

Freezing of Gait in Parkinsonism and its Potential Drug Treatment

Li-Li Zhang^{1,2}, S. Duff Canning³ and Xiao-Ping Wang^{1,*}

¹Department of Neurology, Shanghai First People's Hospital, Shanghai Jiao-Tong University, China. 200080; ²Department of Neurology, Nanjing Brain Hospital, Nanjing Medical University, China. 210029; ³Department of Psychology University of Toronto, Canada

Abstract: Freezing of gait (FOG) is a heterogeneous symptom. Studies of treatment for FOG are scarce. Levodopa and monoamine oxidase inhibitors (rasagiline and selegiline) have shown effective improvement for FOG. Other drugs, such as L-threo-3, 4-dihydroxyphenylserine, amantadine, and botulinum toxin have exhibited some beneficial effects. The present review summarizes the potential drug treatment for FOG in Parkinsonism.



Keywords: Drug treatment, freezing of gait, Levodopa, Parkinson's disease, Parkinsonism.

1. INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disorder, impacting about 1% of adults over 60 years of age. This incidence increases from 3% to 5% in people aged above 85 years [1]. Primary features contain bradykinesia, resting tremor, rigidity and loss of postural reflexes. Loss of postural reflexes develops in most patients with PD as the disease progresses, leading to gait difficulties and balance problems. Typical gait disorders of PD include stooped posture, freezing of gait (FOG) festination, shuffling steps, and falling. FOG, defined as an onset of inability to start effective steps without known cause, is most commonly experienced during step initiation and turning, especially facing with obstacles, doorways, stress, and distraction. Simply put, it is "unexpected, small, absence or remarkable reduction of walk forward progression in spite of the intention to walk" [2, 3]. FOG accompany with some features: (1) the foot or toe cannot leave the floor; (2) commutative trembling of the legs starts with a 3–8 Hz frequency; (3) speeding up and reducing step length are often observed before FOG; (4) feeling of the feet sticking on the floor accompanies with FOG; (5) FOG is commonly a variety of relief with cues (6) FOG can be asymmetrical, affecting mainly one foot or in one direction [4-6]. It is estimated to affect around 7% of people with early disease and over half of patients with advanced PD [7], leading to loss of life quality, independence, and mobility [8].

FOG is a symptom that can be divided into dopaminergic-sensitive, dopaminergic-resistant, and dopaminergic drug-provoked categories. Medications showing clinical benefit to FOG include levodopa, dopamine agonists, and monoamine oxidase type B inhibitors [9]. The use of methylphenidate for gait impairment in PD remains controversial [10, 11]. A

preliminary study showed that intravenous amantadine may be effective for FOG that is resistant to dopaminergic drugs, suggesting that amantadine may exert its benefits independent on a dopaminergic mechanism [12]. The present review summarizes clinical medical treatments for FOG.

2. LEVODOPA

To date, Levodopa is the gold standard for the treatment of Parkinson's disease. Levodopa can significantly improve the symptoms of movement. Levodopa can improve FOG [13]. Compared to placebo or low-dose levodopa, high dosage levodopa can delay FOG and reduce FOG occurrence, [14]. The number of episodes with akinesia and FOG can be significantly decreased by levodopa. The frequency and duration of 'off-related FOG also can be reduced by levodopa [15]. Meanwhile, another trial confirmed levodopa was the treatment of choice for patients with FOG: a short-term levodopa response only was detected in 40% of patients, however; a large number of patients with FOG do not improve with short-term levodopa effects, and need other treatment, e.g. activating therapy with cues [16]. In a study with 20 patients, after intake levodopa, a less degree of FOG was examined in 95% of the PD patients after. Levodopa significantly reduced the FOG sum score, and most patients with FOG (80%) still continued to undergo a FOG variant after oral levodopa [13]. A recent study confirmed 24h Levodopa-carbidopa intestinal gel therapy may reduce levodopa "unresponsive" FOG and associated falls [17].

