sometimes
- O Moderate, or often
- O Severe, or (nearly) always

A.4. Excessive worrying about everyday matters

- O Not at all, or never
- O Very mild, or rarely
- O Mild, or sometimes
- O Moderate, or often
- O Severe, or (nearly) always

A.5. Fear of something bad, or even the worst, happening

- O Not at all, or never
- O Very mild, or rarely
- O Mild, or sometimes
- O Moderate, or often
- O Severe, or (nearly) always

B. Episodic Anxiety

Please mark one circle for each item below

In the past four weeks, did you experience episodes of the following symptoms?

B.1. Panic or intense fear

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

B.2. Shortness of breath

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

B.3. Heart palpitations or heart beating fast (not related to physical effort or activity)

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

B.4. Fear of losing control

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

Date:_____

C. Avoidance Behavior

Please mark one circle for each item below

In the past four weeks, to what extent did you fear or avoid the following situations?

C.1. Social situations (where one may be observed, or evaluated by others, such as speaking in public, or talking to unknown people)

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

C.2. Public setting (situations from which it may be difficult or embarrassing to escape, such as queues or lines, crowds, bridges, or public transportation)

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

C.3. Specific objects or situations (such as flying, heights, spiders or other animals, needles, or blood)

- O Never
- O Rarely
- O Sometimes
- O Often
- O Nearly Always

Anxiety Goes Untreated in Parkinson's

- 40-60% even in the most severe cohorts are receiving no treatment.
- WHY?
- COLLUSION:
  - The false belief that anxiety is a by-product of chronic disability (externalized locus of control) is shared by caregivers, professionals, and patients
  - Minimal research support due to placebo confound

Treating Anxiety in Parkinson's

- Treatment principles
  - Minimize OFF periods (COMT/MAO-B inhibitors/Sinemet CR/rotigotine)
  - Anti-parkinsonian agents do not improve anxiety (e.g. sinemet)
  - Anti-parkinsonian agents may provoke initially (in up to 20%)
  - Understand the underlying source of anxiety or situations provoking anxiety and use cognitive-behavioural therapy to diminish apprehension
  - Medications
    - Enhancing dopamine replacement does not alleviate anxiety
    - Anxiolytics are often poorly tolerated (high degrees of medication sensitivity)

Treating Anxiety in Parkinson's

- Cognitive-Behavioural Therapy
  - Gold standard in non-Parkinson's populations
  - Few single-case and open label studies in PD and 1 controlled trial
  - Basics
    - Limit avoidance
    - Slowly do more of what you fear
    - Limit catastrophizing and dread
    - Neutral probability estimates of a negative outcome
    - Involve caregivers
  - Controlled trial of 10 weekly sessions showed benefit on PAS with respect to episodic situational anxiety, avoidance behaviour, and social anxiety at 3 and 6 months

Movement Disorders / Early View

Research Article | Open Access

Cognitive Behavioral Therapy for Anxiety in Parkinson's Disease: A Randomized Controlled Trial

Anja J.H. Moonen PhD, Anne E.P. Mulders PhD, Luc Defebvre MD, PhD, Annelien Duits PhD, Bérengère Flinois MSc, Sebastian Köhler PhD, Mark L. Kuijf MD, PhD, Anne-Claire Leterme Dominique Servant, Marjolein de Vugt PhD, Kathy Dujardin PhD, Albert F.G. Leentjens MD, PhD

... See fewer authors

First published: 22 February 2021

Treating Anxiety in Parkinson's

- Other therapies
  - Yoga and mindfulness
    - Limited data but no harm
  - Non-invasive brain stimulation techniques: rTMS; tDCS; ECT
  - Invasive brain stimulation techniques: DBS

Letter to the Editor: Successful Use of Electroconvulsive Therapy for Refractory Anxiety in Parkinson's Disease

Louis Marino & Joseph H. Friedman

To cite this article: Louis Marino & Joseph H. Friedman (2012) Letter to the Editor: Successful Use of Electroconvulsive Therapy for Refractory Anxiety in Parkinson's Disease, International Journal of Neuroscience, 123:1, 70-71, DOI: 10.3109/00207454.2012.726300

