Complementary and Alternative Medicine and Exercise in Nonmotor Symptoms of Parkinson’s Disease

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Abstract

The use of complementary and alternative medicine (CAM) therapy in nonmotor symptoms (NMS) for Parkinson disease (PD) is growing worldwide. Well-performed, systematic evidence-based research is largely lacking in this area and many studies include various forms of CAM with small patient numbers and a lack of standardization of the approaches studied. Taichi, Qigong, dance, yoga, mindfulness, acupuncture, and other CAM therapies are reviewed and there is some evidence for the following: Taichi in sleep and PDQ39; dance in cognition, apathy, and a mild trend to improved fatigue; yoga in PDQ39; and acupuncture in depression, PDQ39, and sleep.
Exercise including occupational therapy (OT) and physical therapy (PT) has been studied in motor symptoms of PD and balance but only with small studies with a mounting evidence base for use of exercise in NMS of PD including PDQ39, sleep, fatigue, depression, and some subsets of cognition. Studies of OT and PT largely show some benefit to depression, apathy, and anxiety. Sustainability of an improvement has not been shown given short duration of follow up. Finding optimal control groups and blind for these interventions is also an issue. This is a very important area of study since patients want to be self-empowered and they want guidance on which form of exercise is the best. Additionally, evidence for PT and OT in NMS would give added weight to get these interventions covered through medical insurance.

ABBREVIATIONS

AS  Apathy Scale
BAI  Beck Anxiety Index
BDI  Beck Depression Inventory
Brooks spatial task
ESS  Epworth Sleep Scale
EWB  emotional well-being score
FAB  frontal assessment battery
Flanker task
FSS  Fatigue Severity Scale
GDS  Geriatric Depression Scale
HADS  Hospital Anxiety and Depression Scale
HAM-D  Hamilton Rating Scale for Depression
Krups Fatigue Scale
LARS  Lille Apathy Rating Scale
LPDQ  Levine–Pilowsky Depression Questionnaire
MADRS  Montgomery–Asberg Depression Rating Scale
MAQ  Multidimensional Anxiety Questionnaire
MoCA  Montreal Cognitive Assessment
MRT  mental rotation task
NMSS  Nonmotor Symptoms Scale
PDQ8  Parkinson Disease Questionnaire Short Form (PDQ8)
PDQ39  Parkinson Disease Questionnaire (PDQ39) Bodily Discomfort, Mobility, Activities of Daily Living, Emotional Well Being, Communication, Cognitive Impairment, Stigma, and Social Support
PDSS  PD Sleep Scale
PFS-16  Parkinson Disease Fatigue Scale
PRM  pattern recognition memory
rev. Corsi block
SDS  Zung Self-Rating Depression Scale
SES  Self-Efficacy Scale
SF-12  12-item short form health survey
SF-36  QOL Short Form Health Survey (SF-36)
SRM  spatial recognition memory
There is an increasing interest in the use of CAM in patients with PD worldwide. A 2001 survey of outpatient PD clinics in the United States found that 40% of patients were using CAM therapies (Rajendran, Thompson, & Reich, 2001) compared to 60% in Dublin, Ireland in 2008 (Murphy, Rogers, Hutchinson, & Tubridy, 2008), and 61% in Singapore in 2006 (Tan, Lau, Jamora, & Chan, 2006). CAM therapy is even more commonly sought out in Korea where up to 76% sought out CAM treatments in 2012 (Kim & Jeon, 2012), in contrast to 38% in Argentina in 2010 (Pecci et al., 2010) and 46% in India in 2016 (Pandit et al., 2016).

CAM is a broad term that is made up of a number of unrelated treatments and practices but globally may be connected with a holistic approach to wellness. The National Center for Complementary and Alternative Medicine (NCCAM) classifies CAM interventions into (1) natural products such as herbals, vitamins, minerals, and probiotics; (2) mind body practices such as acupuncture, massage, meditation, movement therapies, relaxation techniques, Tai Chi, and Yoga; and (3) alternative systems such as Chinese medicine, homeopathy, or Ayurveda. Over $14 billion dollars per year are spent on CAM therapy in the United States alone. There has been a good review by Bega in 2014 (Bega & Zadikoff, 2014) on motor issues in PD and CAM. In this review, we will focus on CAM therapies and their effects on NMS in PD.

1.1 Qigong and Taichi in NMS of PD

Tai Chi is an ancient Chinese martial arts tradition combining deep breaths and relaxation with slow movements that are fluid with some holding of postures. Tai Chi has been found to be both safe and feasible in PD patients.
Referring to Table 1, three trials compared forms of Tai Chi to controls looking largely at PDQ39 and some cognitive measures. Kurt et al. (2017) had 40 patients randomized to Aichi vs land-based exercise for 5 weeks and found improved PDQ39. Nocera et al. (2013) studied 16 patients doing Taichi vs 5 control patients for 16 weeks and found improved PDQ39 total and in the emotional well-being score (EWB) but not in digit span, verbal fluency, Stroop, or trail A and B tests. Li et al. (2014) randomized patients to Taichi vs resistance training vs stretching and showed improved vitality plus scale and PDQ8.

