Pisa syndrome in Parkinson's disease and parkinsonism: clinical features, pathophysiology, and treatment

Paolo Barone, Gabriella Santangelo, Marianna Amboni, Maria Teresa Pellecchia, Carmine Vitale

Pisa syndrome is defined as a reversible lateral bending of the trunk with a tendency to lean to one side. It is a frequent and often disabling complication of Parkinson's disease, and has also been described in several atypical forms of parkinsonism and in neurodegenerative and psychiatric disorders after drug exposure and surgical procedures. Although no consistent diagnostic criteria for Pisa syndrome are available, most investigations have adopted an arbitrary cutoff of at least 10° of lateral flexion for the diagnosis of the syndrome. Pathophysiological mechanisms underlying Pisa syndrome have not been fully explained. One hypothesis emphasises central mechanisms, whereby Pisa syndrome is thought to be caused by alterations in sensory–motor integration pathways; by contrast, a peripheral hypothesis emphasises the role of anatomical changes in the musculoskeletal system. Furthermore, several drugs are reported to induce Pisa syndrome, including antiparkinsonian drugs. As Pisa syndrome might be reversible, clinicians need to be able to recognise this condition early to enable prompt management. Nevertheless, further research is needed to determine optimum treatment strategies.

Lancet Neurol 2016; 15: 1063–74

Neurodegenerative Diseases Centre, Department of Medicine and Surgery, University of Salerno, Salerno, Italy (P Barone MD, M Amboni MD, M T Pellecchia MD)**; Department of Psychology, Second University of Naples, Caserta, Italy** (G Santangelo PhD)**; IDC-Hermitage-Capodimonte, Naples, Italy** (G Santangelo, M Amboni, C Vitale MD)**; and Department of Motor Sciences and Wellness, University Parthenope, Naples, Italy** (C Vitale)

Correspondence to: Carmine Vitale, Department of Motor Sciences and Wellness, University Parthenope, Napoli, Italy
cavit69@hotmail.com

Introduction

Patients with Parkinson's disease or atypical parkinsonism can present with abnormal postures that cause substantial disability and can affect quality of life. Pisa syndrome, defined as a lateral deviation of the spine with a corresponding tendency to lean to one side,[1,2] is one of the most common postural deformities seen in these patients, and lateral flexion of the trunk has been described as "the scoliosis of parkinsonism".[3,4] The term Pisa syndrome was originally used to describe trunk dystonia or pleurothotonus secondary to antipsychotic treatment.[5] Subsequently, the term was applied to patients with dementia,[6–18] parkinsonism,[19–27] and other neurodegenerative diseases[28–32] or neurological disorders including normal pressure hydrocephalus and subdural haematoma[33,34] who developed lateral trunk flexion without exposure to antipsychotic drugs. Additionally, Pisa syndrome has been reported as a primary idiopathic disorder.[35] More recently, Pisa syndrome has been described in patients with Parkinson's disease after modification of dopaminergic treatment or as a complication of surgical procedures for Parkinson's disease management, such as pallidotomy and deep brain stimulation (DBS).[36–47]

Occurrence of postural deformities, in the sagittal or coronal plane or both, have been increasingly recognised as a common complication of Parkinson's disease and have been associated with disease progression and treatment.[1,2] Other common postural abnormities that present in patients with Parkinson's disease and atypical forms of parkinsonism include camptocormia, antecollis, retrocollis, and scoliosis (panel).[1]

In this Review, we focus on Pisa syndrome in the context of both Parkinson's disease and atypical parkinsonism. We provide a detailed update on the definition, epidemiology, and clinical presentation of this postural deformity. We discuss the possible pathophysiological mechanisms underlying Pisa syndrome and emphasise areas in need of further research, and explore the possible treatment options. Because Pisa syndrome is a potentially reversible condition, early recognition and management is crucial to limit the development of structural deformities that can cause severe and irreversible mechanical constraints affecting respiration, mobility, and postural stability.

Definition and epidemiology

The clinical definition of Pisa syndrome is derived mainly from studies of Parkinson's disease rather than atypical parkinsonism. Despite decades of research, there is no consensus on the degree of lateral trunk flexion needed to define Pisa syndrome in Parkinson's disease. In 2007, Bonanni and colleagues[48] defined Pisa syndrome as a lateral flexion of the trunk of more than 15° that increases during walking, is not present when supine, and occurs in the absence of any mechanical restriction to trunk movement, with continuous electromyographic (EMG) activity in the lumbar paraspinal muscles ipsilateral to the bending side. More recently, in 2011, Doherty and colleagues[1] defined Pisa syndrome as a pronounced lateral flexion of greater than 10° while standing, which can be almost completely reversed by passive mobilisation or supine positioning. These authors further differentiate between mobile deformity (Pisa syndrome) and fixed deformity (scoliosis), the latter being diagnosed when there is concomitant lateral trunk flexion and vertebral rotation with a Cobb angle of 10° in the coronal plane.[1,49] Accordingly, radiological confirmation in standing and supine positions is needed for differential diagnosis of Pisa syndrome. The proposed diagnostic criteria of 10 or 15° of lateral trunk flexion might lack sensitivity, as they exclude all patients with flexion of less than 10 or 15°, which could evolve into clinically detectable Pisa syndrome. Nevertheless, by proposing the use of electrophysiological assessment in the diagnosis of Pisa syndrome, Bonanni and colleagues[48] focused mainly on a restricted subset of patients with dystonic features. To

***Panel*: Definitions of postural deformities in Parkinson's disease and parkinsonism**

Camptocormia
Severe flexion (more than 45°) of the thoracolumbar spine in the sagittal plane during standing and walking, almost completely resolving in the recumbent position.

Antecollis
Severe forward flexion (more than 45°) of the head in the sagittal plane, partially overcome by voluntary movement but unable to fully extend the neck against gravity. Rarely seen in Parkinson's disease, it is frequent in multiple system atrophy.

Retrocollis
Abnormal posture of the neck that is held in extension in the sagittal plane. Rare in Parkinson's disease, it is typical of progressive supranuclear palsy.

Scoliosis
Flexion (more than 10°, according to the Cobb method) of the spine in the coronal plane not overcome by voluntary or passive movement, combined with axial rotation of the vertebrae confirmed by radiograph.

overcome such limitations, further validation of diagnostic criteria should be investigated in the context of longitudinal studies with larger study populations.

The absence of a consensus on diagnostic criteria and definition for Pisa syndrome contributes to the inconsistent prevalence rates among studies, ranging from 1·9% to 91%.[1,2,48,50–52] These discrepancies might also be explained by the inclusion of scoliosis as well as Pisa Syndrome and forms of parkinsonism other than Parkinson's disease in some studies, and by the small sample size of most studies.[1–3,5,25,50,51] Two large Italian studies have assessed the prevalence of Pisa syndrome in Parkinson's disease.[48,52] Bonanni and colleagues[48] found a 1·9% prevalence rate in a population of 1400 patients with Parkinson's disease and parkinsonism when using a lateral trunk flexion criteria of 15°. In a multicentre cross-sectional study of 1631 consecutive patients with Parkinson's disease, Tinazzi and colleagues[52] reported a prevalence of Pisa syndrome of 8·8% using the 10° lateral flexion criteria. Conversely, Cervantes and colleagues[53] found no cases of Pisa syndrome or antecollis in a cohort of 416 consecutive patients with Parkinson's disease assessed for musculoskeletal deformities with the clinical criteria proposed by Doherty and colleagues[1] (ie, lateral trunk flexion ≥10° for Pisa syndrome and neck forward flexion ≥45° for antecollis). The absence of Pisa syndrome was interpreted by the authors as the result of milder disease stages in their Parkinson's disease cohort.[53]

Pisa syndrome can occur in patients affected by atypical forms of parkinsonism, especially multiple system atrophy (MSA). The first description of probable Pisa syndrome in a case of pathologically proven striatonigral degeneration—a feature of MSA—was reported in 1978 by Kan,[20] who described a 64-year-old patient who developed "a lumbar scoliosis resulting from muscular dystonia" 2 years after onset of motor symptoms.[20] Two decades later, Colosimo and colleagues[21] reported a second case of Pisa syndrome, with sudden onset, alongside a clinical diagnosis of probable MSA. Postural abnormalities, including severe antecollis and Pisa syndrome, are now recognised as potential indicators of MSA. In a multicentre study from the European MSA Study Group,[24] Pisa syndrome was found in 42% of 57 patients with MSA with a predominant parkinsonian phenotype (both probable and possible according to the first consensus criteria) compared with 2·5% of 116 patients with Parkinson's disease matched for age, sex, and disease duration, reaching a specificity of 97·5% in the differential diagnosis of these disorders.[24] However, the study lacks post-mortem confirmation of MSA or Parkinson's disease diagnosis, and the clinical diagnosis of MSA was the gold standard used to assess the validity of antecollis and Pisa syndrome as warning signs for this disease.