3. MONOAMINE OXIDASE B INHIBITOR

A case report of an 84-year-old man, diagnosed primary progressive freezing gait (PPFG), had a four-year history of FOG. Rasagiline, the new irreversible monoamine oxidase B inhibitor, at standard doses showed a fast, dramatic, and persistent improvement of the duration and frequency of FOG episodes [18]. A 76-year-old woman with progressive primary freezing of gait, after taking selegiline in doses up to 20 mg/d, showed a remarkable improvement of the gait disorder [19]. Deprenyl (selegiline) postpones the need for

*Address correspondence to this author at the Department of Neurology, Shanghai First People's Hospital, Shanghai Jiao-Tong University, China. 200080; Tel: 86-21-63240090; Fax: 86-21-63243755; E-mail: x_p_wang@sjtu.edu.cn

levodopa treatment in early PD patients. After about 5 years, levodopa-treated PD patients, treated with deprenyl for up to 7 years, showed slower motor decline and were less likely to develop FOG, compared with patients who were changed to a placebo [20]. An open observational 3-month study demonstrated that rasagiline effectively reduced the off-time duration as well as the disability in off- and on-time and optimizes levodopa efficacy in the routine clinical practice setting [21].

4. AMANTADINE

From the late sixties, amantadine is used for the treatment of PD [22]. A trial compared the efficacy of 5 days intravenous amantadine and placebo treatments on FOG in 42 subjects randomly allocated 2:1 to amantadine or placebo groups. There was no serious adverse event reported during the study. The intravenous amantadine therapy did not show a significant improvement on overall freezing of gait questionnaire scores in patients with moderate-to-severe freezing; however, it might be beneficial by attenuating freezing severity and improving patients' mobility [23]. One study's data suggest in PD patients with STN-DBS amantadine may have some kind of effects on axial symptoms. In this trial, improvement in speech, gait and balance occurred in 35 (76.1%) patients, on the other hand, improvement in gait and balance occurred 30(65.2%) patients [24]. In 2011, Kim performed a trial to find the effect of IV amantadine in dopaminergic-drug-unresponsive FOG. This study involved 15 patients: 6 with PD and 4 with multiple system atrophy (MSA), 2 with progressive supranuclear palsy (PSP), and 3 with PFFG. Along with the pre-existing dopaminergic and non-dopaminergic medication, their standard project was IV amantadine at 200 mg in 500 cm³ of saline solution, given over a 3-h period and twice daily for 2 days. Five of six PD patients showed improvement and one PSP had mild improvement of FOG, whereas, the remaining patients showed no response [12]. A trial of oral amantadine in PD patients with FOG suggested amantadine had self-reported improvement but this effect may be transient. In this trial, median amantadine dose was 100 mg twice a day and duration of treatment was 20 months (range 6–66) [25]. In contrast, amantadine (400 mg/day) injected over 2 days with a 52-hour washout period failed to show an effect on FOG [26]. These contradictory findings raise the possibility that the NMDA receptor antagonist, the antidyskinetic mechanism of amantadine, does not have beneficial effects on FOG.

5. L-THREO-3,4-DIHYDROXYPHENYLSERINE

L-threo-3,4-dihydroxyphenylserine (L-DOPS, droxidopa), originally used as a therapy for orthostatic hypotension, was a precursor of noradrenaline [27], but later was discovered to have potential as a treatment for FOG [28]. It implied that dysfunction of noradrenergic neurons involved in the pathogenesis of levodopa-resistant FOG [29]. The co-administration of L-DOPS and entacapone can significantly improve FOG [30]. Once across the blood–brain barrier, the administration of L-DOPS might aid noradrenaline to preganglionic noradrenergic systems and then might lead to improved FOG.