Qigong is an older practice and a predecessor to Taichi. The focus is on meditation and slow movement. Referring to Table 1, there are four studies that looked at Qigong with nonmotor measures ranging from sleep, fatigue, depression, cognition, and PDQ39. Three out of four studies were controlled studies. Schmitz-Hubsch et al. (2006) studied 56 patients, 32 in qigong and 24 in a control group. Qigong was performed for 90 min sessions over 6 months. There were some issues with the study design but there was no clear improvement in Montgomery–Asberg Depression Rating Scale (MADRS) and PDQ39 in this study. There was a trend to improved daytime sleepiness and constipation in the Qigong group. Xiao and Zhuang (2016) studied Qigong in 100 patients randomized to Qigong plus walking vs walking alone. There was an improvement in the PD sleep scale (PDSS) but not in the PD fatigue scale (PFS-16). Burini et al. (2006) studied Qigong in a randomized control trial with crossover design in 26 patients. There were no differences seen in BDI, fatigue, or PDQ39 with this trial. Wassom et al. (2015) did a small trial with pre- and posttest comparison with a 6-week Qigong intervention. There was a mild change in sleep scale but not in other PDQ39, EWB, digit span, verbal fluency, Stroop, or trails A and B.

As a summary, Taichi has some increasing evidence in helping sleep and PDQ39 and 8.

### 1.2 Dance in NMS of PD

The broad classification of dance includes many forms of movement that may involve individual, partnered, or group dancing and is enriched by aspects of social engagement and music.

Tango dance includes complex movement, social interaction, and incorporates challenging movements from a balance, cognitive, and motor learning standpoint. Referring to Table 2, there were six trials of Tango looking
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz-Hubsch et al. (2006)</td>
<td>56 patients—32 patients vs 24 controls</td>
<td>Qigong 90 min, weekly for 2 month Then 2 month pause, then 2 month Qigong; control no treatment</td>
<td>MADRS PDQ39</td>
<td>No improvement in these measures? improved constipation and daytime sleeping in QG group</td>
</tr>
<tr>
<td>Xiao and Zhuang (2016)</td>
<td>100 patients</td>
<td>Qigong baduanjin 45 min 4 ×/week + daily walking 30 min vs walking only for 6 months</td>
<td>PDSS-2 PFS-16</td>
<td>PDSS-2 improved</td>
</tr>
<tr>
<td>Burini et al. (2006)</td>
<td>26 patients—active treatment (AT) 1 + Qigong (QG) 2 or QG1 + AT2 (20 sessions each with 2 month interval)</td>
<td>Qigong 3 ×/week, 7 week RCT crossover</td>
<td>BDI Fatigue PDQ39</td>
<td>No difference in these measures</td>
</tr>
<tr>
<td>Wassom, Lyons, Pahwa, and Liu (2015)</td>
<td>7 patients</td>
<td>Qigong-6 week Pre- and posttest comparison</td>
<td>PDSS PDQ39 EWB</td>
<td>Mild change in PDSS, not in others</td>
</tr>
<tr>
<td>Kurt, Buyukturan, Buyukturan, Erdem, and Tuncay (2017)</td>
<td>40 patients</td>
<td>Aichi vs land-based exercise; 5 weeks</td>
<td>PDQ39</td>
<td>Better in Ai-chi group</td>
</tr>
<tr>
<td>Nocera, Amano, Vallabhajosula, and Hass (2013)</td>
<td>21 patients</td>
<td>15 Taichi, 6 controls 60 min Taichi 3 ×/week; 16 week Taichi</td>
<td>PDQ39 EWB Digit span Verbal fluency Stroop Trails A and B</td>
<td>PDQ39 total and emotional well-being Improved in Taichi group Not the other measures</td>
</tr>
<tr>
<td>Li et al. (2014)</td>
<td>195 patients</td>
<td>60 min 2 ×/week, 24 weeks, RCT Taichi vs resistance vs stretching</td>
<td>PDQ8 Vitality plus scale</td>
<td>PDQ8 and VPS improved in Taichi group</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Number of Patients/Arms</td>
<td>Intervention Description</td>
<td>Nonmotor Measures</td>
<td>Outcome of Study</td>
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<tr>
<td>Rios Romenets, Anang, Fereshtehnejad, Pelletier, and Postuma (2015)</td>
<td>33 patients</td>
<td>Tango vs self-directed exercise 2×/week 12 week, 1 h, RCT</td>
<td>MOCA BDI Krups fatigue SS AS PDQ39</td>
<td>MOCA and Fatigue Severity Scale (FSS) nonsignificant trend to improvement in tango group</td>
</tr>
<tr>
<td>Hackney and Earhart (2009b)</td>
<td></td>
<td>Tango/ ballroom vs Taichi 13 weeks, 2×/week, 60 min</td>
<td>PDQ39</td>
<td>Improved social support PDQ39 SI with tango and not others including control</td>
</tr>
<tr>
<td>Duncan and Earhart (2014) Tango vs none 10 patients</td>
<td></td>
<td>Tango-12 week, 1 h, 2×/week, 2 years RCT</td>
<td>UPDRS2</td>
<td>UPDRS 2 improved</td>
</tr>
<tr>
<td>McKee and Hackney (2013) 33 patients—24 vs 9</td>
<td></td>
<td>Tango vs group lecture</td>
<td>PDQ39 BDI MOCA SF-12 FAB Rev. Corsi block Brooks spatial task</td>
<td>Improved executive function/spatial cognition-Brooks and FAB</td>
</tr>
<tr>
<td>Hashimoto, Takabatake, Miyaguchi, Nakanishi, and Naitou (2015) 46 patients</td>
<td></td>
<td>Dance 60 min, 1 time per week 12 week vs control</td>
<td>Mood/AS FAB MRT (mental rotation task) Self-rated depression scale</td>
<td>Improved AS and SDS</td>
</tr>
<tr>
<td>Volpe, Signorini, Marchetto, Lynch, and Morris (2013) 24 patients</td>
<td></td>
<td>Irish set vs PT 6 months, 1 time per week, 90 min</td>
<td>PDQ39</td>
<td>No difference in PDQ39</td>
</tr>
</tbody>
</table>
at a range of NMS including depression, apathy, PDQ39, and cognitive measures. Rios Romenets et al. (2015) randomized 33 patients to tango vs self-directed exercise for 12 weeks and found that there was a trend to improved Montreal Cognitive Assessment (MOCA) and Krups fatigue scale. There was no change in BDI, Apathy Scale (AS), or PDQ39. Hackney and Earhart (2009a) studied tango/ballroom dance compared to Taichi for 13 weeks and found that PDQ39 social isolation was improved with tango but no other parts of the PDQ39. Duncan and Earhart (2014) studied 10 patients randomized to tango vs usual activity for 12 weeks. The UPDRS 2 scale improved with the tango group. McKee and Hackney (2013) studied 33 patients who were randomized to 24 weeks of tango vs 9 patients who attended lectures. The tango group had improved executive function on frontal assessment battery (FAB) and spatial cognition on Brooks spatial task. Hashimoto et al. (2015) studied 46 patients with dance vs a control and showed improved apathy on the AS and self-reported depression on the Zung Self-Rating Depression Scale (SDS). No changes were seen on mood scale, mental rotation task, or FAB. Volpe et al. (2013) studied 24 patients with Irish set dancing vs physical therapy (PT) for 6 months. There was no difference in the groups with PDQ39. Dance appears to have some evidence in cognition, apathy, and mild trend to improved fatigue.