Present evidence suggests that Pisa syndrome is a rare feature of progressive supranuclear palsy (PSP). In a series of 202 consecutive patients with Parkinson's disease, MSA, and PSP assessed for the presence of joint and skeletal deformities, Ashour and colleagues[25] reported camptocormia in 5·3% of patients with PSP compared with 12·2% of patients with Parkinson's disease and 26·3% of patients with MSA, and scoliosis was described in 5·3% of patients with PSP compared with 8·5% of patients with Parkinson's disease and 10·5% of patients with MSA. Ashour and colleagues found no cases of Pisa syndrome in their patient series, although this might be due to the absence of validated diagnostic criteria and the retrospective design of the study. Solla and colleagues[26] described a 69-year-old patient with a diagnosis of probable PSP who presented with a tonic flexion of the trunk of at least 10° to the right that occurred 3 years after the onset of motor symptoms. Furthermore, Noda and colleagues[27] have reported a case of probable PSP with lateral flexion of the trunk, which worsened when the patient was sitting (in a wheelchair) but was alleviated in the supine position.

Clinical features and concomitant medical conditions

Pisa syndrome can develop chronically with subtle onset and gradual progression, or with an acute onset followed by rapid worsening over months.[1,51,52,54] The pattern of onset has been classified according to the time taken to develop clinically definite Pisa syndrome: acute (<1 month), subchronic (≥1 month to <3 months), and chronic (≥3 months). Using these definitions, Tinazzi and colleagues[52] found that most patients in their cohort developed Pisa syndrome chronically. In chronic forms of Pisa syndrome, a slight reversible tilting behaviour

might occur when the patient is sitting or walking, which precedes the later occurrence of clinically definite Pisa syndrome; patients often do not perceive themselves as leaning to one side.[1,51,52,54] In such cases, progression of the syndrome is slow, and causal factors might be difficult to detect. Although acute onset is more likely to be associated with drug exposure according to anecdotal reports, there are no available data for the frequency of Pisa syndrome onset after initiation of treatment with dopaminergic drugs. In the only study that has systematically explored the prevalence of drug-induced Pisa syndrome, only 15% of patients with Parkinson's disease developed Pisa syndrome after changes to their drug regimen, whereas no correlation with drug exposure or treatment modification was noted in the remaining 85% of cases, regardless of whether the onset of the syndrome was acute, subchronic, or chronic.[52] This absence of correlation might have been due to the cross-sectional design of this study, which did not allow accurate definition of the temporal relationship between change in pharmacological regimen and Pisa syndrome onset.

Drug-induced Pisa syndrome in Parkinson's disease can arise from an increase or decrease in the dose of dopaminergic drugs, or might be due to insufficient dose of antiparkinsonian treatments. In this regard, almost all dopaminergic drugs, including levodopa, monoamine oxidase inhibitors (MAO-I), catechol-O-methyltransferase (COMT) inhibitors, and dopamine agonists, have been associated with Pisa syndrome occurrence, with no clear association between drug type and pattern of clinical onset.[36–43] Tinazzi and colleagues[52] have also reported that patients with Pisa syndrome in their cohort received higher doses of daily levodopa than patients without Pisa syndrome, and were more likely to be treated with a combination of levodopa and dopamine agonists; however, longitudinal studies are needed to confirm this association. Acute Pisa syndrome with a close temporal relation to drug exposure and transient relief after a sensory trick to overcome abnormal posture (eg, any motor act able to transiently improve posture alteration not due to a mechanical effect) has been reported in patients with Parkinson's disease associated with a dystonic-like cause (possible dystonic etiology of Pisa syndrome in some Parkinson's disease patients).[1,50–52,55]

Although most patients with Parkinson's disease and Pisa syndrome have been reported to lean towards the side of their body that is less affected by Parkinson's disease, a 2015 study[52] reported no difference in bending between ipsilateral and contralateral sides, and others have reported lateral flexion even in the absence of clear asymmetry of parkinsonian signs.[1,50] Finally, a recurrent and alternating leaning behaviour towards both sides (ie, metronome sign) has also been reported in patients with Parkinson's disease and Pisa syndrome.[52,56]

Patients with Pisa syndrome are usually older, have a substantially longer disease duration, more severe disease by Hoehn and Yahr scale (H&Y) staging, and worse quality of life compared with patients without Pisa syndrome.[52] Vitale and colleagues[57] reported a significant association of Pisa syndrome with altered attention and visuoperceptual dysfunction in patients with Parkinson's disease. Co-occurrence of other medical conditions such as osteoporosis and arthrosis with lower body mass index might increase the risk of developing Pisa syndrome, whereas female gender decreases the risk of having severe Pisa syndrome.[2,52] Moderate-to-severe lower back pain is sometimes reported by patients with Pisa syndrome irrespective of the severity of lateral trunk flexion and clinical onset.[48,52] Finally, falls and veering gait (ie, the progressive deviation of 30° or more towards one side in three consecutive trials of 5 m walking distance) are more likely to occur in patients with Parkinson's disease and Pisa syndrome than in patients with Parkinson's disease who do not have Pisa syndrome.[52]

Pisa syndrome can occur concomitantly with other postural abnormalities. In some patients with Parkinson's disease, forward trunk flexion is associated with the development of Pisa syndrome, especially in the advanced stages of Parkinson's disease.[48,49,51] Co-occurrence of postural deformities has been investigated with conflicting results. Bonanni and colleagues[48] found that 2·6% of patients in their cohort had Pisa syndrome in association with anterior axial flexion, the classic feature of camptocormia (forward trunk flexion greater than 45°). The co-occurrence of a lateral flexion of greater than 10° and a forward flexion of greater than 45° would probably lead to more severe mechanical constraints and disability (figure 1). Conversely, Tinazzi and colleagues[52] did not report any patients who fulfilled the diagnostic criteria for camptocormia or other rarer postural disorders such as antecollis (forward neck flexion greater than 45°) and retrocollis associated with Pisa syndrome. These discrepancies might be due in part to the sample sizes of the studies, which were not statistically powered to detect associations between postural abnormalities, and by the recruitment of patients from outpatient clinics.

As parkinsonism progresses and postural deformities become increasingly severe, pathological changes in the soft tissues might promote the transition from a reversible syndrome to a more permanent syndrome, in turn leading to dyspnoea, exacerbation of pain, and balance difficulties (table 1).[1,49–52]

Pathogenesis

The role of dopamine

The mechanisms underlying Pisa syndrome are probably multifactorial and might differ according to the associated disease. In non-parkinsonian patients, subacute onset of Pisa syndrome has been associated with exposure to or dose changes in both typical and atypical antipsychotics,[58–92] other psychotropic drugs including mood stabilisers, antidepressants, cholinesterase inhibitors,[6–18,93–96] and even antiemetics.[97,98] Most of these studies were reports of