6. METHYLPHENIDATE

Methylphenidate (MPH), is a mainstay of drug for attention-deficit/hyperactivity disorder in adults, adolescents and children [31, 32]. It is an inhibitor of the dopamine transporter. By measuring with walking speeds, dyskinesia and vital signs, oral MPH alone or with levodopa on parkinsonism indicate that the residual the dopamine transporter is functional in PD and the dopamine transporter is a potential target for symptomatic treatment of PD [33]. Dopamine transporters can be effectively blocked by oral MPH, and more than 50% of dopamine transporters are likely consumed at the weight-adjusted doses using therapeutically (0.3 to 0.6 mg/kg) [34]. Firstly, a study showed MPH (0.2 mg/kg) increased the motor effects of levodopa with minimal effects on cognitive or affective functions [35]. Without need for exogenous levodopa, low dose of MPH may improve gait, and especially freezing in advanced PD patients [36, 37]. Another trial observed gait and motor symptoms that could be improved by chronic, high doses of MPH without levodopa and the intensity of response of these symptoms could be increased to levodopa in advanced PD [38]. But the effects of MPH at 0.4 mg/kg 3 times per day only reached significance in the decrease in tremor [39]. A crossover design study showed MPH failed to take a turn for the better of FOG [11]. Between October, 2009 and December, 2011, Moreau designed a multicentre, parallel, double-blind, placebo-controlled, randomised trial, in 13 French movement disorders departments. They randomly assigned patients to receive MPH (1 mg/kg per day) or placebo capsules for 90 days. Gait hypokinesia and freezing could be improved by MPH in advanced PD patients receiving subthalamic nucleus stimulation. The proportion of FOG patients decreases from 86% to 67% in MPH group, without decrease was observed in the placebo group. However, MPH group had significantly more adverse events compared with those in placebo group. Increasing in heart rate (mean 3.6 [SD 7.2] beats per min) and decreasing in weight (mean 2.2 [SD 1.8] kg) occurred in patients who received MPH treatment compared with those in placebo group. An increase in dopaminergic, and probably noradrenergic activity is associated with this benefit of FOG: Dopamine and noradrenaline presynaptic transporters could be inhibited by MPH in the striatum and prefrontal cortex. 123I-FP-CIT SPECT indicated that the striatal dopamine transporter density was decreased in the MPH group, which was suggested in synaptic dopamine [10]. The various pharmacodynamic effects of MPH mean that the drug may have significant value in the treatment of PD [40, 41].

7. BOTULINUM TOXIN

Botulinum toxin (BoNT) can be used in the treatment of PD-related disorders and different dystonia: for instance limb dystonia, hand and jaw tremor, freezing of gait, cervical dystonia (anterocollis), dysphagia (achalasia), rigidity (painful shoulder), *etc* [42]. Giladi found Botox-A injection into calf muscles of patients with PD and improvement of FOG had a distinct temporal relationship [43, 44]. However, later studies showed that neither BTX-A nor BTX-B improved FOG, and BoNT may increase the risk of fall [45, 46].

Table 1. Summary of drugs for freezing of gait in Parkinsonism.

Drug	Response	Refs.
levodopa	effective	[13-17]
monoamine oxidase B inhibitor	effective	[18, 21]
rasagiline	effective	[19, 20]
selegiline		
Amantadine	effective	[23]
	effective for PD	[12]
	no response for Parkinsonism	[12]
	self-reported improvement	[25]
	no improvement	[26]
L-DOPS	effective	[28, 30]
Methylphenidate	effective, with adverse events	[10, 36, 37]
	no improvement	[11]
BOTULINUM TOXIN	little improvement	[43-46]

8. OTHER TREATMENTS

Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) can improve FOG, and reduce falls in FOG [47,48]. Repetitive transcranial magnetic stimulation (rTMS) also has effective improvement for FOG [49]. A cross-over, double-blind, sham-controlled study of the motor cortex showed that transcranial direct current stimulation could reduce the number and duration of FOG [50]. Repetitive exercises of cueing could reduce the severity of FOG [51], including auditory [52], and visual cueings [53]. These new rehabilitation techniques are effective, because FOG is a complicated symptom of PD caused by motor, cognitive, and affective factors [54-56]. Both basal ganglia and extrastriatal brain areas may be involved in the pathogenesis of FOG in PD [57, 58].

CONCLUSION

Levodopa has been proved to be an effective drug treatment for FOG, and new drug delivery methods may provide even better effectiveness. Monoamine oxidase inhibitors and methylphenidate also showed improvement for FOG in several studies, and may have clinical value in the treatment of PD patients with FOG in the future. Amantadine, L-threo-3,4-dihydroxyphenylserine, and botulinum toxin showed less evidence for effective treatment of FOG, moreover, they are associated with some adverse effects. Deep brain stimulation, and rehabilitation exercises can relieve symptoms of FOG in some patients. Therefore, developing effective treatment strategies is in need of further explorations.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported by grants from the National Natural Science Foundation of China (81071065).