Treating Anxiety in Parkinson's

- Pharmacological Treatments
  - Serotonergic medications
  - No DBPCTs
  - In ATDP trials for PD depression, paroxetine, venlafaxine, desipramine, citalopram did not show significant effect on benefit secondarily for anxiety (but TCAs and SSRIs show modest effect size)

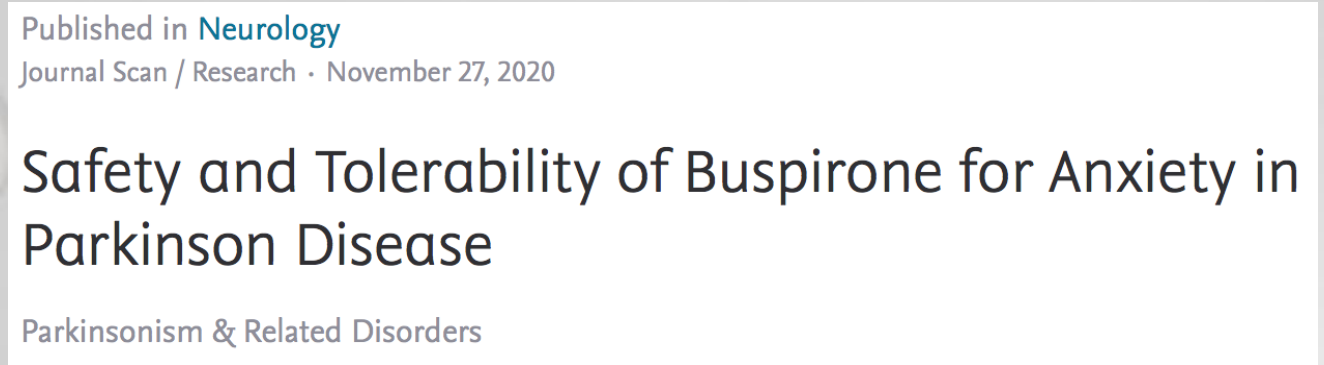
Pharmacological interventions for anxiety in Parkinson's disease sufferers

Hideyuki Sawada, Atsushi Umemura, Masayuki Kohsaka, Satoshi Tomita, Kwiyoung Park, Tomoko Oeda & Kenji Yamamoto ...show less

Pages 1071-1076 | Received 02 Apr 2018, Accepted 04 Jun 2018, Published online: 25 Jun 2018

Treating Anxiety in Parkinson's

- Pharmacological Treatments
  - Serotonergic medications
  - Buspirone (15 mg/day) worsened motor function (and pain) and was poorly tolerated in combination with other anxiolytics but improved anxiety scores
  - Gold standard therapy with CBT for non-PD anxiety: high dose SSRI or SNRI or serotonergic medication


Published in Neurology

Journal Scan / Research · November 27, 2020

Safety and Tolerability of Buspirone for Anxiety in Parkinson Disease

Parkinsonism & Related Disorders

Treating Anxiety in Parkinson's

- Pharmacological Treatments
  - Benzodiazepines
  - Side effects of sedation, cognitive impairment, and imbalance
  - Risk of tolerance
  - Highly effective for short-term use

[Treatment of anxiety in Parkinson's disease with bromazepam].

M. Casacchia, A. Zamponi, G. Squitieri, G. Meco less • Published 1 July 1975 • Medicine • Rivista di neurologia

Treating Anxiety in Parkinson's

- Pharmacological Treatments
  - Cannabinoids
  - Physicians can prescribe nabilone (a THC analogue) with risk of sedation only (0.5 mg bid up to 2 mg tid)
  - One trial in PD: 300 mg CBD subjects significant decrease in anxiety during public speaking paradigm and decreased tremor amplitude in anxiety-provoking situation

Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease

Stephanie Martins de Faria, Daiene de Morais Fabrício, Vitor Tumas, Paula Costa Castro, Moacir Antonelli Ponti, Jaime EC Hallak, Antonio W Zuardi, José Alexandre S Crippa, Marcos Hortes Nisihara Chagas