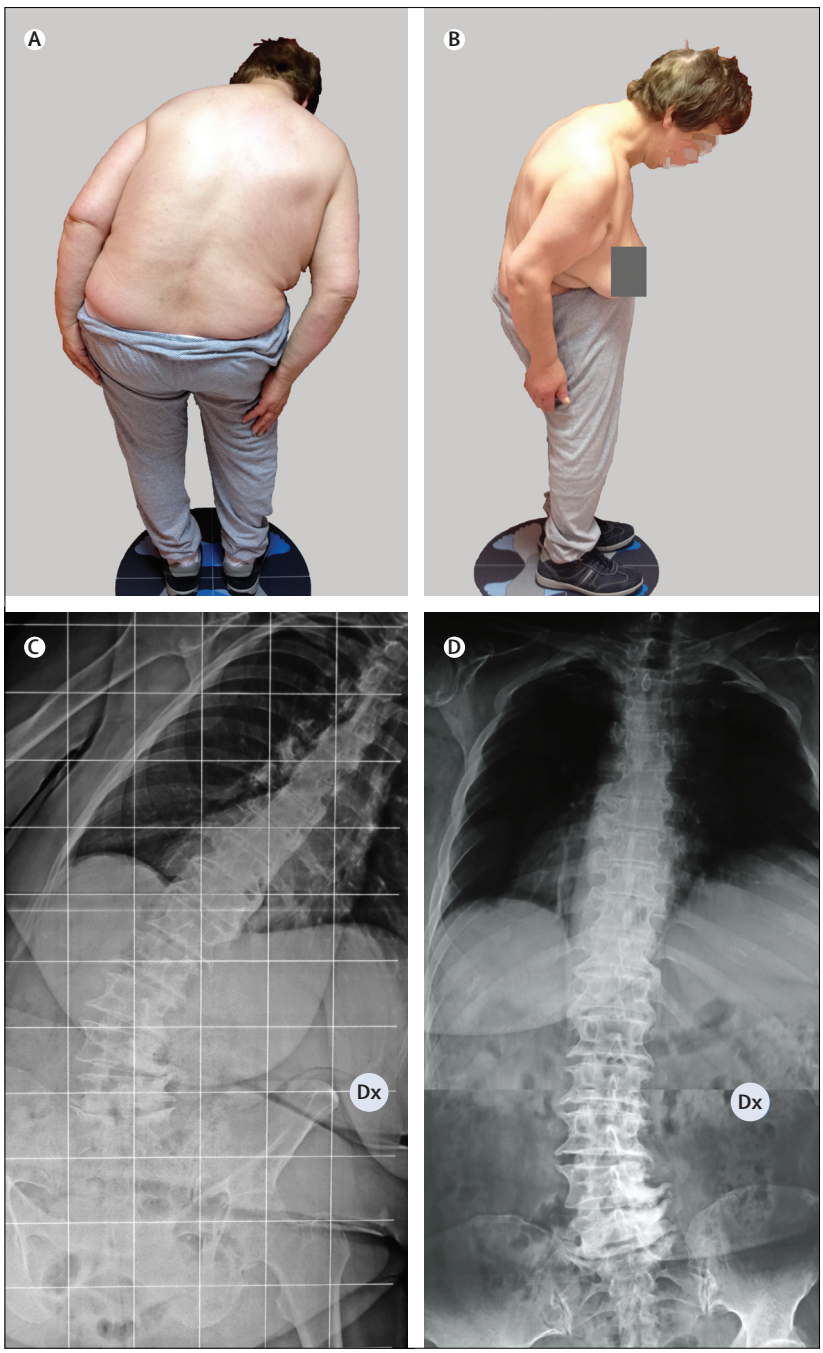

Figure 1: **Clinical appearance of a patient with Parkinson's disease and Pisa syndrome**
(A and B) 69-year-old female patient with Parkinson's disease and Pisa syndrome with forward flexion of the trunk (mixed deformity), with a predominantly coronal plane deformity. (C) Anteroposterior radiograph of the same patient standing, showing right leaning of the trunk. Note that the spinous processes are aligned without rotation of vertebral bodies, thus differentiating Pisa syndrome from scoliosis. The lines provide a goniometric reference. (D) Supine projection showing a complete resolution of Pisa syndrome while lying down. Dx=patient's right side.

anecdotal cases with no discussion of associated drug-induced parkinsonism. In parkinsonian patients, Pisa syndrome has been associated with the initiation or change in dose of dopamine agonists,[36,39,41] variation in levodopa regimen,[38,39] and addition of rasagiline and COMT inhibitors to levodopa treatment.[40,42,43,99] Accordingly, it has been hypothesised that a cholinergic–dopaminergic imbalance is involved in the development of drug-induced Pisa syndrome.[11] Dopamine-replacement therapy might promote development of Pisa syndrome in predisposed patients by priming the basal ganglia circuitry. Priming is a pharmacological occurrence after denervation of the nigrostriatal pathway (such as in Parkinson's disease) associated with sensitisation of dopaminergic receptors.[100] However, axial symptoms in Parkinson's disease respond poorly to dopaminergic treatment, suggesting that dysregulation of other neurotransmitter systems might have a role in the development of lateral trunk flexion. Apart from neurotransmitter dysfunction, Pisa syndrome might be explained by dysfunction of postural control systems that maintain balance and orientation in response to both internal and external perturbation and require a complex interaction between motor, sensory, and cognitive systems (figure 2).[101–103]

The role of the basal ganglia

Motor dysfunction, including bradykinesia, rigidity, and postural instability, are integral characteristics of parkinsonism, and the associated body asymmetry might predispose patients to lateral trunk flexion. The basal ganglia seem to have a primary role in the pathogenesis of Pisa syndrome, as suggested by the observation of lateral trunk flexion contralateral to the side of unilateral stereotactic subthalamotomy or pallidotomy.[44–46] Nevertheless, as noted above, in patients with Pisa syndrome, there is no clear laterality as they can either lean towards or away from the side most affected by Parkinson's disease, suggesting the contribution of factors other than basal ganglia asymmetry in Pisa syndrome development. Furthermore, no pathological evidence of asymmetry was found in the only reported autopsy of a patient with Pisa syndrome and Parkinson's disease.[104] In MSA, a marked asymmetry of striatal degeneration, as a proposed cause of Pisa syndrome, has been suggested by asymmetry in hypoperfusion on SPECT imaging, a slit-like hyperintensity at the outer margin of one putamen on MRI imaging and putaminal neuronal loss and astrogliosis at autopsy.[22] However, as these observations were made in only one case of MSA, confirmation in future studies is needed.

The role of sensorimotor dysfunction

The dysfunction of sensory and somatosensory systems (ie, visual and vestibular systems) and its contribution to postural control has previously been investigated in patients with Parkinson's disease without Pisa syndrome with inconclusive results.[105–111] Patients with Parkinson's disease are unable to properly control their postural orientation based on sensory information from the

muscles and joints, suggesting that a deficit in proprioceptive information processing might contribute to poor signal integration in posture control.[50,51,111] Furthermore, patients with Parkinson's disease and Pisa syndrome have more difficulty in achieving good postural alignment with gravity and have a greater velocity of body sway than patients without Pisa syndrome.[112] There is evidence to suggest a link between vestibular dysfunction and lateral trunk flexion.[100,113] Mamo and colleagues[113] reported vestibular dysfunction in patients with Parkinson's disease who developed transient contralateral trunk flexion after unilateral thalamotomy and subthalamotomy. These investigators concluded that vestibular dysfunction, although necessary, was not sufficient to induce postural abnormalities.

Peripheral unilateral vestibular hypofunction, ipsilateral to the leaning side and contralateral to the side most affected by Parkinson's disease, has recently been described in a small series of patients with Parkinson's disease and Pisa syndrome, and might contribute to the patients' postural abnormalities. Subclinical vestibular hypofunction might also occur before the onset of Pisa syndrome in patients with Parkinson's disease without lateral trunk flexion.[100] It is possible that as the disease progresses and vestibular deficits increase alongside the development of proprioceptive impairments, an adaptive reweighting of sensory inputs occurs, leading to the lateral trunk flexion observed in patients with Parkinson's disease and Pisa syndrome. Although these findings suggest a link between sensorimotor integration failure and postural abnormalities, the role of proprioceptive and vestibular dysfunctions and their contribution to Pisa syndrome pathogenesis needs to be further validated in the context of larger study populations.

The role of body schema perception and cognition

Alterations in the perception of postural alignment and abnormalities in subjective visual perception of verticality have also been reported in patients with Parkinson's disease and Pisa syndrome, and might contribute to postural deformity.[1,50,52–54,114,115] Whether these alterations are the result of defective integration of somatosensory and vestibular input or secondary to abnormal spatial cognition and body schema needs to be further investigated. Postural control requires complex motor–cognitive interactions that rely on high attentional resources and preserved executive functions;[101–103] however, until now, few studies have investigated the association between cognitive deficits and postural deformities in patients with Parkinson's disease. In a small sample of patients with Parkinson's disease, impaired executive function, assessed with the Montreal Cognitive Assessment and the Frontal Assessment Battery, was recorded in those with Pisa syndrome compared with those without Pisa syndrome.[49] A 2015 study[57] investigated cognitive function in patients with Parkinson's disease with and without Pisa syndrome

	≥15° lateral flexion of the trunk[48]		≥10° lateral flexion of the trunk[52]	
	Participants	Mean (SD) or %	Participants	Mean (SD) or %
Prevalence	26/1400*	1·9%	143/1631†	8·8%
Age (years)	9	72 (5·7)	143	71·1 (8·0)
Sex				
Men	5/9	56%	79/143	55%
Women	4/9	44%	64/143	45%
Disease duration (years)	9	10·3 (7·2)	143	9·6 (5·3)
UPDRS-III score	9	21 (5)	143	27·9 (10·4)
Hoehn & Yahr score	9	2·5 (0·5)	143	2·6 (0·8)
Pisa syndrome degrees	9	30 (7·2)	143	17 (7·4)
MMSE score	9	21 (3·3)	..	..
Levodopa equivalent dose (mg)	9	858 (58·2)	143	570·4 (272·6)
Latency of Pisa syndrome after onset of Parkinson's disease (years)	..	..	141	7 (5)
Pisa syndrome duration (years)	9	2·4 (0·9)	143	2·6 (2·5)
Pisa syndrome direction				
Right	4/9	44%	99/143	69%
Left	5/9	56%	44/143	31%
Side of Parkinson's disease symptoms at onset and Pisa syndrome inclination				
Ipsilateral	..	..	58/143	41%
Contralateral	..	..	59/143	41%
Bilateral	..	..	26/143	18%
Pisa syndrome pattern of onset				
<1 month (acute)	..	..	19/143	13%
≥1 month to <3 months (subchronic)	..	..	24/143	17%
≥3 months (chronic)	..	..	100/143	70%
Pisa syndrome development after drug modification				
Yes	..	..	21/143	15%
No	..	..	122/143	85%
Pisa Syndrome awareness				
Yes	..	..	119/143	83%
No	..	..	24/143	17%
Back pain				
Yes	9/9	100%	101/143	71%
No	0/9	0%	42/143	29%
VAS pain score	9	71·8 (5·7)‡	101/143	6 (2·3)§
Metronome Pisa syndrome				
Yes	..	..	13/134	10%
No	..	..	121/134	90%
Head compensation				
Yes	..	..	59/138	43%
No	..	..	79/138	57%
Compensatory effect of a sensory trick				
Yes	..	..	24/143	17%
No	..	..	119/143	83%
Electromyographic recordings	26/26	100%	..	..