1.3 Yoga/Mindfulness on NMS in PD

Yoga is a unique exercise/CAM therapy which includes movement, breath work, and meditation. It is part of the ancient Ayurvedic tradition and has been around for over 2000 years. There have been four trials in yoga only three of which have controls looking at mood and PDQ39. Sharma, Robbins, Wagner, and Colgrove (2015) did a RCT of yoga vs control with measures of SF-36 depression, QOL, and Geriatric Depression Scale (GDS). The only positive result was in SF-36 depression. Ni studied 26 patients randomized to power yoga vs control. There was an improvement in PDQ39. Bega, Gonzalez-Latapi, Zadikoff, and Simuni (2014) did a study on yoga vs resistance training in a small group of PD patients. There was no change in PDQ39 in this study that had a large dropout rate. Boulgarides, Barakatt, and Coleman–Salgado (2014) did an 8-week yoga intervention with pre- and postintervention scales. There was an improvement in the Hospital Anxiety and Depression Scale (HADS).
Mindfulness is a form of meditation and is an approach that is reproducible and easily taught. It’s feasibility in the PD population is only recently being explored. Mindfulness was studied in a small study by Advocat et al. (2016) with 24 patients vs 33 patients on a wait list control. There was a significant improvement in PDQ39 ADL and a trend to improvement in PDQ39SI. Yoga may help PDQ39 and mood (Table 3).

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma et al. (2015)</td>
<td>8 patients and 5 controls</td>
<td>Yoga–RCT 2 ×/week, 12 weeks</td>
<td>QOL SF36-depression GDS</td>
<td>Significant improvement in PDQ39-ADL</td>
</tr>
<tr>
<td>Ni et al. (2016)</td>
<td>26 patients</td>
<td>Power Yoga–RCT Yoga 3 months 2 ×/week</td>
<td>PDQ39</td>
<td>PDQ39 overall improved score</td>
</tr>
<tr>
<td>Bega et al. (2016)</td>
<td>17 patients</td>
<td>Yoga vs resistance exercise—12 weeks, 2 ×/week, 1 h</td>
<td>PDQ39</td>
<td>No difference in groups</td>
</tr>
<tr>
<td>Boulgarides et al. (2014)</td>
<td>10 patients</td>
<td>Yoga—8 week yoga pre- and postcomparison</td>
<td>HADS</td>
<td>Improved HADS depression subscale</td>
</tr>
<tr>
<td>Advocat et al. (2016)</td>
<td></td>
<td>Mindfulness—6 weeks vs wait list control—24/35 vs 33/37</td>
<td>PDQ39</td>
<td>Significant improvement in PDQ39-ADL</td>
</tr>
</tbody>
</table>

1.4 Miscellaneous CAM Interventions on NMS in PD

Active theater was studied by Modugno et al. (2010) vs PT in 20 patients. Epworth sleep scale (ESS), PDQ39, HADS, and UPDRS2 were measured. There was an improvement in all of these measures.