REFERENCES

- Samii, A.; Nutt, J.G.; Ransom, B.R. Parkinson's disease. *Lancet*, **2004**, *363*(9423), 1783-1793. PMID: 15907740. [http://dx.doi.org/10.1016/S0140-6736\(04\)16305-8](http://dx.doi.org/10.1016/S0140-6736(04)16305-8)
- Fahn, S. Description of Parkinson's disease as a clinical syndrome. *Ann. N.Y. Acad. Sci.*, **2003**, *991*, 1-14. PMID: 12846969. <http://dx.doi.org/10.1111/j.1749-6632.2003.tb07458.x>
- Giladi, N.; Nieuwboer, A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. *Mov. Disord.*, **2008**, *23*(11), 423-425. PMID: 18668629. <http://dx.doi.org/10.1002/mds.21927>
- Schaafsma, J.D.; Balash, Y.; Gurevich, T.; Bartels, A.L.; Hausdorff, J.M.; Giladi, N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur. J. Neurol.*, **2003**, *10*(4), 391-398. PMID: 12823491. <http://dx.doi.org/10.1046/j.1468-1331.2003.00611.x>
- Moore, S.T.; MacDougall, H.G.; Ondo, W.G. Ambulatory monitoring of freezing of gait in Parkinson's disease. *J. Neurosci. Methods*, **2008**, *167*(2), 340-348. PMID: 17928063. <http://dx.doi.org/10.1016/j.jneumeth.2007.08.023>
- Nieuwboer, A.; Dom, R.; De-Weerd, W.; Desloovere, K.; Fieus, S.; Broens-Kaucsik, E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Mov. Disord.*, **2001**, *16*(6), 1066-1075. PMID: 11748737. <http://dx.doi.org/10.1002/mds.1206>
- Nutt, J.G.; Bloem, B.R.; Giladi, N.; Hallett, M.; Horak, F.B.; Nieuwboer, A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neuro.*, **2011**, *10*(8), 734-744. PMID: 21777828. [http://dx.doi.org/10.1016/S1474-4422\(11\)70143-0](http://dx.doi.org/10.1016/S1474-4422(11)70143-0)
- Panisset, M. Freezing of gait in Parkinson's disease. *Neurol. Clin.*, **2004**, *22*(3), 53-62. PMID: 1550136. <http://dx.doi.org/10.1016/j.ncl.2004.05.004>
- Giladi, N. Medical treatment of freezing of gait. *Mov. Disord.*, **2008**, *23*(11), 1639-1640. PMID: 18668620. <http://dx.doi.org/10.1002/mds.21914>
- Moreau, C.; Delval, A.; Defebvre, L.; Dujardin, K.; Duhamel, A.; Petyt, G.; Vuillaume, I.; Corvol, J.C.; Brefel-Courbon, C.; Ory-Magne, F.; Guehl, D.; Eusebio, A.; Fraix, V.; Saulnier, P.J.; Lagha-Boukbiza, O.; Durif, F.; Faighel, M.; Giordana, C.; Drapier, S.; Maltête, D.; Tranchant, C.; Houeto, J.L.; Debû, B.; Sablonniere, B.; Azulay, J.P.; Tison, F.; Rascol, O.; Vidailhet, M.; Destée, A.; Bloem, B.R.; Bordet, R.; Devos, D. Parkgait-II study group. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neuro.*, **2012**, *11*(7), 589-596. PMID: 22658702. [http://dx.doi.org/10.1016/S1474-4422\(12\)70106-0](http://dx.doi.org/10.1016/S1474-4422(12)70106-0)