UPDRS=Unified Parkinson's Disease Rating Scale. MMSE=Mini mental State Examination. VAS=Visual Analogue Scale. *In this study of 1400 patients with parkinsonism, 4726 had Pisa syndrome and underwent EMG assessment; nine were further admitted to botulin toxin versus placebo treatment. †In this study of 1631 patients with Parkinson's disease,[51] 143 had Pisa syndrome, all of whom were selected for further assessment. ‡VAS interval 0–100. §VAS interval 1–10.

Table 1: **Clinical and demographic features of patients with Parkinson's disease and Pisa syndrome according to diagnostic criteria of ≥15° and ≥10° lateral trunk flexion, respectively**

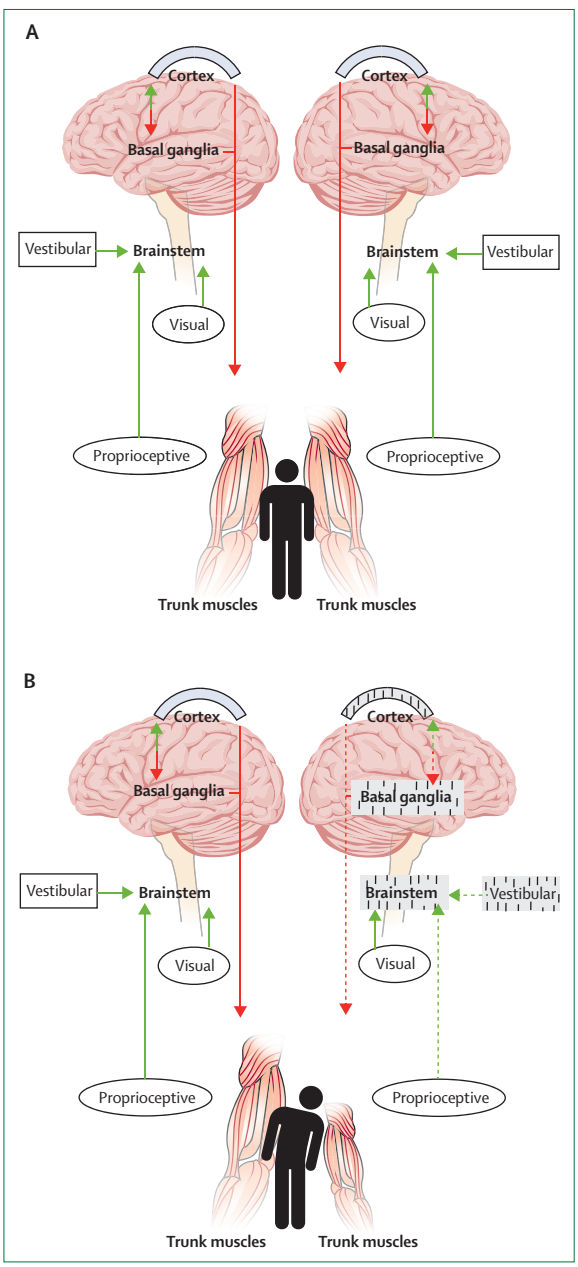

Figure 2: **Central control mechanisms of postural stability**
(A) Normal conditions. (B) Parkinson's disease. Postural control in healthy individuals relies on network interactions of the cortex, basal ganglia, and brainstem, which integrate motor (trunk muscles), sensory (visual, vestibular, and proprioceptive), and cognitive systems. In a patient with Parkinson's disease and Pisa syndrome, asymmetrical basal ganglia functioning together with impaired processing of sensory information (visual, vestibular, and proprioceptive), cognitive dysfunctions, and altered perception of body alignment (cortex) might lead to asymmetric trunk muscle stimulation. Green and red lines indicate input and output pathways, respectively. Shaded areas and lines indicate alterations of brain structures and pathways, respectively. Such alterations might be due to the Parkinson's disease pathology (brainstem, basal ganglia, and cortex) or to concomitant medical conditions (vestibular or proprioceptive dysfunctions)

who did not differ on demographic features (ie, age at Parkinson's disease onset and disease duration) but did have differences in motor disability and levodopa-equivalent daily dose. After controlling for motor disability and levodopa dose, patients with Pisa syndrome scored significantly lower on specific tasks exploring executive functions (ie, divided attention, inhibitory control, and delayed free recall in verbal learning) and perceptual visuospatial functions than patients with Parkinson's disease without postural deformities.[57] Because Pisa syndrome has been reported in more severe cases of Parkinson's disease, it is possible that as the disease progresses, cognitive dysfunction becomes more severe, which in turn contributes to development of Pisa syndrome.

The role of the trunk muscles

Pisa syndrome has been interpreted by some investigators as a dystonic posture on the basis of both EMG findings (showing a tonic activation either in paraspinal muscles or in the abdominal oblique muscles ipsilateral to the side affected by deviation) and reports of improvement after administration of botulinum toxin type A to the paraspinal muscles.[48,116] However, the dystonic posture hypothesis has been criticised because of the absence of clinical characteristics of dystonia, such as overflow, twisting, and compensatory effects of sensory tricks in patients with Pisa syndrome.[52] Furthermore, two studies by the same group of investigators, using the same diagnostic criteria for Pisa syndrome, reported contradictory EMG patterns—hyperactivity of paraspinal muscles ipsilateral to the leaning side versus continuous activity contralateral to the leaning side—thus only partially confirming the dystonic theory.[117,118] The differences in EMG findings between these two studies might be explained by the EMG testing paradigms used (static *vs* dynamic or standing *vs* sitting) and the limited number of muscles assessed. Tinazzi and colleagues[117,118] extended their EMG study to more muscles in both static and dynamic conditions (eg, paraspinal lumbar, paraspinal thoracic, abdominal oblique, iliopsoas, and rectus femoris) and found two different EMG patterns.[118] The first pattern was characterised by hyperactivity of lumbar paraspinal muscles contralateral to the leaning side; half of the patients with Parkinson's disease also showed ipsilateral hyperactivity of thoracic paraspinal muscles. The second pattern, thoracic paraspinal hyperactivity, was contralateral in all patients. The investigators also found hyperactivity of non-paraspinal muscles in both ipsilateral and contralateral sides, and concluded that hyperactivity of contralateral paraspinal muscles probably compensates for the trunk leaning.[118]

Although a primitive myopathy has been suggested to explain Pisa syndrome,[116] no pathological study exists to prove this hypothesis. In a study involving CT scans of paraspinal muscles, Tassorelli and colleagues found

muscular atrophy that was more pronounced on the leaning side, with a cranio-caudal gradient involving the multifidus and latissimus dorsi muscles.[116] An MRI study has confirmed the presence of atrophy of the lumbar paraspinal muscles with fatty degeneration that is greater, and more prevalent, on the leaning side.[118] Such muscular atrophy might be explained as the consequence of chronically altered posture rather than as a causative factor, but further investigation is needed to understand the role of muscular atrophy.

Management of Pisa syndrome

The management of Pisa syndrome represents a clinical challenge mainly owing to the absence of high-quality, specifically designed studies addressing this syndrome. On the basis of the available data, Parkinson's disease drug revision and adjustment can be considered as the first-line intervention, and pharmacological, non-pharmacological, and surgical strategies as second-line interventions. Owing to the lack of evidence for the management of Pisa syndrome in atypical forms of parkinsonism, we specifically focus on Pisa syndrome treatment in idiopathic Parkinson's disease. However, it should be noted that the literature remains inconclusive and definitive recommendations for treatment strategies cannot be made (table 2).