Music therapy has been implicated in imaging improvements in fMRI gray matter volume in motor and auditory cortex in animal and human studies, music is shown to release neurochemicals and hormones. Increased
limbic activity in the orbitofrontal cortex and increased mesolimbic dopamine release has been triggered by music. Pleasant music in particular has been shown to increase PET and fMRI in the nucleus accumbens and midbrain nuclei that can inhibit pain. Thus, music therapy has been of interest in treating NMS in PD patients.

Music therapy was studied in three studies, two of which had controls and looked at mood, QOL, and PDQ39. Pacchetti et al. (2000) studied 32 patients with 3 month of musical therapy vs controls. They studied QOL and a happiness measure which both improved. Elefant, Baker, Lotan, Lagesen, and Skeie (2012) studied a 20-week active music therapy intervention with a single 1 h session per week in 10 patients on MADRS depression and anxiety scores and did not show a change. A drum circle randomized control trial study for 6 weeks in 10 patients vs 10 control patients showed improved PDQ39 but not depression in the GDS by Pantelyat, Syres, Reichwein, and Willis (2016).

Donoyama and Ohkoshi (2012) and Donoyama, Suoh, and Ohkoshi (2014) studied Japanese Massage for 30 min in a single patient and showed improved pain on a visual analog scale. This study did not have a control. Brefel studied spa therapy in 31 PD patients randomized to early vs late spa therapy for 3 weeks including massage and PT. They found that PDQ39, SF-36, GHQ-28 improved right after intervention but this was not sustained at 20 weeks. Johns, Blake, and Sinclair (2010) looked at PDQ39 (Brefel-Courbon et al., 2003) pre and post 8 reflexology sessions in 16 PD patients and showed improvement. The Alexander technique uses hand contact to assess and manipulate changes in muscle activity. Stallibrass, Sissons, and Chalmers (2002) studied Alexander technique vs massage vs control. They used BDI at a 6-month follow up and the attitudes to self-scale. Both of these scales improved with the Alexander technique.

Cash and Lageman (2015) studied expressive writing vs nonexpressive writing in 28 patient and 15 caregivers of PD patients. He found that there was improved anxiety in both groups regardless of type of writing. Combs et al. (2011) studied boxing drills (with a bit of stretching, strength, and endurance) in a case series of six patients. There was no control group. There is improved PDQOL with boxing. Herz et al. (2013) studied Wi playing over 4 weeks for three sessions per week including two games of tennis and bowling and one game of boxing per session. There was improved PDQ39 and a trend toward improved HAM.
Nordic walking was studied in two studies looking at nonmotor issues. Cugusi et al. (2015) studied 20 patients with Nordic walking for 12 weeks and measured PFS-16, Beck Depression Inventory-II (BDI-II), Starkstein Apathy Scale, and Nonmotor Symptoms Scale (NMSS), and PDQ8. There was an improvement in PFS-16, BDI-II, SAS, PDQ8, and NMSS. Reuter et al. (2011) studied Nordic walking vs walking/flexibility exercises in 90 patients in a RTC for 6 months, 3 times per week for 70 min sessions. There was no difference between groups in the PDQ39 (Table 4).