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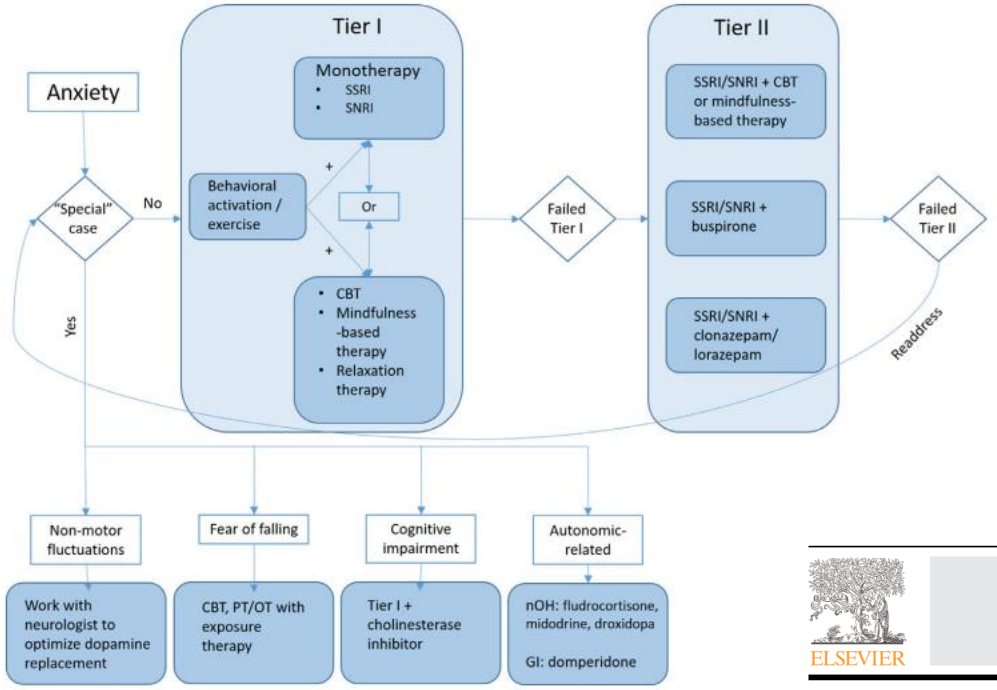
First Published January 7, 2020 | Research Article | Find in PubMed | Check for updates


Systematic Reviews
Randomized Controlled Trials
Cohort Studies
Case-Control Studies
Case Series, Case Reports
Editorials, Expert Opinion

Treating Anxiety in Parkinson's

- Suggested Treatment Algorithm

FIGURE 2. Suggested algorithm for management of anxiety in Parkinson's disease. SSRI: serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; CBT: cognitive-behavioral therapy; PT: physical therapy; OT: occupational therapy; nOH: neurogenic orthostatic hypotension; GI: gastrointestinal symptoms.



Am J of Geriatric Psychiatry 29:6 (2021) 530–540

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journal homepage: www.ajgponline.org