- [11] Espay, A.J.; Dwivedi, A.K.; Payne, M.; Gaines, L.; Vaughan, J.E.; Maddux, B.N.; Slevin, J.T.; Gartner, M.; Sahay, A.; Revilla, F.J.; Duker, A.P.; Shukla, R. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology*, **2011**, *76*(14), 125-162. PMID: 21464430.<http://dx.doi.org/10.1212/WNL.0b013e3182143537>
- [12] Kim, Y.E.; Yun, J.Y.; Jeon, B.S. Effect of intravenous amantadine on dopaminergic drug-resistant freezing of gait. *Parkinsonism Relat. Disord.*, **2011**, *17*(6), 491-492. PMID: 21463965. <http://dx.doi.org/10.1016/j.parkreldis.2011.03.010>
- [13] Fietzek, U.M.; Zwosta, J.; Schroeteler, F.E.; Ziegler, K.; Ceballos-Baumann, A.O. Levodopa changes the severity of freezing of gait in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2013**, *19*(10), 894-896. PMID: 23642712. doi: 10.1016/j.parkreldis.2013.04.004.
- [14] Fahn, S. Study Parkinson Group. Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J. Neurol.*, **2005**, *252* (Suppl 4), IV37-IV42. PMID: 16222436.<http://dx.doi.org/10.1007/s00415-005-4008-5>
- [15] Schaafsma, J.D.; Balash, Y.; Gurevich, T.; Bartels, A.L.; Hausdorff, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur. J. Neurol.*, **2003**, *10*(4), 391-398. PMID: 12823491.<http://dx.doi.org/10.1046/j.1468-1331.2003.00611.x>
- [16] Fietzek, U.M.; Schroeteler, F.E.; Ziegler, K.; Zwosta, J.; Ceballos-Baumann, A.O. Randomized cross-over trial to investigate the efficacy of a two-week physiotherapy programme with repetitive exercises of cueing to reduce the severity of freezing of gait in patients with Parkinson's disease. *Clin. Rehabil.*, **2014**, *28*(9), 902-911. PMID: 24691217.<http://dx.doi.org/10.1177/0269215514527299>
- [17] Chang, F.C.; Tsui, D.S.; Mahant, N.; Wolfe, N.; Kim, S.D.; Ha, A.D.; Drury, M.; Griffith, J.M.; Fung, V.S. 24 h Levodopa-carbidopa intestinal gel may reduce falls and "unresponsive" freezing of gait in Parkinson's disease. *Parkinsonism and Related Disorders*, **2015**, *21*(3), 317-320. PMID: 25578290.<http://dx.doi.org/10.1016/j.parkreldis.2014.12.019>
- [18] Coria, F.; Cozar, S.; Mdel, P. Rasagiline improves freezing in a patient with primary progressive freezing gait. *Mov. Disord.*, **2008**, *23*(3), 449-451. PMID: 18067186.<http://dx.doi.org/10.1002/mds.21868>
- [19] Zúñiga, C.; Lester, J.; Cersósimo, M.G.; Díaz, S.; Micheli, F.E. Treatment of primary progressive freezing of gait with high doses of selegiline. *Clin. Neuropharmacol.*, **2006**, *29*(1), 20-21. PMID: 16518130.<http://dx.doi.org/10.1097/00002826-200601000-00007>
- [20] Shoulson, I.; Oakes, D.; Fahn, S.; Lang, A.; Langston, J.W.; LeWitt, P.; Olanow, C.W.; Penney, J.B.; Tanner, C.; Kieburtz, K.; Rudolph, A. Parkinson Study Group. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of Parkinsonism trial. *Ann. Neurol.*, **2002**, *51*, 604-612. PMID: 12112107.<http://dx.doi.org/10.1002/ana.10191>
