with exclusive or predominant involvement of upper motor neurons (n=16) in the nabiximols group, in whom spasticity is the prevailing symptom. These patients could have benefited more than the 13 patients with classic amyotrophic lateral sclerosis, which involves both upper and lower motor neurons. There are divergent opinions on the occurrence of spasticity in classic amyotrophic lateral sclerosis. Some authors reported that stiffness or spasticity were presenting symptoms only rarely in amyotrophic lateral sclerosis compared with in primary lateral sclerosis.[2] However, in a questionnaire-based study,[7] spasticity affecting quality of life was reported by roughly 80% of patients with amyotrophic lateral sclerosis (based on numeric rating scale spasticity responses). The authors of that study acknowledged that these findings were not validated by clinical examination, but they also questioned whether clinician assessment should be the gold-standard measure of spasticity. They did not detail the phenotypes of the included patients, so the proportion of patients with upper-motor-neuron-dominant amyotrophic lateral sclerosis is unknown.

Second, Riva and colleagues did not distinguish between upper and lower limb spasticity, or whether or not patients had bulbar spasticity. These patients could perhaps be differently affected by spasticity. Third, the MAS has been used in previous positive studies of the efficacy of other antispastic treatments but, as Riva and colleagues acknowledge, it lacked sensitivity in studies of the efficacy of cannabinoids in patients with multiple-sclerosis-related spasticity, and new spasticity numeric rating or visual analogue scales are being adopted.[8] A novel Rasch-based scale for patient-reported spasticity has been developed, but its responsiveness in amyotrophic lateral sclerosis has yet to be proven.[7] Finally, the fact that the number of adverse effects was substantially higher in the active treatment group than in the placebo group might have resulted in unblinding, which could have had a role in the significant findings.

Before regulatory approval of cannabinoids for symptomatic treatment of spasticity in patients with amyotrophic lateral sclerosis, further studies are needed to establish the frequency of spasticity in the various presentations of motor neuron disease, and also whether reductions in spasticity improve quality of life. Natural history studies including all subtypes of motor neuron disease and better outcome measures of spasticity are required. Riva and colleagues' data are encouraging, and larger multicentre randomised controlled trials should be done to identify which subgroups of patients derive clinically significant benefits from nabiximols.

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The hunt for better treatments for Huntington's disease

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Huntington's disease is an autosomal dominant condition that typically presents in midlife as a combination of motor, cognitive, and psychiatric problems, along with sleep and metabolic abnormalities. Its clinical course runs over 15–20 years and eventually leads to death as patients develop dementia and become bed-bound. At present, no disease-modifying therapy is approved for patients with Huntington's disease. Although research on antisense therapies that target the huntingtin gene has generated much excitement, these therapies have not yet been shown to lead to measurable changes in disease progression.[1,2] Furthermore, given that they aim to modify and not cure the disease, adjunct symptomatic treatments would still be required. Symptomatic therapies


Gary Waters/Ikon Images/SCP

for Huntington's disease do exist and are widely used for treating chorea and some of the psychiatric aspects of the condition, although the extent to which they are effective varies between patients,[3] and many patients experience clinically significant side-effects. Therefore, there is a need to develop better symptomatic therapies, ideally single drugs that can treat more than one sign or symptom.

One such potential drug is pridopidine (TV-7820; formerly known as ACR16), a dopamine stabiliser with high affinity for the sigma-1 receptor chaperone protein. In *The Lancet Neurology*, Ralf Reilmann and colleagues[4] report the results of the PRIDE-HD study, a phase 2, randomised, placebo-controlled, double-blind, dose-ranging trial of pridopidine in patients with Huntington's disease. In two earlier trials, HART3[6] and MermaiHD,[7] pridopidine was well tolerated but did not lead to any improvement in the primary endpoint, assessed by the modified motor score (a subscale of the Unified Huntington's Disease Rating Scale total motor score [UHDRS-TMS] that reflects voluntary motor function). However, in both trials, exploratory evidence indicated that the drug might have conferred global motor benefits that were not detected by the modified motor score but reflected by changes in the overall UHDRS-TMS. This finding provided the rationale for continued development of the drug under a revised protocol in the PRIDE-HD study, in which around 400 patients with Huntington's disease received one of four doses of pridopidine (45 mg, 67·5 mg, 90 mg, or 112·5 mg twice daily) or placebo. The primary endpoint was change in the UHDRS-TMS at 26 weeks. This score captures all the motor features of Huntington's disease, including abnormalities of eye movement, speech, dexterity, and motor sequencing, as well as degrees of bradykinesia, chorea, dystonia, and the ability to walk and balance. PRIDE-HD did not show any significant benefit of pridopidine, at any dose, on the UHDRS-TMS. So what might explain this lack of effectiveness?