1.5 Acupuncture for NMS in PD

There are 11 studies looking at acupuncture, only 1 of which had a sham control, 7 had a control group that did not get an intervention, and 3 had pre- and postintervention measures. Referring to Table 5, these studies looked at sleep, fatigue, PDQ39, anxiety depression, and some looked at bladder function and constipation. Eng et al. (2006) studied Tuina massage/acupuncture/instrument-delivered Qigong in 25 patients for 6 months with improved BDI and PDQ39 pre- vs postintervention. Shulman et al. (2002) did an open label trial on 20 patients and showed improved sleep and rest. Looking at the RCTs, Christian did a RCT with acupuncture in 14 patients looking at PDQ8, PDQ39, and GDS with no significant change in these measures. Chen, Zhang, Li, and Holscher (2015) studied 40 patients with acupuncture 2 times per week along with Western medicine vs Western medicine alone for 18 weeks and 36 weeks in 13 patients. They studied BDI-II, Beck Anxiety Index (BAI), WHOqol, and UPDRS and showed improvements in the BDI-II, WHOqol, and UPDRS-mind, behave, and mood. Cho et al. (2012) studied 22 patients in a randomized single blind control trial looking at BDI and PDQOL and showed improved BDI. Zhang et al. (2015) did a RCT for 8 weeks with acupuncture + madopar/tolteridine (M/T) vs M/T alone and showed improved bladder function in the acupuncture group. Kluger et al. (2016) did a study on 94 patients with acupuncture vs sham acupuncture 2 times per week for 6 months. He found no difference in the modified fatigue impact scale between the groups but both groups improved on this measure. Acupuncture may help depression, PDQ39, and sleep.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modugno et al. (2010)</td>
<td>40 patients</td>
<td>20 patients in active theater vs 10 patients in PT vs 10 patients in control group 3 years</td>
<td>PDQ39, ESS, HADS, UPDRS1</td>
<td>PDQ39 scale, Epworth sleepiness scale, and Hamilton depression, UPDRS 1 improvement; improved daytime sleepiness, depression</td>
</tr>
<tr>
<td>Donoyama and Ohkoshi (2012)</td>
<td>1 patient</td>
<td>Massage Japanese 30 min</td>
<td>Visual analog scale for pain</td>
<td>Pain improved by this scale</td>
</tr>
<tr>
<td>Brefel-Courbon et al. (2003)</td>
<td>31 patients</td>
<td>Spa therapy—massage daily/physical therapy × 3 weeks, delayed start in other group RCT</td>
<td>PDQ39, SF-36, GHQ-28</td>
<td>PDQ39 improved SF-36 improved GHQ-28 improved at week 4 but not sustained improvement at 20 weeks</td>
</tr>
<tr>
<td>Johns et al. (2010)</td>
<td>16 patients</td>
<td>Reflexology—pre- and posttreatment 8 treatment sessions</td>
<td>PDQ39</td>
<td>PDQ39 improved</td>
</tr>
<tr>
<td>Pacchetti et al. (2000)</td>
<td>32 patients</td>
<td>Music 3 months RCT</td>
<td>QOL, Happiness measure</td>
<td>Happiness measure; QOL improved</td>
</tr>
<tr>
<td>Elefant et al. (2012)</td>
<td>10 patients</td>
<td>Music—60 min, once per week, 20 weeks</td>
<td>MADRS</td>
<td>No change in MADRS at 10 weeks or 20 weeks</td>
</tr>
<tr>
<td>Pantelyat et al. (2016)</td>
<td>20 patients</td>
<td>Drum circle—6 weeks; 10 patients vs 10 controls</td>
<td>PDQ39, GDS</td>
<td>PDQ39 improved No mood change</td>
</tr>
<tr>
<td>Cugusi et al. (2015)</td>
<td>20 patients</td>
<td>Nordic walking 2 ×/week, 1 h, 12 weeks</td>
<td>PFS-16, Beck Depression Inventory-II, Starkstein AS, and NMSS, PDQ8</td>
<td>PFS-16, BDI-II, SAS, PDQ8, NMSS improved No other scales</td>
</tr>
</tbody>
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Continued
2. PART 2: EXERCISE ON NMS IN PD

There have been various areas of investigation in the nonmotor realm in PD using exercise. Here we describe exercise not largely using PT or occupational therapy (OT) guidance. Many of these interventions involve group classes with a personal trainer guiding the class. Studies have looked...
Table 5  Acupuncture for NMS in PD

<table>
<thead>
<tr>
<th>Author/Year</th>
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<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eng, Lyons, Greene, and Pahwa (2006)</td>
<td>25 patients</td>
<td>6 months Tuina massage, Acupuncture, QIGONG instrument pre- and postintervention</td>
<td>BDI PDQ39</td>
<td>BDI and PDQ39 improvement</td>
</tr>
<tr>
<td>Shulman et al. (2002)</td>
<td>20 patients</td>
<td>Open label</td>
<td>Anecdotal sleep and rest reports</td>
<td>Improved sleep and rest</td>
</tr>
<tr>
<td>Cristian, Katz, Cutrone, and Walker (2005)</td>
<td>14 patients</td>
<td>RCT of acupuncture vs no treatment</td>
<td>PDQ8 PD39 GDS</td>
<td>No significant change in these measures</td>
</tr>
<tr>
<td>Chen, Change, et al. (2015)</td>
<td>40 patients</td>
<td>40 patients, 2×/week vs Western medicine only for 18 weeks, 13 patients had acupuncture for 36 week RCT</td>
<td>BDI-II BAI WHOqol UPDRS-MBM</td>
<td>Improved BDI-II Improved WHOqol UPDRS-MBM</td>
</tr>
<tr>
<td>Cho et al. (2012)</td>
<td>22 patients</td>
<td>Randomized single blind control trial</td>
<td>BDI PDQ3OL</td>
<td>Improved BDI</td>
</tr>
<tr>
<td>Chen, Feng, and Zhang (2012)</td>
<td>60 patients</td>
<td>RCT 8 weeks; madopar/tolteridine (M/T) vs M/T + acupuncture</td>
<td>Bladder function</td>
<td>Improved bladder Function in acupuncture group</td>
</tr>
<tr>
<td>Kluger et al. (2016)</td>
<td>94 patients</td>
<td>RCT of acupuncture vs sham points 2×/week</td>
<td>Fatigue impact scale</td>
<td>No change in fatigue; modified fatigue impact scale vs sham—both groups were less fatigued</td>
</tr>
</tbody>
</table>