Revision of drug regimen

When considering treatment options for Pisa syndrome, the first step is to characterise its onset and progression (acute, subchronic, or chronic) in relation to the patient's antiparkinsonian treatment regimen. In particular, Pisa syndrome has been associated with initiation and dose changes of dopamine agonists,[36,39,41] levodopa,[38,39] and addition of MAO and COMT inhibitors.[40,42,43,99] A close temporal relation between Pisa syndrome occurrence and dopaminergic therapy modification might enable early recognition of the offending drug and its prompt withdrawal or dose adjustment as a first-line treatment option. Improvement of Pisa syndrome has been reported after discontinuation or reduction of antiparkinsonian drugs that had been initiated before the onset of Pisa syndrome.[36,38–43,99] Data are not available on the risk associated with developing Pisa syndrome for specific antiparkinsonian drugs, so it is not possible to speculate about drug-specific mechanisms. However, Pisa syndrome has been observed during off periods (ie, worsening of parkinsonian symptoms when treatment is less effective) in two patients with Parkinson's disease and motor fluctuations, which improved after an increase of levodopa dose.[38] In these cases, lateral trunk flexion might have resembled end-of-dose deterioration or off-period dystonia, suggesting that Pisa syndrome could be associated with striatal dopamine deficiency or an imbalance in the dopaminergic–cholinergic systems.

Pharmacological treatment

In patients with Parkinson's disease, according to the assumption that Pisa syndrome could be due to paraspinal muscles dystonia, treatment with botulinum toxin has been used, although results have been inconclusive. Bonanni and colleagues[48] did a randomised, double-blind, crossover, placebo-controlled trial in a small cohort of patients with Parkinson's disease and Pisa syndrome; they found that injection of botulinum toxin A into paraspinal muscles on the side of the trunk flexion resulted in an improvement of the lateral bending by 50–87·5% in six of nine patients.[48] However, the reason why some patients benefit from this treatment and other do not is unexplained. More recently, the injection of botulinum toxin A into the hyperactive trunk muscles has been found to improve the effectiveness of rehabilitation in a series of patients with Parkinson's disease and Pisa syndrome in a small, randomised, placebo-controlled trial.[119] Consistent with this, Dupeyron and colleagues[120] reported complete resolution of abnormal posture after botulinum toxin A injection into hyperactive quadratus lumborum muscles on the leaning side in a patient with Parkinson's disease. There have not yet been any clinical trials assessing pharmacological treatment approaches for pain in Pisa syndrome.

Non-pharmacological treatment

Only two small studies have assessed the effectiveness of non-pharmacological treatment—ie, rehabilitation—for Pisa syndrome in Parkinson's disease. Findings have been inconsistent and further studies assessing the long-term effects are warranted. The first study was an open trial including a group of 22 patients with Parkinson's disease with lateral trunk flexion (ranging from mild to severe) and a control group of 22 patients with Parkinson's disease without lateral trunk flexion, matched for age, disease duration, and severity. The intervention consisted of a 4-week rehabilitation programme specifically aimed at reducing rigidity and improving flexibility and mobility of the trunk. The investigators reported significant reduction of lateral trunk flexion, which was maintained at 6 months after the end of the rehabilitation programme.[121] Capecci and colleagues[122] did a single-blind, randomised controlled trial in which they assessed the efficacy of a 4-week patient-tailored programme consisting of proprioceptive and tactile stimulation combined with stretching and postural re-education in 13 patients with Parkinson's disease and postural abnormalities of the trunk. Six of 13 treated patients also received kinesio taping of the trunk muscles as additional treatment. The investigators reported that at the end of the programme, the treated patients had substantial but not lasting improvement of the lateral bending. Furthermore, there was no difference between patients who received combined rehabilitation and kinesio taping and patients who received rehabilitation only.[123]

Surgical treatment

Few studies have specifically assessed the effects of DBS on lateral trunk flexion. The available studies are mainly case series or case reports and the results have been inconclusive. In a retrospective study[47] of ten patients with Parkinson's disease who had symptoms of Pisa syndrome during on periods (ie, when parkinsonian symptoms were adequately controlled with anti-parkinsonian drugs), efficacy of subthalamic DBS in reducing postural abnormalities was assessed. The investigators reported substantial improvement in the posture of patients who had mild-to-moderate Pisa syndrome, but less consistent results in patients with severe lateral trunk flexion, including no improvement in some. Two studies[124,125] have reported a beneficial effect of DBS of the pedunculopontine nucleus in patients with Pisa syndrome. However, this benefit was observed only at a 6-month follow-up assessment and was not maintained over time.[125] On the basis of the few available studies, it is not possible to determine whether DBS has a direct effect on Pisa syndrome or whether any positive effects associated with DBS might be attributed to post-surgical modifications to the dopaminergic drug regimen. Aside from its inconclusive role in the management of Pisa syndrome, Parkinson's disease surgery has been suggested to be responsible for Pisa syndrome in some cases; a long-term follow-up study has shown that patients with Parkinson's disease treated with either unilateral subthalamotomy[44] or pallidotomy[45,46] occasionally develop postural abnormalities.

Finally, spinal realignment surgery might be required in severe cases of Pisa syndrome associated with compression fracture, osteonecrosis, and intractable radicular and back pain. Spinal surgery in patients with Parkinson's disease is challenging owing to commonly occurring complications—namely construct or fusion-related complications, infection, and a frequent need for revision surgery, mainly for progressive kyphosis or spine segmental instability. In particular, postoperative sagittal imbalance would represent one of the main factors responsible for construct failure and the need for revision surgery. Risk factors for surgical complications include advanced Parkinson's disease, severe disability, and poor functional status.[124] A 2015 review of case series suggests that a favourable outcome depends on appropriate selection of surgical patients on the basis of an interdisciplinary approach involving both surgeons and movement disorders specialists.[126]

Conclusions and future directions

Pisa syndrome in Parkinson's disease could be the result of multiple factors including asymmetric basal ganglia function, impaired processing of sensory information, cognitive dysfunction, and altered perception of body alignment. Co-occurrence of concomitant medical conditions such as osteoporosis and arthrosis might further increase the risk of developing postural abnormalities and promote the transition from a reversible syndrome to a chronic condition with irreversible structural deformities (structured Pisa syndrome). Overlap between complex central (dopaminergic and non-dopaminergic) and peripheral mechanisms could explain the clinical heterogeneity and prognosis of Pisa syndrome in Parkinson's disease and other forms of parkinsonism, but more research is needed to better define this syndrome and to optimise its management.

	Action	Commentary on action	Level of evidence*
First-line approach	Accurate review of introduction or modification of antiparkinsonian drugs to adjust or discontinue the possible inducing drugs[36,39-43,99,113]	Antiparkinsonian drug changes or discontinuation could worsen Pisa syndrome	C
Second-line approach			
Pharmacological treatment	Botulinum toxin A in hyperactive paraspinal muscles[48,118,119]	Effectiveness of botulinum toxin A injections is inconsistent between patients	B
Non-pharmacological treatment	Rehabilitation programmes specifically aimed at reducing rigidity and improving flexibility and mobility of the trunk[120] Patient-tailored proprioceptive and tactile stimulation, combined with stretching and postural re-education[121]	Few data are available; trials of rehabilitation programmes have been done in small cohorts and data on long-term effects are inconsistent	B and C
Surgical treatment	Subthalamic deep brain stimulation[47] Pedunculopontine deep brain stimulation[122,123] Spinal realignment surgery[124]	Few data are available: data suggest subthalamic deep brain stimulation might be effective in mild or moderate Pisa syndrome; pedunculopontine deep brain stimulation could be beneficial but its effects are not lasting; owing to the high risk of complications, spinal surgery should be reserved for selected cases associated with compression fracture, osteonecrosis, and intractable pain	C

* Level A=recommendation based on consistent and good-quality patient-oriented evidence (randomised double-blind controlled trials of sufficient size and consistency). Level B=recommendation based on inconsistent or limited-quality patient-oriented evidence (randomised clinical trials of insufficient size or other comparative trials). Level C=recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series.

Table 2: **Treatment options for the management of Pisa syndrome in Parkinson's disease**

Consensus on diagnostic criteria are needed for Pisa syndrome, which should include goniometric and radiological measures. The current absence of both validated diagnostic criteria and longitudinal studies prevent us from determining the timing of Pisa syndrome onset and defining the risk factors, including drug exposure or specific parkinsonian clinical features, which might predispose patients to development of this syndrome. The common clinical observation of a reversible and unconscious tilting behaviour (less than 10°) in some patients with Parkinson's disease raises the question of whether these patients are at risk of developing structured Pisa syndrome. Early detection of lateral trunk flexion, irrespective of its goniometric values, would be relevant in preventing fixed, non-reversible deformities, thereby avoiding complications that might arise from such a disabling condition.