Treatment in Geriatric Mental Health: Research in Action

Optimal Treatment of Depression and Anxiety in Parkinson's Disease

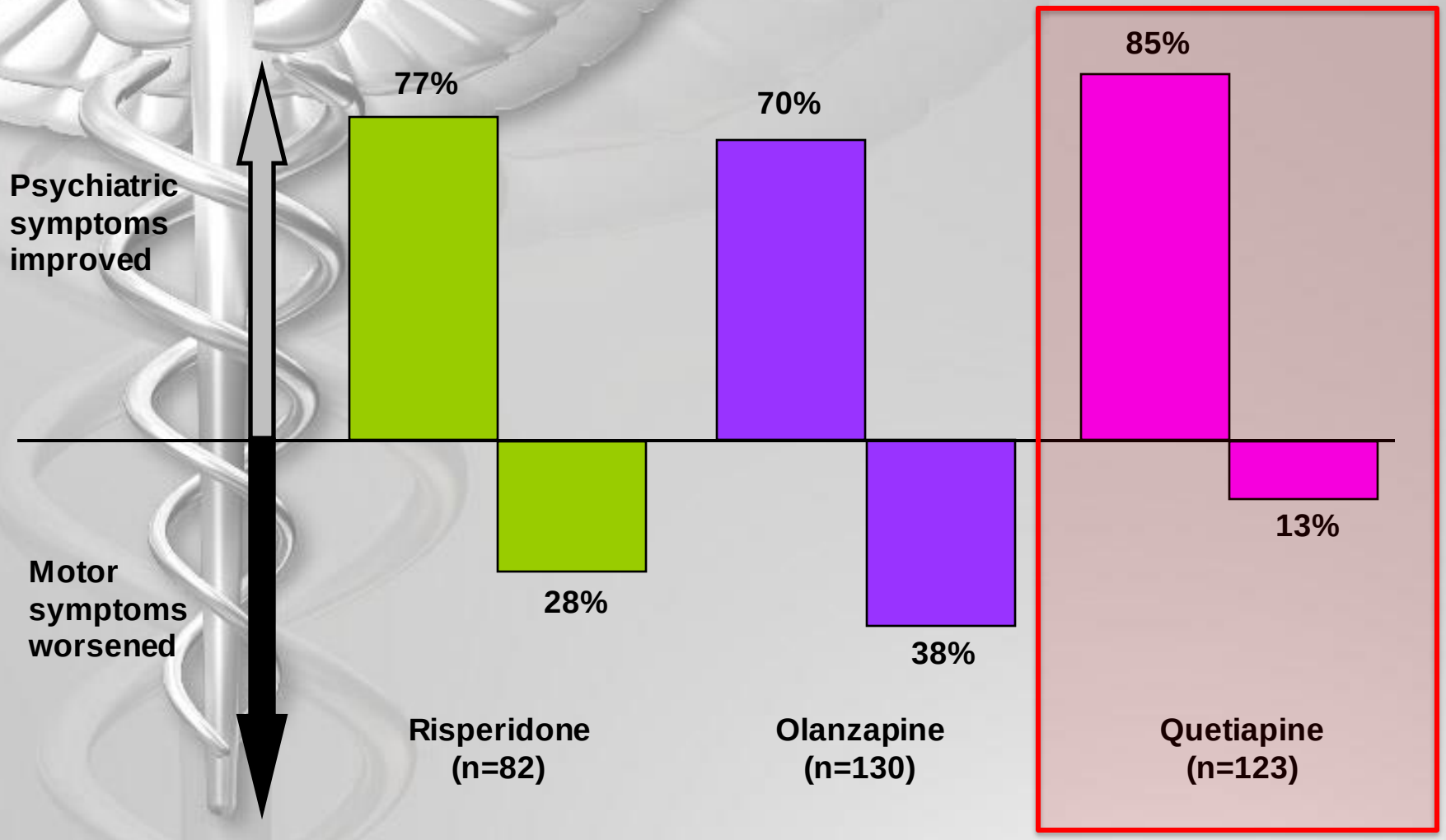
Gregory M. Pontone, M.D., M.H.S., Kelly A. Mills, M.D., M.H.S.

Treating Anxiety in Parkinson's

- How about antipsychotics (major tranquilizers)?
  - By far the most effective anxiolytics prescribed by psychiatrists
  - One one trial reported in PD back in 1966 using fluphenazine
  - These agents conventionally worsen motor symptoms in PD

Strang, R.R.
The treatment of the 'anxiety-tension syndrome', in Parkinson's disease with fluphenazine (pacinol). *Acta Neurologica et Psychiatrica Belgica*, **66**(3):218-222, March 1966. Abs:Excerpta Medica, Section 8B 20(3):No.903, March 1967. 0 Refs. (Clin. Study). Eng. Belgium.