at PDQ39, cognition, mood, sleep, fatigue, and apathy. The description of the studies is under the heading of the NMS measures. In this review, we again focus on the NMS described in Tables 6–9. In the next session, the focus is on specific OT and PT intervention and NMS outcomes.
<table>
<thead>
<tr>
<th>Author/Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Morberg, Jensen, Bode, and Wermuth (2014)</td>
<td>12 patients and 12 controls</td>
<td>High-intensity personalized physical training—32 weeks, 2–3 ×/week</td>
<td>PDQ39 total Body discomfort, EWB subscore</td>
<td>Body discomfort and EWB subscore improved; not total PDQ39</td>
</tr>
<tr>
<td>Schenkman et al. (2012)</td>
<td>121 patients</td>
<td>Flexibility individualized followed by group with physical therapy vs aerobic exercise by trainer, vs home-based exercise; 30 min; 16 month RCT</td>
<td>PDQ39</td>
<td>No difference in groups</td>
</tr>
<tr>
<td>Park et al. (2014)</td>
<td>31 patients</td>
<td>Early vs late start 1 h 3 ×/week, 48 weeks vs 24 weeks</td>
<td>PDQ39 BDI</td>
<td>Early start improved on BDI</td>
</tr>
<tr>
<td>Rodrigues de Paula, Teixeira-Salmela, Coelho de Morais Faria, Rocha de Brito, and Cardoso (2006)</td>
<td>20 patients</td>
<td>36 group sessions, 75 min, 3 ×/week for 3 months, aerobic conditioning/muscle strengthening (pre- and postintervention comparison)</td>
<td>QOL-Nottingham health proof</td>
<td>Improved social interaction, emotional reaction, physical ability, NHP-S sleep improved</td>
</tr>
<tr>
<td>Corcos et al. (2013)</td>
<td>51 patients</td>
<td>20 in weightlifting (PRE) vs 18 modified fitness counts (MFC) (stretch, balance, strengthening) 2 ×/week for 24 months</td>
<td>PDQ39</td>
<td>PDQ39 improved in PRE vs MFC</td>
</tr>
<tr>
<td>Dibble, Hale, Marcus, Gerber, and LaStayo (2009)</td>
<td>20 patients with PD vs aged match control</td>
<td>12 week High-intensity eccentric resistance training</td>
<td>PDQ39</td>
<td>PDQ39 improved in exercise group</td>
</tr>
<tr>
<td>van Nimwegen et al. (2013)</td>
<td>540 patients</td>
<td>ParkFit (inc. regular physical therapy) vs control</td>
<td>PDQ39</td>
<td>No change in PDQ39</td>
</tr>
</tbody>
</table>
Table 7 Exercise Effects on Sleep/Fatigue in PD

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazzitta et al. (2015)</td>
<td>89 patients + 49 controls</td>
<td>RCT-89 patients vs 49 controls; 28 days—three 1-h sessions of cardio, stretching, balance, gait with OT for ADLs</td>
<td>PD sleep scale</td>
<td>Improved PDSS for sleep quality, motor symptoms, daytime somnolence</td>
</tr>
<tr>
<td>Nascimento et al. (2014)</td>
<td>34 patients</td>
<td>RCT vs usual are 3 ×/week, 6 month, muscular resistance, balance/motor coordination, aerobic fitness</td>
<td>MSQ sleep</td>
<td>Improved sleep disturbance (insomnia, daytime somnolence)</td>
</tr>
<tr>
<td>Winward et al. (2012)</td>
<td>39 patients</td>
<td>Gym vs nothing RCT 30–45 min, 12 weeks, varied frequency</td>
<td>Fatigue SS</td>
<td>Nonsignificant improvement</td>
</tr>
</tbody>
</table>

Table 8 Exercise Effects on Depression in PD

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uc et al. (2014)</td>
<td>49 patients</td>
<td>45 min aerobic walking no control 3 ×/week for 6 months at home</td>
<td>GDS Flanker task, MOCA</td>
<td>Decreased depression Improved flanker task</td>
</tr>
<tr>
<td>Bridgewater and Sharpe (1998)</td>
<td>26 patients</td>
<td>20–30 min aerobic pilot RCT vs usual care</td>
<td>LPDQ depression</td>
<td>Improved mood in exercise group</td>
</tr>
<tr>
<td>Nadeau, Pourcher, and Corbeil (2014)</td>
<td>45 patients</td>
<td>Speed vs mixed treadmill exercise, RCT 24 weeks, 1 h, 3 ×/week</td>
<td>BDI MMSE UPDRS1</td>
<td>No significant improvement</td>
</tr>
</tbody>
</table>