- [21] Levin, O.S.; Bojko, A.N.; Ivanov, A.K. Efficacy of rasagiline in patients with advanced Parkinson's disease with motor fluctuation (azimut study). *Zh. Nevrol. Psikhiatr. Im. S. S. Korsakova.*, **2010**, *110*(11 Pt 2), 42-47. Russian. PMID: 21389939.
- [22] Schwab, R.S.; England, A.C.; Poskanzer, D.C.; Young, R.R. Amantadine in the treatment of Parkinson's disease. *JAMA*, **1969**, *208*, 1168-1170. PMID: 5818715.<http://dx.doi.org/10.1001/jama.1969.03160070046011>
- [23] Lee, J.Y.; Oh, S.; Kim, J.M.; Kim, J.S.; Oh, E.; Kim, H.T.; Jeon, B.S.; Cho, J.W. Intravenous amantadine on freezing of gait in Parkinson's disease: a randomized controlled trial. *J. Neurol.*, **2013**, *260*(12), 3030-3038. PMID: 24057149.<http://dx.doi.org/10.1007/s00415-013-7108-7>
- [24] Chan, H.F.; Kukkle, P.L.; Merello, M.; Lim, S.Y.; Poon, Y.Y.; Moro, E. Amantadine improves gait in PD patients with STN stimulation. *Parkinsonism Relat. Disord.*, **2013**, *19*(3), 316-319. PMID: 23218842.<http://dx.doi.org/10.1016/j.parkreldis.2012.11.005>
- [25] Malkani, R.; Zadikoff, C.; Melen, O.; Videnovic, A.; Borushko, E.; Simuni, T. Amantadine for freezing of gait in patients with Parkinson disease. *Clin. Neuropharmacol.*, **2012**, *35*(6), 266-268. PMID: 23123688.<http://dx.doi.org/10.1097/WNF.0b013e31826e3406>
- [26] Kim, Y.E.; Yun, J.Y.; Yang, H.J.; Kim, H.J.; Gu, N.; Yoon, S.H.; Cho, J.Y.; Jeon, B.S. Intravenous amantadine for freezing of gait resistant to dopaminergic therapy: a randomized, double-blind, placebo-controlled, cross-over clinical trial. *PLoS One*, **2012**, *7*(11), 488-490. PMID: 23185280.<http://dx.doi.org/10.1371/journal.pone.0048890>
- [27] Suzuki, T.; Higa, S.; Sakoda, S.; Hayashi, A.; Yamamura, Y.; Takaba, Y.; Nakajima, A. Orthostatic hypotension in familial amyloid poly-neuropathy: treatment with DL-threo-3,4-dihydroxyphenylserine. *Neurology*, **1981**, *31*(10), 1323-1326. PMID: 6287350.<http://dx.doi.org/10.1212/WNL.31.10.1323>
- [28] Ogawa, N.; Kuroda, H.; Yamamoto, M.; Nukina, I.; Ota, Z. Improvement in freezing phenomenon of Parkinson's disease after DL-threo-3, 4-dihydroxyphenylserine. *Acta. Med. Okayama*, **1984**, *38*(3), 301-304. PMID: 6431755.
- [29] Kondo, T. D,L-threo-3,4-dihydroxyphenylserine (D,L-threo-DOPS) treatment on the patients with Parkinson's disease or pure akinesia. *Rinsho. Shinkeigaku.*, **1984**, *24*(3), 280-288. PMID: 6432393.
- [30] Fukada, K.; Endo, T.; Yokoe, M.; Hamasaki, T.; Hazama, T.; Sakoda, S. L-threo-3,4-dihydroxyphenylserine (L-DOPS) co-administered with entacapone improves freezing of gait in Parkinson's disease. *Med. Hypotheses*, **2013**, *80*, 209-212. PMID: 23265352. doi: 10.1016/j.mehy.2012.11.031.