The dopamine stabilising function of pridopidine, which allows it to treat both hyperactive and hypoactive dopaminergic states,[8] makes it a rational choice as a potential new therapy for Huntington's disease. It has long been known that the dopamine system is abnormal in patients with Huntington's disease; these patients experience early loss of dopamine receptors in the brain, possibly secondary to increased dopamine release, and are most effectively treated with drugs that reduce dopamine release or block dopamine receptors.[3] However, this proposed increase in dopamine release is yet to be confirmed; perhaps these changes relate to primary transcriptional abnormalities across dopaminergic synapses. Furthermore, the pathology of Huntington's disease is not limited to the dopaminergic network,[9] and the contribution of this wider pathology to the clinical features of the disease is unknown. Therefore, stabilising dopaminergic function in the brain of patients with Huntington's disease might be of limited value, as suggested by the results of PRIDE-HD.

Of course, the negative findings of this study might result from the use of the wrong primary endpoint, dose of medication, or duration of treatment, although this explanation seems unlikely considering the number of previous trials with this drug. Some benefit was seen in exploratory endpoints (quantitative motor scores) at 52 weeks of treatment, but it is hard to explain why these effects would take so long to emerge if they were due to dopamine stabilisation. The observed benefit might relate more to the nondopaminergic effects of pridopidine on the sigma-1 receptor chaperone protein than to its dopaminergic effects;[10] regardless, the effect size was small and seen only at certain doses in Reilmann and colleagues' study,[4] and the clinical significance of their findings is unknown.

Finally, the value of this entire therapeutic approach could be debated given that therapies targeting the motor aspects of Huntington's disease already exist. There is a greater need for symptomatic therapies that target features of the disease for which no treatments are available (eg, cognitive deficits). All of which would argue against proceeding to further trials of pridopidine for patients with Huntington's disease.

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Understanding frailty to predict and prevent dementia

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Frailty is a crucial intermediate state of the ageing process, characterised by an increased risk of negative health-related events, including hospitalisation and death.[1] More than 40 operational definitions of frailty have been proposed, but three main approaches are commonly used. The first approach is based on the notion of a physical and biological frailty phenotype, for which the operational definition assumes that there is a state of negative energy balance, sarcopenia, diminished muscle strength, and low tolerance for exertion.[1] An alternative, and potentially complementary, definition of frailty is provided by the so-called deficit accumulation model, which incorporates several factors ranging from disease states, symptoms, and signs, to abnormal laboratory values. Deficits are listed and then divided by the total number of deficits identified in a patient to yield a frailty index.[1] The third approach to frailty is based on the biopsychosocial model, which mixes physical and psychosocial domains, and expands the construct of frailty toward the social sciences.[1,2] Due to its multidimensional and multisystem nature, frailty includes physical, cognitive, and psychosocial phenotypes. Different frailty phenotypes are related to neuropathological features of Alzheimer's disease and other dementias.[1] These frailty–cognition links and the potential for reversibility of frailty phenotypes suggest that these phenotypes might be important targets for the prevention of dependency and for secondary dementia prevention in the early or asymptomatic stages of the disease.

The strong links of frailty with Alzheimer's disease and other dementias are now confirmed in *The Lancet Neurology* by Lindsay Wallace and colleagues[3] in a cross-sectional analysis of data from 456 participants from the Rush Memory and Aging Project. Wallace and colleagues suggest that frailty, identified with a deficit accumulation-based frailty index, might be a substantial moderator of the relationship between Alzheimer's disease pathology (derived from counts of neuritic plaques, diffuse plaques, and neurofibrillary tangles) and dementia status, such that frailty makes people more susceptible to dementia. They found a significant interaction between frailty and Alzheimer's disease pathology (odds ratio 0·73, 95% CI 0·57–0·94; p=0·015). The frailty–pathology interaction remained significant after excluding from the frailty index variables on activities of daily living (eg, shopping, handling finances, and meal preparation) and controlling for the effects of risk factors linked to both frailty and Alzheimer's disease pathology (eg, history of stroke, hypertension, diabetes, congestive heart failure, and depression).[3]

Frailty is considered primary or preclinical when the state is not associated directly with a specific disease or when there is no substantial disability.[4] In this context, the physical or biopsychosocial models seem more appropriate to define primary frailty. By contrast, frailty is considered secondary or clinical when it is associated with known comorbidities, such as overt cardiovascular disease, depression, disability, or a combination thereof,[4] which is better defined with the deficit-accumulation-based frailty index used in the study by Wallace and colleagues.[3] This distinction is central in identifying frailty phenotypes with the potential to predict and prevent dementia, using novel models of risk that introduce modifiable factors.

Among frailty phenotypes, cognitive frailty is a clinical construct with operationalised criteria that describe