2.1 Exercise Effects on Quality of Life as Measured by PDQ39 in PD

Referring to Table 6, Morberg et al. (2014) did a study on high-intensity personalized physical training on 12 patients vs 12 controls. The sessions were 2–3 times per week for 32 weeks. PDQ39 was measured and
showed improved body discomfort and well-being scores but not total PDQ39. Park et al. (2014) looked at 31 patients randomized to early vs late start exercise 1 h 3 times per week for 48 weeks vs 24 weeks. They measured PDQ39 and BDI and found that there was an improvement
in the Beck score in the early start group. Schenkman et al. (2012) looked at 121 patients randomized to one of three arms: flexibility (individualized followed by group class supervised by PT) vs aerobic exercise supervised by an exercise trainer vs home-based exercise looking at PDQ39. There was no difference between the groups with this quality of life measure. Rodrigues de Paula et al. (2006) studied 20 patients with 36 group sessions lasting 75 min each, 3 times per week for 3 months including pre- and postintervention measures. The intervention included aerobic conditioning and muscle strengthening. The Nottingham health profile was used to measure quality of life. There was improved social interacting, emotional reaction, physical ability, and sleep with a trend toward improved pain after the intervention. Corcos et al. (2013) studied 51 patients—20 in progressive resistance exercise, 18 in modified fitness class (stretch, balance, and strengthening) 2 times per week for 24 months. They measured PDQ39 and found an improvement in this measure in the progressive resistance exercise group. Dibble et al. (2009) studied 20 patients with high-intensity eccentric resistance training for 12 weeks and found that PDQ39 improved in the exercise group. van Nimwegen et al. (2011, 2013) studied 540 patients with ParkFit intervention (including regular PT) vs control. There was no change in PDQ39 in this study.

In summary, exercise improves QOL measured by PDQ39 in a few studies.

### 2.2 Exercise Effects on Sleep/Fatigue in PD

Frazzitta et al. (2015) reported on rehab. intervention of 28 days of a combination of three 1-h session of cardio, stretching, balance, and gait along with OT for ADLs in 89 patients vs 49 controls and measure the PDSS. They showed that PDSS for sleep quality, motor symptoms, and daytime somnolence improved. Nascimento et al. (2014) studied 34 patients in a RCT for 3 times per week for 6 months using muscular resistance, balance/motor coordination, and aerobic fitness vs usual care and looked at MSQ sleep. They showed that there was improved sleep disturbance in the intervention including insomnia and daytime somnolence. Winward et al. (2012) studied 39 patients in a RCT with gym vs no exercise and found that there was no significant improvement in the fatigue SS. In summary, exercise improves sleep in a couple of studies.
2.3 Exercise Effects on Depression in PD

Uc et al. (2014) studied 49 patients with a 45 min aerobic walking intervention with no control. The patients walked 3 times per week for 6 months at home. They looked at the GDS and MOCA and the flanker task and showed improved flanker task and decreased depression with walking. Nadeau et al. (2014) studied 45 patients with speed vs mixed treadmill in a RCT trial for 24 weeks. The patients did the exercise for 24 weeks for 1 h per session for 3 sessions per week. BDI, MMSE, and UPDRS1 were studied but were not changed. Bridgewater and Sharpe (1998) studied 26 patients doing 20–30 min aerobic exercise vs usual care in a RCT. They showed improved mood in the exercise group on Levine–Pilowsky Depression Questionnaire (LPDQ) and depression. Hence, exercise improves depression in a couple of small studies.

2.4 Exercise Effects on Cognition in PD

Picelli et al. (2016) looked at 17 patients, 9 in the intervention group looking at 12 sessions of treadmill for 45 min, 3 times per week for 4 weeks. They measured a FAB which improved with exercise. David et al. (2015) studied 51 patients for 2 sessions per week, 60–90 min progressive resistance training (PRET) vs stretching, balance, nonprogressive training for 24 month. They studied the BTA, digit span, and Stroop and showed improvements in all three for PRET but only the digit span and Stroop in the stretch group. There was no difference between 12 and 24 months. Pohl et al. (2013) studied the Ronnie Gardner Rhythm and music method and showed no change in cognition. Ridgel et al. (2011) studied passive leg cycling as the intervention with pre- and postintervention measures of the trials making test A and B with improved TMT-B scores and improved times for performing both types of trail tests.

Cruise et al. (2011) performed a RCT on 28 patients for 60 min 2 times per week for 3 months doing aerobic exercise vs usual care. They looked at MMSE, pattern recognition memory (PRM), spatial recognition memory (SRM), SOC, and spatial working memory (SWM). They found that the exercise group improved with executive function. Shulman et al. (2013) studied 67 patients in a RCT of 30 min of high-intensity treadmill vs 50 min of low-intensity treadmill vs stretching and resistance 3 times per week for 3 months. Outcome measures included BDI, PFS-16, and fatigue and showed no change in any group. Almost all of the trials reviewed, showed some modest improvement in a subsection of cognition in many patients with PD.
3. PART 3: THERAPY: PT AND OT EFFECTS ON NMS

PT is defined as a therapy for the preservation, enhancement, or restoration of movement and physical function impaired or threatened by disease, injury, or disability that utilizes therapeutic exercise, physical modalities (such as massage and electrotherapy), assistive devices, and patient education and training—called also physiotherapy. This therapy is administered to the patient by a physical therapist usually on an individual basis. OT is a therapy based on engagement in meaningful activities of daily life (as self-care skills, education, work, or social interaction) especially to enable or encourage participation in such activities despite impairments or limitations in physical or mental functioning. This therapy is administered by an occupational therapist usually in a one-on-one basis. This is in contrast to the studies described in the exercise section above which were usually group classes with a personal trainer as the instructor.