Future studies on Pisa syndrome pathogenesis should explore pathological changes in basal ganglia with a special focus on asymmetry of neural degeneration, which has been proposed as a possible mechanism causing Pisa syndrome, but never fully demonstrated. There is an absence of both functional MRI and diffusion tractography studies, which could provide evidence for both hemispheric asymmetries and alterations in connections of specific brain structures. Only three groups of researchers have reported the results of EMG studies in patients with Pisa syndrome and findings are inconsistent. These discrepancies might be due to differences in patient selection criteria or experimental procedures, especially those related to dynamic or static assessments and the number of studied muscles. Establishing a consensus for experimental EMG procedures might increase understanding of the physiology of trunk movements in both unaffected and affected participants. This approach might help to better understand the crucial issue of possible overlap between Pisa syndrome and other postural abnormalities in Parkinson's disease. Similarly, clinical and functional comparisons between Pisa syndrome associated with Parkinson's disease and atypical parkinsonism and drug-induced Pisa syndrome could be useful to understand the pathological mechanisms that predispose patients with Parkinson's disease to the development of Pisa syndrome and consequent preventive actions.

The present data on interventions for Pisa syndrome provide only weak evidence for treatment recommendations. Adjustments in drug regimen and the second-line strategies botulinum toxin injection, rehabilitation, and surgery might be considered as treatment options for Pisa syndrome in Parkinson's disease, although their efficacy needs to be further explored in well designed studies involving larger populations of patients with Parkinson's disease and in patients with atypical forms of parkinsonism.

Search strategy and selection criteria

We searched PubMed, Scopus, and ISI Web of Science for articles published up to May 30, 2016 with the terms "Pisa syndrome", "lateral trunk flexion", "trunk bending", "pleurothonus", "Parkinson's disease/parkinsonism", "multiple system atrophy", and "progressive supranuclear palsy". Selected articles were also obtained from the reference lists of papers identified by the previous searches. Apart from a few key studies, only reports published in English were included. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Contributors

All authors contributed equally to this Review.

Declaration of interests

PB reports personal fees from Acorda, personal fees from Union Chimique Belge, personal fees from Zambon, grants from Abbvie, grants from Biotie, and grants from Zambon. GS, MTP, MA, and CV declare no competing interests.

References

1 Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. *Lancet Neurol* 2011; **10:** 538–49.
2 Kashihara K, Imamura T. Clinical correlates of anterior and lateral flexion of the thoracolumbar spine and dropped head in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2012; **18:** 290–93.
3 Sicard JA, Alquier L. Les deviations de la colonne vertebrale dans la maladie de Parkinson. *Nouvelle Iconographie de la Salpetriere* 1905; **16:** 377–84.
4 Duvoisin RC, Marsden CD. Note on the scoliosis of Parkinsonism. *J Neurol Neurosurg Psychiatry* 1975; **38:** 787–93.
5 Ekbom K, Lindholm H, Ljungberg L. New dystonic syndrome associated with butyrophenone therapy. *Z Neurol* 1972; **202:** 94–103.
6 Davidson M, Powchik P, Davis KL. Pisa syndrome in Alzheimer's disease. *Biol Psychiatry* 1988; **23:** 213.
7 Patel S, Tariot PN, Hamill RW. Pisa syndrome without neuroleptic exposure in a patient with dementia of the Alzheimer type. *J Geriatr Psychiatry Neurol* 1991; **4:** 48–51.
8 Kwak YT, Han IW, Baik J, Koo MS. Relation between cholinesterase inhibitor and Pisa syndrome. *Lancet* 2000; **355:** 2222.
9 Miyaoka T, Seno H, Yamamori C, et al. Pisa syndrome due to a cholinesterase inhibitor (donepezil): a case report. *J Clin Psychiatry* 2001; **62:** 573–74.
10 Suzuki T, Matsuzaka H. Drug-induced Pisa syndrome (pleurothotonus): epidemiology and management. *CNS Drugs* 2002; **16:** 165–74.
11 Villarejo A, Camacho A, García-Ramos R, et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol* 2003; **26:** 119–21.
12 Cossu G, Melis M, Melis G, et al. Reversible Pisa syndrome (pleurothotonus) due to the cholinesterase inhibitor galantamine: case report. *Mov Disord* 2004; **19:** 1243–44.
13 Vanacore N, Suzzareddu G, Maggini M, Casula A, Capelli P, Raschetti R. Pisa syndrome in a cohort of Alzheimer's disease patients. *Acta Neurol Scand* 2005; **111:** 199–201.
14 Chen CF, Hsu HC, Ouyang WC, Lin YC. Galantamine-induced pisa syndrome: memantine as an alternative. *Int J Geriatr Psychiatry* 2008; **23:** 660–61.
15 Leelavathi M, Rosdinom R, Suguna M. Pisa syndrome secondary to rivastigmine: a case report. *Clin Ter* 2012; **163:** 31–32.
16 Shinfuku M, Nakajima S, Uchida H, Watanabe K, Kocha H, Kashima H. Pisa syndrome caused by an acetylcholinesterase inhibitor in a patient with dementia with Lewy bodies. *Psychiatry Clin Neurosci* 2011; **65:** 299.
17 Huvent-Grelle D, Boulanger E, Puisieux F. Relationship between Pisa syndrome and cholinesterase inhibitor use for elderly adults with Alzheimer's disease. *J Am Geriatr Soc* 2014; **62:** 2450–53.

18 Zannas AS, Okuno Y, Doraiswamy PM. Cholinesterase inhibitors and Pisa syndrome: a pharmacovigilance study. *Pharmacotherapy* 2014; **34:** 272–78.

19 Martin JP. Curvature of the spine in post-encephalitic parkinsonism. *J Neurol Neurosurg Psychiatry* 1965; **28:** 395–400.

20 Kan AE. Striatonigral degeneration. *Pathology* 1978; **10:** 45–52.

21 Colosimo C. Pisa syndrome in a patient with multiple system atrophy. *Mov Disord* 1998; **13:** 607–09.

22 Hozumi I, Piao YS, Inuzuka T, et al. Marked asymmetry of putaminal pathology in an MSA-P patient with Pisa syndrome. *Mov Disord* 2004; **19:** 470–72.

23 Sławek J, Derejko M, Lass P, Dubaniewicz M. Camptocormia or Pisa syndrome in multiple system atrophy. *Clin Neurol Neurosurg* 2006; **108:** 699–704.

24 Köllensperger M, Geser F, Seppi K, et al, and the European MSA Study Group. Red flags for multiple system atrophy. *Mov Disord* 2008; **23:** 1093–99.

25 Ashour R, Jankovic J. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Mov Disord* 2006; **21:** 1856–63.

26 Solla P, Cannas A, Costantino E, Orofino G, Lavra L, Marrosu F. Pisa syndrome in a patient with progressive supranuclear palsy. *J Clin Neurosci* 2012; **19:** 922–23.

27 Noda K, Kawajiri S, Tomizawa Y, Hattori N, Okuma Y. Pisa syndrome in progressive supranuclear palsy: A case report. *Parkinsonism Relat Disord* 2015; **21:** 1115–16.

28 Salazar Z, Tschopp L, Calandra C, Micheli F. Pisa syndrome and parkinsonism secondary to valproic acid in Huntington's disease. *Mov Disord* 2008; **23:** 2430–31.

29 Deriu M, Murgia D, Paribello A, Marcia E, Melis M, Cossu G. Pisa syndrome as presenting symptom of amyotrophic lateral sclerosis. *J Neurol* 2011; **258:** 2087–89.

30 Malhotra HS, Garg RK. Pearls & Oy-sters: Pisa syndrome: an unusual feature of adult-onset fulminant SSPE. *Neurology* 2015; **84:** e12–14.

31 Abboud H, Sivaraman I, Ontaneda D, Tavee J. Camptocormia and Pisa syndrome as manifestations of acute myasthenia gravis exacerbation. *J Neurol Sci* 2015; **359:** 8–10.

32 Cannas A, Solla P, Mascia M, et al. Pisa-like syndrome under Baclofen in a patient with spastic hemiparesis due to ischemic stroke. *Clin Neuropharmacol* 2015; **38:** 217–19.

33 Leon-Sarmiento FE, Pradilla G, Del Rosario Zambrano M. Primary and reversible Pisa syndrome in juvenile normal pressure hydrocephalus. *Acta Neuropsychiatr* 2013; **25:** 57–60.

34 Marchione P, Spallone A, Valente M, Giannone C, De Angelis F, Meco G. Reversible Pisa syndrome associated to subdural haematoma: case-report. *BMC Neurol* 2014; **14:** 149.

35 Bhattacharya KF, Giannakikou I, Munroe N, Chaudhuri KR. Primary anticholinergic-responsive Pisa syndrome. *Mov Disord* 2000; **15:** 1285–87.