Atypical antipsychotics in Parkinson's disease



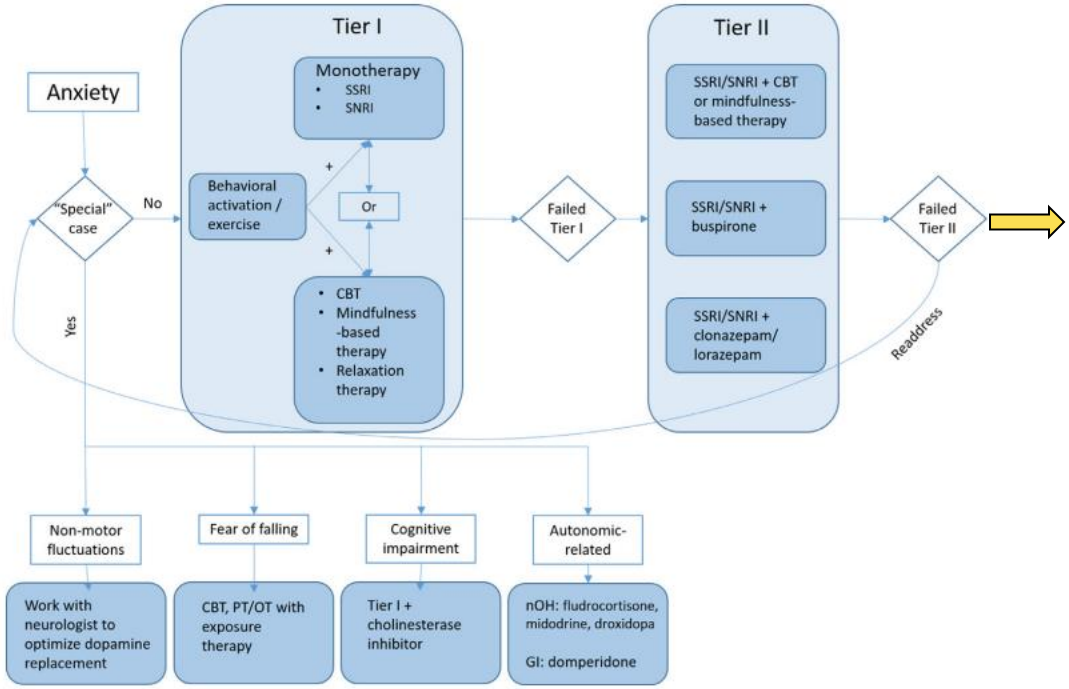
Data from Friedman & Factor 2000

Antipsychotics in Parkinson's

- How about antipsychotics (major tranquilizers)?
  - Quetiapine is a highly effective anxiolytic
  - Quetiapine starts 12.5 mg or even 6.25 mg at bedtime and effective anxiolytic doses are between 50 and 150 mg daily
  - There is an extended release version which is not covered by pharmacare
  - It can exacerbate constipation and thereby worsen mobility by worsening motility
  - Other side effects may include sedation, dizziness, and weight gain

Treatment Algorithm Addendum

FIGURE 2. Suggested algorithm for management of anxiety in Parkinson's disease. SSRI: serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; CBT: cognitive-behavioral therapy; PT: physical therapy; OT: occupational therapy; nOH: neurogenic orthostatic hypotension; GI: gastrointestinal symptoms.



Quetiapine trial and psychiatric referral for consideration of alternate therapies

Under Investigation Internationally

- Other behavioural therapies
  - Mindfulness
  - Yoga
  - Meditation
  - CBT
- Psilocybin
- Cannabinoids
- Probiotics

Under Investigation at Pacific Parkinson's Research Group

Protocol Number	*TAP-05*
Phase	*Phase 2*
Design	*A 12-week randomized, triple-blind, placebo controlled clinical trial of* Ecologic® BARRIER *probiotics in anxiety in Parkinson's disease (PD)*
Study Duration	*13 weeks per subject/18 months for completion of study*
Study Centres	*Djavad Mowafaghian Centre for Brain Health, University of British Columbia, BC*
Objectives	*To assess the effects of probiotics on anxiety symptoms in PD and to monitor changes to the gut microbiome*
Number of Subjects	*72*
Diagnosis and Main Inclusion Criteria	– *Age 40-80 years* – *Confirmed diagnosis of Parkinson's disease (based on* Queen Square *Brain Bank criteria)* – *Mild to moderate PD (Hoehn and Yahr score of 1-3)* – *Anxiety score (*PAS) of ≥14
Study Product, Dose, Route, Regimen	*Ecologic® BARRIER 849 (*Maize starch, maltodextrin, vegetable protein, potassium chloride, +/- probiotic bacteria (B. bifidum W23, B. lactis W51, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, Lc. lactis W19, Lc. lactis W58; ≥ 2,5*10^9 cfu/g), magnesium sulphate, manganese sulphate.*) sachet, two times daily dosing for a total of 2 grams twice a day (viable cell count of 2.5 × 10^9 CFU/gram) per day*
Duration of	*Total exposure of 12 weeks of treatment for each subject to complete per*

Don't suffer unnecessarily

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