- [31] Kooij, S.J.; Bejerot, S.; Blackwell, A.; Caci, H.; Casas-Brugué, M.; Carpentier, P.J.; Edvinsson, D.; Fayyad, J.; Foeken, K.; Fitzgerald, M.; Gaillac, V.; Ginsberg, Y.; Henry, C.; Krause, J.; Lensing, M.B.; Manor, I.; Niederhofer, H.; Nunes-Filipe, C.; Ohlmeier, M.D.; Oswald, P.; Pallanti, S.; Pehlivanidis, A.; Ramos-Quiroga, J.A.; Rastam, M.; Ryffel-Rawak, D.; Stes, S.; Asherson, P. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry*, **2010**, *10*, 67. doi: 10.1186/1471-244X-10-67. PMID: 20815868.
- [32] Subcommittee Disorder Attention-Deficit/Hyperactivity on; Steering Committee on Quality Improvement and Management, Wolraich, M.; Brown, L.; Brown, R.T.; DuPaul, G.; Earls, M.; Feldman, H.M.; Ganiats, T.G.; Kaplanek, B.; Meyer, B.; Perrin, J.; Pierce, K.; Reiff, M.; Stein, M.T.; Visser, S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, **2011**, *128*(5), 1007-1022. PMID: 22003063.
- [33] Nutt, J.G.; Carter, J.H.; Sexton, G.J. The dopamine transporter: Importance in Parkinson's disease. *Ann. Neurol.*, **2004**, *55*(6), 766-773. PMID: 15174010. <http://dx.doi.org/10.1002/ana.20089>
- [34] Volkow, N.D.; Wang, G.J.; Fowler, J.S.; Gatley, S.J.; Logan, J.; Ding, Y.S.; Hitzemann, R.; Pappas, N. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am. J. Psychiatry*, **1998**, *155*(10), 1325-1331. PMID: 9766762.<http://dx.doi.org/10.1176/ajp.155.10.1325>
- [35] Camicioli, R.; Lea, E.; Nutt, J.G.; Sexton, G.; Oken, B.S. Methylphenidate increases the motor effects of L-dopa in Parkinson's disease: a pilot study. *Clin. Neuropharmacol.*, **2001**, *24*(4), 208-213. PMID: 11479391.<http://dx.doi.org/10.1097/00002826-200107000-00003>
- [36] Auriel, E.; Hausdorff, J.M.; Herman, T.; Simon, E.S.; Giladi, N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin. Neuropharmacol.*, **2006**, *29*(1), 15-17. PMID: 16518128.<http://dx.doi.org/10.1097/00002826-200601000-00005>
- [37] Pollak, L.; Dobronevsky, Y.; Prohorov, T.; Bahunker, S.; Rabey, J.M. Low dose methylphenidate improves freezing in advanced Parkinson's disease during on state. *J. Neural. Transm. Suppl.*, **2007**, *72*, 145-148. PMID: 17982887.http://dx.doi.org/10.1007/978-3-211-73574-9_17
- [38] Devos, D.I.; Krystkowiak, P.; Clement, F.; Dujardin, K.; Cottencin, O.; Waucquier, N.; Ajebbar, K.; Thielemans, B.; Kroumova, M.; Duhamel, A.; Destée, A.; Bordet, R.; Defebvre, L. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **2007**, *78*(5), 470-475. PMID: 17098845.
- [39] Nutt, J.G.; Carter, J.H.; Carlson, N.E. Effects of Methylphenidate on response to oral levodopa: a double-blind clinical trial. *Arch. Neurol.*, **2007**, *64*(3), 319-323. PMID: 17353373.<http://dx.doi.org/10.1001/archneur.64.3.319>
- [40] Devos, D.; Moreau, C.; Delval, A.; Dujardin, K.; Defebvre, L.; Bordet, R. Methylphenidate: a treatment for Parkinson's disease? *CNS Drugs*, **2013**, *27*(1), 1-14. PMID: 23160937.<http://dx.doi.org/10.1007/s40263-012-0017-y>
- [41] Delval, A.; Moreau, C.; Bleuse, S.; Guehl, D.; Bestaven, E.; Guillaud, E.; Dujardin, K.; Defebvre, L.; Devos, D. Gait and