36 Cannas A, Solla P, Floris G, Borghero G, Tacconi P, Spissu A. Reversible Pisa syndrome in Parkinson's disease during treatment with pergolide: a case report. *Clin Neuropharmacol* 2005; **28:** 252.

37 Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. *Mov Disord* 2005; **20** (suppl 11): S11–16.

38 Kim JS, Park JW, Chung SW, Kim YI, Kim HT, Lee KS. Pisa syndrome as a motor complication of Parkinson's disease. *Parkinsonism Relat Disord* 2007; **13:** 126–28.

39 Cannas A, Solla P, Floris G, et al. Reversible Pisa syndrome in patients with Parkinson's disease on dopaminergic therapy. *J Neurol* 2009; **256:** 390–95.

40 Fasano A, Di Matteo A, Vitale C, et al. Reversible Pisa syndrome in patients with Parkinson's disease on rasagiline therapy. *Mov Disord* 2011; **26:** 2578–80.

41 Galati S, Möller JC, Städler C. Ropinirole-induced Pisa syndrome in Parkinson disease. *Clin Neuropharmacol* 2014; **37:** 58–59.

42 Solla P, Cannas A, Orofino G, Marrosu F. Rasagiline and Pisa syndrome in Parkinson's disease patients. *Neurol Sci* 2015; **36:** 485–86.

43 Valentino F, Cosentino G, Fierro B, et al. Pisa syndrome after rasagiline therapy in a patient with Parkinson's disease. *Neurol Sci* 2015; **36:** 2305.

44 Su PC, Tseng HM, Liou HH. Postural asymmetries following unilateral subthalomotomy for advanced Parkinson's disease. *Mov Disord* 2002; **17:** 191–94.

45 van de Warrenburg BP, Bhatia KP, Quinn NP. Pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event? *J Neurol Neurosurg Psychiatry* 2007; **78:** 329–30.

46 Spanaki C, Zafeiris S, Plaitakis A. Levodopa-aggravated lateral flexion of the neck and trunk as a delayed phenomenon of unilateral pallidotomy. *Mov Disord* 2010; **25:** 655–56.

47 Umemura A, Oka Y, Ohkita K, Yamawaki T, Yamada K. Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease. *J Neurosurg* 2010; **112:** 1283–88.

48 Bonanni L, Thomas A, Varanese S, Scorrano V, Onofrj M. Botulinum toxin treatment of lateral axial dystonia in Parkinsonism. *Mov Disord* 2007; **22:** 2097–103.

49 Doherty KM, Davagnanam I, Molloy S, Silveira-Moriyama L, Lees AJ. Pisa syndrome in Parkinson's disease: a mobile or fixed deformity? *J Neurol Neurosurg Psychiatry* 2013; **84:** 1400–03.

50 Castrioto A, Piscicelli C, Pérennou D, Krack P, Debû B. The pathogenesis of Pisa syndrome in Parkinson's disease. *Mov Disord* 2014; **29:** 1100–07.

51 Michel SF, Arias Carrión O, Correa TE, Alejandro PL, Micheli F. Pisa Syndrome. *Clin Neuropharmacol* 2015; **38:** 135–40.

52 Tinazzi M, Fasano A, Geroin C, et al, and the Italian Pisa Syndrome Study Group. Pisa syndrome in Parkinson disease: An observational multicenter Italian study. *Neurology* 2015; **85:** 1769–79.

53 Cervantes-Arriaga A, Rodríguez-Violante M, Morales-Briceño H, Neri-Nani G, Millán-Cepeda R, Velázquez-Osuna S. Frequency and clinical correlates of postural and striatal deformities in Parkinson's disease. *Clin Neurol Neurosurg* 2016; **142:** 140–44.

54 Yokochi F. Lateral flexion in Parkinson's disease and Pisa syndrome. *J Neurol* 2006; **253** (suppl 7): VII17–20.

55 de Pablo-Fernández E, Villarejo-Galende A. Clinical heterogeneity and underlying pathophysiological mechanisms of lateral flexion of the trunk in Parkinson's disease. *J Neurol* 2012; **259:** 771–72.

56 Pellene A, Saenz-Farret M, Micheli F. Recurrent and Alternating Pisa Syndrome. *Clin Neuropharmacol* 2015; **38:** 252–54.

57 Vitale C, Falco F, Trojano L, et al. Neuropsychological correlates of Pisa syndrome in patients with Parkinson's disease. *Acta Neurol Scand* 2015; published online Oct 2. DOI:10.1111/ane.12514.

58 Arora M, Praharaj SK, Sarkar S. Clozapine effective in olanzapine-induced Pisa syndrome. *Ann Pharmacother* 2006; **40:** 2273–75.

59 Bruneau MA, Stip E. Metronome or alternating Pisa syndrome: a form of tardive dystonia under clozapine treatment. *Int Clin Psychopharmacol* 1998; **13:** 229–32.

60 Chen HK, Wu BJ, Shao CH. Drug-induced Pisa syndrome associated with aripiprazole during clozapine treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34:** 707–08.

61 Cordeiro Q, Zung S, Vallada H. Pisa syndrome induced by rapid increase and high dosage of risperidone. *Arq Neuropsiquiatr* 2008; **66:** 896–97.

62 De Risio L, Pettorruso M, Di Nicola M, Martinotti G, Janiri L, Fasano A. Management of aripiprazole-induced tardive Pisa syndrome: a case report and literature review. *Int Clin Psychopharmacol* 2016; **31:** 57–60.

63 Duggal HS, Mendhekar DN. Risperidone-induced tardive pharyngeal dystonia presenting with persistent Dysphagia: a case report. *Prim Care Companion J Clin Psychiatry* 2008; **10:** 161–62.

64 Duggal HS, Sivamony S, Umapathy C. Pisa syndrome and atypical antipsychotics. *Am J Psychiatry* 2004; **161:** 373.

65 Duggal HS. Acute pisa syndrome and pharnygolaryngeal dystonia due to ziprasidone. *J Neuropsychiatry Clin Neurosci* 2008; **20:** 108–09.

66 Dunayevich E, Strakowski SM. Olanzapine-induced tardive dystonia. *Am J Psychiatry* 1999; **156:** 1662.

67 Güneş S, Ekinci Ö, Direk MÇ, Yıldırım V, Okuyaz Ç, Toros F. Risperidone Induced Pisa Syndrome in a Male Adolescent. *Clin Psychopharmacol Neurosci* 2016; **14:** 104–06.

68 Harada K, Sasaki N, Ikeda H, Nakano N, Ozawa H, Saito T. Risperidone-induced Pisa syndrome. *J Clin Psychiatry* 2002; **63:** 166.

69 Huang YC, Lee Y, Lin PY. Reversible Pisa syndrome associated with switching from haloperidol to aripiprazole during lithium treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33:** 1284–85.

70 Hung TH, Lee Y, Chang YY, Chong MY, Lin PY. Reversible Pisa syndrome induced by clozapine: a case report. *Clin Neuropharmacol* 2007; **30:** 370–72.

71 Iuppa CA, Diefenderfer LA. Risperidone-induced Pisa syndrome in MS: resolution with lurasidone and recurrence with Chlorpromazine. *Ann Pharmacother* 2013; **47:** 1223–28.

72 Jagadheesan K, Nizamie SH. Risperidone-induced Pisa syndrome. *Aust NZ J Psychiatry* 2002; **36:** 144.

73 Kaufmann A, Boesch S, Fleischhacker WW, Hofer A. Management of a risperidone-induced tardive Pisa syndrome: a case report. *J Clin Psychopharmacol* 2012; **32:** 418–20.

74 Krebs MO, Olie JP. Tardive dystonia induced by risperidone. *Can J Psychiatry* 1999; **44:** 507–08.

75 Kuo SC, Yeh YW, Chen CY, Chen CL. Low-dose amisulpride induced Pisa syndrome in an alcohol-dependent patient with liver cirrhosis. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33:** 1080–81.

76 Mason MN, Johnson CE, Piasecki M. Ziprasidone-induced acute dystonia. *Am J Psychiatry* 2005; **162:** 625–26.

77 Miletić V, Radić B, Relja M. Acute pisa syndrome as a neurological emergency. *J Neuropsychiatry Clin Neurosci* 2015; **27:** e159–60.

78 Miodownik C, Lerner V, Witztum E. Pisa syndrome and laryngeal dystonia induced by novel antipsychotics. *Isr J Psychiatry Relat Sci* 2011; **48:** 195–200.

79 Nishimura K, Mikami Y, Tsuchibuchi S, Horikawa N. Pisa syndrome resolved after switching to olanzapine. *J Neuropsychiatry Clin Neurosci* 2007; **19:** 202–03.

80 Padberg F, Stübner S, Buch K, Hegerl U, Hampel H. Pisa syndrome during treatment with sertindole. *Br J Psychiatry* 1998; **173:** 351–52.

