on existing therapy. However, the unexpected adverse effects of intensive early mobilisation in acute stroke shown in the AVERT trial raise some interesting clinical and research questions about the organisation of acute stroke general care, early rehabilitation, and how to determine the effects of each of the separate elements that contribute to the clear benefits of organised stroke unit care.[7] Most acute stroke trials have assessed outcome at only 90 days after stroke, which has advantages, but two of the intravenous thrombolysis trials have underlined the value of collecting longer-term post-trial follow-up mortality data.[16,17]

The cost in money, time, equipment, and personnel in the delivery of endovascular therapy is potentially substantial, so long-term data on mortality and disability are needed to provide realistic estimates of cost-effectiveness and to help decide whether treatment really is affordable. Future research should therefore include long-term survival studies, at least for endovascular therapy trials (in countries in which research can be done through central death registries).

Acute stroke treatment is changing rapidly, and health systems will be under increasing pressure from patients and their advocates to implement this novel evidence and ensure that clinical services deliver stroke unit care and reperfusion therapy in an affordable and equitable way. In low-income and middle-income countries, although some high-income individuals might have access to such advanced care, for the majority, the priority must be to deliver basic acute stroke care for all.

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# Unfreezing of gait in patients with Parkinson's disease

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Freezing of gait is an episodic disorder of human locomotion, characterised by sudden and brief episodes of inability to produce effective forward stepping.[1] The most common cause of freezing of gait is Parkinson's disease, and prevalence ranges from about 10% in Hoehn and Yahr stage 1 to more than 90% in stage 4.[2] Freezing of gait is a frequent cause of falls and a major determinant of quality of life for patients with Parkinson's disease, far beyond some better recognised and more stigmatising symptoms. Freezing of gait can be classified on the basis of its phenomenology and response to dopaminergic treatments (table). Classification is important to guide management of freezing of gait.

In this issue of *The Lancet Neurology*, an international panel of experts presents a practical algorithm for the medical and non-medical management of freezing of gait.[3] This type of algorithm is helpful for general neurologists; however, as stated by Nonnekes and colleagues,[3] most recommendations are not supported by good quality studies, but rather represent expert opinion. Among these recommendations, the usefulness of physiotherapy is emphasised, which is a helpful strategy but is often unavailable and not tailored to patients' specific needs (eg, the need for physiotherapy in a patient with mild, purely off-state freezing of gait is questionable). Much attention is given to levodopa, which is suggested as a first-choice approach in treatment-naive patients or in patients already taking dopamine agonists. Although the role of levodopa has been favourably reconsidered in recent years, and increased doses can improve freezing of gait, such an approach still warrants caution because high levodopa doses clearly have a role in the development of motor fluctuations and worsening of pre-existing dyskinesias. In this respect, the construct of pseudo-on-state freezing of gait is important (table); in fact, levodopa can sometimes improve gait only at doses that cause disabling dyskinesias, and, in our experience, even continuous infusion of enteral levodopa might not help. Furthermore, the potential role of dopamine agonists in causing or aggravating freezing of gait is based mainly on the personal experience of the authors or on accidental findings from trials not focused on freezing of gait. Although we have had similar experiences, whether this exacerbation of freezing is any more or less common with dopamine agonists than with levodopa is not clear.

| | Possible characteristics |
|---|---|
| **Phenomenological classification*** | |
| Akinetic freezing of gait (occurs at gait initiation) | Start hesitation<br>Total akinesia |
| Motor freezing of gait (arrests during ongoing gait) | Freezing without alteration of the motor pattern†: on an open runway (usually preceded by festination)<br>Freezing with alteration of the motor pattern†: during turning, reaching a destination or an obstacle, passing through a doorway, or increasing gait velocity<br>Triggered by external circumstances—eg, anxiety or dual tasking (cognitive, motor, or both) |
| **Pharmacological classification*** | |
| Off-state freezing of gait | Most frequent type, relieved by dopaminergic medications |
| Pseudo-on-state freezing of gait | Seen during a seemingly optimum on-state, but which nevertheless improves with increased dopaminergic medication |
| On-state freezing of gait | Rarest form, induced by dopaminergic medication |
| Resistant (or unresponsive) freezing of gait | Indifferent to changes in dopaminergic medication, often seen in parkinsonian disorders other than Parkinson's disease, or in the late stages of Parkinson's disease |

*Different freezing of gait types can appear in one patient. †Can be triggered or worsened by external circumstances.