- attentional performance in freezers under methylphenidate. *Gait Posture.*, **2015**, *41*(2), 384-388. PMID: 25468682.<http://dx.doi.org/10.1016/j.gaitpost.2014.10.022>
- [42] Sheffield, J.K.; Jankovic, J. Botulinum toxin in the treatment of tremors, dystonias, sialorrhea and other symptoms associated with Parkinson's disease. *Expert Rev. Neurother.*, **2007**, *7*(6), 637-647. PMID: 17563247.<http://dx.doi.org/10.1586/14737175.7.6.637>
- [43] Giladi, N.; Honigman, S. Botulinum toxin injections to one leg alleviate freezing of gait in a patient with Parkinson's disease. *Mov. Disord.*, **1997**, *12*(6), 1085-1086. PMID: 9399243.<http://dx.doi.org/10.1002/mds.870120641>
- [44] Giladi, N.; Gurevich, T.; Shabtai, H.; Paleacu, D.; Simon, E.S. The effect of botulinum toxin injections to the calf muscles on freezing of gait in Parkinsonism: a pilot study. *J. Neurol.*, **2001**, *248*(7), 572-576. PMID: 11517998.<http://dx.doi.org/10.1007/s004150170134>
- [45] Gurevich, T.; Peretz, C.; Moore, O.; Weizmann, N.; Giladi, N. The effect of injecting botulinum toxin type a into the calf muscles on freezing of gait in Parkinson's disease: a double blind placebo-controlled pilot study. *Mov. Disord.*, **2007**, *22*(6), 880-883. PMID: 17290455.<http://dx.doi.org/10.1002/mds.21396>
- [46] Wieler, M.; Camicioli, R.; Jones, C.A.; Martin, W.R. Botulinum toxin injections do not improve freezing of gait in Parkinson disease. *Neurology*, **2005**, *65*(4), 626-628. PMID: 16116132.<http://dx.doi.org/10.1212/01.wnl.0000172930.63669.e8>
- [47] Xie, T.; Vigil, J.; MacCracken, E.; Gasparaitis, A.; Young, J.; Kang, W.; Bernard, J.; Warnke, P.; Kang, U.J. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. *Neurology*, **2015**, *84*(4), 415-420. PMID: 25540305.<http://dx.doi.org/10.1212/WNL.0000000000001184>
- [48] Ricchi, V.; Zibetti, M.; Angrisano, S.; Merola, A.; Arduino, N.; Artusi, C.A.; Rizzone, M.; Lopiano, L.; Lanotte, M. Transient effects of 80 Hz stimulation on gait in STN DBS treated PD patients: A 15 months follow-up study. *Brain Stimul.*, **2012**, *5*, 388-392. PMID: 21824834.<http://dx.doi.org/10.1016/j.brs.2011.07.001>
- [49] Lee, S.Y.; Kim, M.S.; Chang, W.H.; Cho, J.W.; Youn, J.Y.; Kim, Y.H. Effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinsonism. *Restor. Neurol. Neurosci.*, **2014**, *32*(6), 743-753. PMID: 250779979. doi: 10.3233/RNN-140397.
- [50] Valentino, F.I.; Cosentino, G.; Brighina, F.; Pozzi, N.G.; Sandrini, G.; Fierro, B.; Savettieri, G.; D'Amelio, M.; Pacchetti, C. Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. *Mov. Disord.*, **2014**, *29*(8), 1064-1069. PMID: 24789677.<http://dx.doi.org/10.1002/mds.25897>
- [51] Fietzek, U.M.; Schroeteler, F.E.; Ziegler, K.I.; Zwosta, J.; Ceballos-Baumann, A.O. Randomized cross-over trial to investigate the efficacy of a two-week physiotherapy programme with repetitive exercises of cueing to reduce the severity of freezing of gait in patients with Parkinson's disease. *Clin. Rehabil.*, **2014**, *28*(9), 902-911. PMID: 24691217.<http://dx.doi.org/10.1177/0269215514527299>
- [52] Delval, A.; Moreau, C.; Bleuse, S.; Tard, C.; Ryckewaert, G.; Devos, D. Defebvre L. Auditory cueing of gait initiation in Parkinson's disease patients with freezing of gait. *Clin. Neurophysiol.*, **2014**, *125*(8), 1675-1681. PMID: 24508190.<http://dx.doi.org/10.1016/j.clinph.2013.12.101>
- [53] Lee, S.J.; Yoo, J.Y.; Ryu, J.S.; Park, H.K.; Chung, S.J. The effects of visual and auditory cues on freezing of gait in patients with Parkinson disease. *Am. J. Phys. Med. Rehabil.*, **2012**, *91*(1), 2-11. PMID: 22157432.<http://dx.doi.org/10.1097/PHM.0b013e31823c7507>
- [54] Raffo-De-Ferrari, A.; Lagravinese, G.; Pelosin, E.; Pardini, M.; Serrati, C.; Abbruzzese, G.; Avanzino, L. Freezing of gait and affective theory of mind in Parkinson disease. *Parkinsonism Relat. Disord.*, **2015**, *21*(5), 509-513. PMID: 25772323.<http://dx.doi.org/10.1016/j.parkreldis.2015.02.023>
- [55] Smulders, K.; Esselink, R.A.; Bloem, B.R.; Cools, R. Freezing of gait in Parkinson's disease in relation to impaired motor switching during stepping. *Mov. Disord.*, **2015**, *30*(8), 1090-7. doi: 10.1002/mds.26133. PMID: 25641204.<http://dx.doi.org/10.1002/mds.26133>
- [56] Factor, S.A.; Scullin, M.K.; Sollinger, A.B.; Land, J.O.; Wood-Siverio, C.; Zanders, L.; Freeman, A.; Bliwise, D.L.; Goldstein, F.C. Freezing of gait subtypes have different cognitive correlates in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2014**, *20*(12), 1359-64. PMID: 25446341.<http://dx.doi.org/10.1016/j.parkreldis.2014.09.023>
- [57] Forsaa, E.B.; Larsen, J.P.; Wentzel-Larsen, T.; Alves, G. A 12-year population-based study of freezing of gait in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2015**, *21*(3), 254-258. PMID: 25603767.<http://dx.doi.org/10.1016/j.parkreldis.2014.12.020>
- [58] Teramoto, H.; Morita, A.; Ninomiya, S.; Shiota, H.; Kamei, S. Relation between freezing of gait and frontal function in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2014**, *20*(10), 1046-1049. PMID: 25042341.<http://dx.doi.org/10.1016/j.parkreldis.2014.06.022>