81 Pan PY, Chou HW, Cheng CC, Hsu YC, Tzeng NS. Pisa syndrome induced by paliperidone. *J Neuropsychiatry Clin Neurosci* 2014; **26:** E07–08.

82 Papapetropoulos S, Wheeler S, Singer C. Tardive dystonia associated with ziprasidone. *Am J Psychiatry* 2005; **162:** 2191.

83 Pinninti NR, Mago R, Adityanjee. Tardive dystonia-associated prescription of aripiprazole. *J Neuropsychiatry Clin Neurosci* 2006; **18:** 426–27.

84 Rota E, Bergesio G, Dettoni E, Demicheli CM. Pisa syndrome during aripiprazole treatment: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31:** 286–87.

85 Teng PR, Lai TJ. Paliperidone-related Pisa syndrome. *J Clin Psychopharmacol* 2013; **33:** 129–31.

86 Tsai CS, Lee Y, Chang YY, Lin PY. Ziprasidone-induced tardive laryngeal dystonia: a case report. *Gen Hosp Psychiatry* 2008; **30:** 277–79.

87 Tseng PT, Chiu NM. Hashimoto's encephalopathy comorbid with Pisa syndrome under quetiapine in one elderly man. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35:** 645–46.

88 Vercueil L, Foucher J. Risperidone-induced tardive dystonia and psychosis. *Lancet* 1999; **353:** 981.

89 Walder A, Greil W, Baumann P. Drug-induced Pisa syndrome under quetiapine. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33:** 1286–87.

90 Weinstein SK, Adler CM, Strakowski SM. Ziprasidone-induced acute dystonic reactions in patients with bipolar disorder. *J Clin Psychiatry* 2006; **67:** 327–28.

91 Yeh YW, Chen YC, Chen CK, Feng HM, Wang TY, Chen CL. Chronic Pisa syndrome associated with switching antipsychotics from olanzapine to ziprasidone. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33:** 162–63.

92 Ziegenbein M, Schomerus G, Kropp S. Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatry Clin Neurosci* 2003; **15:** 458–59.

93 Yohanan M, Aulakh JS, Weith J, Hawkins JW. Pisa syndrome in a patient in a wheelchair taking valproic acid. *Am J Psychiatry* 2006; **163:** 325–26.

94 Suzuki T, Kurita H, Hori T, et al. The Pisa syndrome (pleurothotonus) during antidepressant therapy. *Biol Psychiatry* 1997; **41:** 234–36.

95 Perrone V, Antoniazzi S, Carnovale C, et al. A case of Pisa syndrome during sertraline and quetiapine treatment. *J Neuropsychiatry Clin Neurosci* 2012; **24:** E31–32.

96 Méndez Guerrero A, Llamas S, Murcia FJ, Ruíz J. Acute Pisa syndrome after administration of a single dose of mirtazapine. *Clin Neuropharmacol* 2013; **36:** 133–34.

97 Kropp S, Hauser U, Emrich HM, Grohmann R. Metoclopramide-related pisa syndrome in clozapine treatment. *J Neuropsychiatry Clin Neurosci* 2001; **13:** 427–28.

98 Fichtner CG. Pleurothotonus and the Pisa syndrome. *Biol Psychiatry* 1992; **31:** 534.

99 Solla P, Cannas A, Congia S, et al. Levodopa/carbidopa/entacapone-induced acute Pisa syndrome in a Parkinson's disease patient. *J Neurol Sci* 2008; **275:** 154–56.

100 Vitale C, Marcelli V, Furia T, et al. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Mov Disord* 2011; **26:** 1458–63.

101 Shumway-Cook A, Woollacott M. Attentional demands and postural control: the effect of sensory context. *J Gerontol A Biol Sci Med Sci* 2000; **55:** M10–16.

102 Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing* 2006; **35** (suppl 2)**:** ii7–11.

103 Borel L, Alescio-Lautier B. Posture and cognition in the elderly: interaction and contribution to the rehabilitation strategies. *Neurophysiol Clin* 2014; **44:** 95–107.

104 Solla P, Grau O, Gelpi E, Marrosu F, Martí MJ. Pisa syndrome in a patient with pathologically confirmed Parkinson's disease. *Neuropathol Appl Neurobiol* 2016; DOI:10.1111/nan.12324.

105 Reichert WH, Doolittle J, McDowell FH. Vestibular dysfunction in Parkinson disease. *Neurology* 1982; **32:** 1133–38.

106 White OB, Saint-Cyr JA, Sharpe JA. Ocular motor deficits in Parkinson's disease. I. The horizontal vestibulo-ocular reflex and its regulation. *Brain* 1983; **106:** 555–70.

107 Stamboulis E, Tsakanikas C, Scarpalezos S. [Subclinical vestibular abnormalities in Parkinson's disease (author's transl)]. *Rev Neurol (Paris)* 1981; **137:** 211–16.

108 Henzi S, Stanga Z, Ludin HP. [Vestibular disorders in Parkinson patients]. *Schweiz Med Wochenschr* 1990; **120:** 1297–303.

109 Pastor MA, Day BL, Marsden CD. Vestibular induced postural responses in Parkinson's disease. *Brain* 1993; **116:** 1177–90.

110 Pollak L, Prohorov T, Kushnir M, Rabey M. Vestibulocervical reflexes in idiopathic Parkinson disease. *Neurophysiol Clin* 2009; **39:** 235–40.

111 Vaugoyeau M, Azulay JP. Role of sensory information in the control of postural orientation in Parkinson's disease. *J Neurol Sci* 2010; **289:** 66–68.

112 Geroin C, Smania N, Schena F, et al. Does the Pisa syndrome affect postural control, balance, and gait in patients with Parkinson's disease? An observational cross-sectional study. *Parkinsonism Relat Disord* 2015; **21:** 736–41.

113 Mamo H, Dondey M, Cophignon J, Pialoux P, Fontelle P, Houdart R. [Transitory latero-pulsion after subthalamic and thalamic coagulations in parkinsonism patients]. *Rev Neurol (Paris)* 1965; **112:** 509–20.

114 Scocco DH, Wagner JN, Racosta J, Chade A, Gershanik OS. Subjective visual vertical in Pisa syndrome. *Parkinsonism Relat Disord* 2014; **20:** 878–83.

115 Venhovens J, Meulstee J, Bloem BR, Verhagen WI. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. *Eur J Neurosci* 2016; **43:** 1636–46.

116 Tassorelli C, Furnari A, Buscone S, et al. Pisa syndrome in Parkinson's disease: clinical, electromyographic, and radiological characterization. *Mov Disord* 2012; **27:** 227–35.

117 Di Matteo A, Fasano A, Squintani G, et al. Lateral trunk flexion in Parkinson's disease: EMG features disclose two different underlying pathophysiological mechanisms. *J Neurol* 2011; **258:** 740–45.

118 Tinazzi M, Juergenson I, Squintani G, et al. Pisa syndrome in Parkinson's disease: an electrophysiological and imaging study. *J Neurol* 2013; **260:** 2138–48.

119 Tassorelli C, De Icco R, Alfonsi E, et al. Botulinum toxin type A potentiates the effect of neuromotor rehabilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. *Parkinsonism Relat Disord* 2014; **20:** 1140–44.

120 Dupeyron A, Viollet E, Coroian F, Gagnard C, Renard D, Castelnovo G. Botulinum Toxin-A for treatment of Pisa syndrome: A new target muscle. *Parkinsonism Relat Disord* 2015; **21:** 669–70.

121 Bartolo M, Serrao M, Tassorelli C, et al. Four-week trunk-specific rehabilitation treatment improves lateral trunk flexion in Parkinson's disease. *Mov Disord* 2010; **25:** 325–31.

122 Capecci M, Serpicelli C, Fiorentini L, et al. Postural rehabilitation and Kinesio taping for axial postural disorders in Parkinson's disease. *Arch Phys Med Rehabil* 2014; **95:** 1067–75.

123 Shih LC, Vanderhorst VG, Lozano AM, Hamani C, Moro E. Improvement of pisa syndrome with contralateral pedunculopontine stimulation. *Mov Disord* 2013; **28:** 555–56.

124 Koller H, Acosta F, Zenner J, et al. Spinal surgery in patients with Parkinson's disease: experiences with the challenges posed by sagittal imbalance and the Parkinson's spine. *Eur Spine J* 2010; **19:** 1785–94.

125 Ricciardi L, Piano C, Bentivoglio AR, Fasano A. Long-term effects of pedunculopontine nucleus stimulation for Pisa syndrome. *Parkinsonism Relat Disord* 2014; **20:** 1445–46.

126 Ha Y, Oh JK, Smith JS, et al. Impact of movement disorders on management of spinal deformity in the elderly. *Neurosurgery* 2015; **77** (suppl 4): S173–85.