***Table:*** **Classification of freezing of gait**

In cases complicated by dyskinesias, functional neurosurgery is a promising strategy, although, as discussed by Nonnekes and colleagues,[3] prospective and randomised trials comparing surgical targets with freezing of gait as a primary outcome measure are needed. Furthermore, we strongly agree with the authors that pedunculopontine (PPN) stimulation should only be an experimental treatment at present. Future studies of this and other treatments need to focus on the phenomenology of freezing of gait, because results of a gait analysis study[4] showed that PPN stimulation specifically improves turning behaviour without affecting more standard spatiotemporal measures of human locomotion.

In their Personal View, Nonnekes and colleagues[3] mention several drugs (eg, amantadine, methylphenidate, and duloxetine) and other interventions (eg, exercise) for which very little evidence exists. One of the challenges in the treatment of freezing of gait is the placebo effect in the context of a highly variable phenomenon. Therefore, personal observations—also shared by us—must be considered cautiously, especially when addressing neurologists who are not familiar with such complexity. This caution is especially important when proposing off-label uses (eg, amantadine up to 600 mg/day). Non-dopaminergic treatments are a promising solution, especially for freezing of gait that is resistant to dopaminergic drugs. Although dopamine-resistant freezing of gait is the most troublesome form, often present in atypical parkinsonian disorders, unfortunately the evidence and experience obtained so far for all treatments apply mainly to off-state freezing of gait in patients with Parkinson's disease (ie, dopamine-responsive freezing of gait).

Advances in understanding of the pathogenesis of freezing of gait are a clear prerequisite for much needed breakthroughs in the management of this disorder. The pathophysiology of this motor phenomenon is still unclear, and four main hypotheses have been formulated so far: the threshold, interference, cognitive, and decoupling models.[1] In terms of underlying neurochemical changes, Nonnekes and colleagues[3] mention evidence for cholinergic dysfunction in freezing of gait,[5] but there is also an interesting additional relation with brain amyloid deposition. In the same

study,[5] the highest frequency of freezing of gait was in patients with combined neocortical cholinopathy and amyloidopathy. This finding is especially interesting in view of evidence linking anticholinergic medication exposure to increased incidence of freezing of gait[2] and earlier evidence that use of these drugs is associated with an increased incidence of Alzheimer-type pathology in patients with Parkinson's disease.[6] Thus, the role of mixed pathologies needs to be considered, especially in late-stage levodopa-resistant freezing of gait.

In conclusion, Nonnekes and colleagues[3] have nicely summarised the important outstanding issues in the management of freezing of gait. As mentioned in their concluding remarks, many unmet needs exist, and we fully support each of their recommendations to drive progress in this specialty. First, recognition that freezing of gait is not a uniform or homogeneous symptom is crucial. Freezing of gait is a complex syndrome that needs careful investigation to enable further advances in understanding and to provide appropriately tailored therapy. Hopefully, the proposed algorithm will be a useful first step to unfreezing of gait in patients with Parkinson's disease, and will assist physicians in the practical management of this difficult problem.

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## Corrections

*Simonato M, Brooks-Kayal AR, Engel J Jr, et al. The challenge and promise of anti-epileptic therapy development in animal models.* Lancet Neurol *2014;* **13:** 949–60—In this Personal View, some details of the authors' research funding were omitted. These details have been added to the online version as of May 7, 2015.

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