Teixeira-Machado et al. (2015) studied Feldenkrais PT 2 times per week for 1 h for 25 weeks in an RCT in 30 patients. They measured BDI and found an improvement in this scale in the PT group. Dashtipour studied 60 min of aerobic/resistance training vs LSVT big therapy in 11 patients. They looked at BAI and BDI as outcome measures and found reduced depression in the combined exercise group.

King et al. (2015) performed a RCT study on 58 patients with exercise that was individualized by a PT vs a group class intervention based on an agility boot camp for PD including Taichi, boxing, lunges, kayaking, agility course, and Pilates vs an unsupervised home exercise program for three sessions per week for 4 weeks. They looked at PDQ39, LARS (Lille Apathy Rating Scale), depression, Self-Efficacy Scale (SES) and found that LARS, depression, and SES were best in patients who had the individual PT. Cholewa, Boczarska-Jedynak, and Opala (2013) studied 70 patients in a RTC of PT for 1 h per week for 12 weeks and found an improvement in UPDRS 1. Miyai et al. (2000) did a similar study looking at 24 patients using body weight supported treadmill vs PT 3 times per week for 45 min for 1 month and found no change in UPDRS 1 between groups.

Sturkenboom et al. (2014) studied OT vs control in a RCT looking at fatigue scale and BDI with no change in these outcomes. Tomlinson et al. (2014) studied 39 patients in a RCT of OT vs control. The OT group got 45 min 3 times per month for 2 months. HADS and anxiety scale did not improved.
In summary, studies of OT and PT largely show some benefit to depression, apathy, and anxiety (Table 10).

### Table 10 Physical Therapy/Occupational Therapy Effects on NMS in PD

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients/Arms</th>
<th>Intervention Description</th>
<th>Nonmotor Measures</th>
<th>Outcome of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teixeira-Machado et al. (2015)</td>
<td>30 patients</td>
<td>Feldenkrais PT 2 ×/week 1 h 25 weeks RCT</td>
<td>BDI</td>
<td>BDI improved in PT group</td>
</tr>
<tr>
<td>Dashtipour et al. (2015)</td>
<td>11 patients</td>
<td>60 min aerobic/resistance vs LSVT BIG PT intervention</td>
<td>BAI BDI</td>
<td>Reduced depression in combined exercise group</td>
</tr>
<tr>
<td>King et al. (2015)</td>
<td>58 patients</td>
<td>RCT exercise individual PT vs group class on agility boot camp 3 week for 4 weeks</td>
<td>PDQ39, LARS, depression, SES</td>
<td>LARS, depression, and SES improved in PT group</td>
</tr>
<tr>
<td>Cholewa et al. (2013)</td>
<td>70 patients</td>
<td>PT RCT 1 h for 12 weeks</td>
<td>UPDRS 1</td>
<td>UPDRS1 improved in PT group</td>
</tr>
<tr>
<td>Miyai et al. (2000)</td>
<td>24 patients</td>
<td>Body weight supported treadmill vs PT 3 ×/week, 45 min, for 1 month</td>
<td>UPDRS 1</td>
<td>No change in UPDRS1</td>
</tr>
<tr>
<td>Sturkenboom et al. (2014)</td>
<td>191 patients</td>
<td>OT vs control—10 week, home-based OT vs usual care 124 patients vs 67 controls (RCT 2:1)</td>
<td>Euroqol 5 dimension Fatigue SS BDI</td>
<td>Euroqol 5 improved in OT group</td>
</tr>
<tr>
<td>Tomlinson et al. (2014)</td>
<td>39 patients</td>
<td>OT RCT 45 min 3 ×/month for 2 months</td>
<td>HADS—anxiety/depression</td>
<td>No change</td>
</tr>
</tbody>
</table>

#### 4. CONCLUSIONS

The areas of complementary/alternative medicine and exercise show promise in the treatment of NMS in PD. Well-performed, systematic evidence-based research studies are largely lacking in this area and many studies include various forms of CAM with small patient numbers and a lack of standardization of approaches studied. Taichi, Qigong, dance, yoga,
mindfulness, acupuncture, and other CAM therapies were reviewed and there is some evidence for the following: Taichi in sleep and PDQ39; dance in cognition, apathy, and a mild trend to improved fatigue; yoga in PDQ39; and acupuncture in depression, PDQ39, and sleep. Further studies need to be performed in order to properly counsel patients on which type of CAM therapy could be utilized to help the various NMS.

Exercise including OT and PT has been studied in motor symptoms of PD and balance but there are some small studies with a mounting evidence base for use of exercise in NMS of PD including PDQ39, sleep, fatigue, depression, and some subsets of cognition. Studies of OT and PT largely show some benefit to depression, apathy, and anxiety. Sustainability of an improvement has not been shown given a short duration of follow up. The optimal way to control and blind for these interventions is also an issue. Hence, further studies in exercise including OT and PT are warranted and needed in order to counsel patients on which exercise would be beneficial for their individual motor and NMS. Additionally, evidence for PT and OT in NMS would give added weight to getting these interventions covered through medical insurance.

The future is bright for these fast-paced, ever-changing areas of CAM therapy, and exercise in the treatment of NMS for PD. A basic understanding of these areas is vital for clinicians in order to counsel patients who are hungry to try these novel interventions.

REFERENCES


