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COMMENTARY

Physician perception versus true efficacy of tetrabenazine for Huntington's disease

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At the moment there is no cure for Huntington's disease, so it remains a progressive and ultimately fatal inherited neurodegenerative disorder characterised by motor, cognitive, and behavioural dysfunction, all contributing to cumulative disability and loss of quality of life[1-3].

Clinical trials have had a grim success rate, and the evidence to support symptomatic treatment is weak[4] [5]. All this points to a clear need to develop efficacious therapeutic interventions, and to design and conduct successful and informative clinical trials.

Chorea is the most obvious sign of the disease – indeed it was once called Huntington's chorea. It can be bothersome, contribute to the gait disturbance associated with this condition, and hence the risk of falls, and can cause social stigma; however, it may also go unnoticed, and may not be bothersome[6-9].

In a cross-sectional online survey of neurologists practising in the United States of America, Sung and colleagues explored the physician perceptions of benefit of using tetrabenazine for chorea in people with Huntington's disease. They found that this group of physicians considers treating chorea an important aspect of symptomatic management, but felt limited by the treatment options available at the time of the survey. Tetrabenazine was perceived as a low-to-moderately efficacious intervention with suboptimal tolerability and safety profile, limiting clinical use[10].

Some caution is warranted in interpreting these findings. The survey relied on physician recall on the use of tetrabenazine rather than data from objective records or patient reported outcomes. Some questions were asymmetrical, with different numbers of positive and negative response categories. Only US-based practitioners were included. Most of the participants worked in low-volume centres, with only 18% practicing in Huntington's Disease Society of America Centers of Excellence, and it was unclear how many patients per year each of the participants followed. All these factors limit generalization, especially the fact that the respondants' experience and knowledge of Huntington's disease and its therapeutic approaches may have impacted their therapeutic decisions and expectations of benefit. Such issues are all the more important in the presence of potential funding bias: the study was supported by a corporation that developed and owns the only other FDA-approved competing therapeutic agent for chorea in Huntington's disease - deutetrabenazine.

As of today, tetrabenazine and deutetrabenazine are the only FDA-approved interventions for chorea in Huntington's disease, while in Europe, only the former is available. Tetrabenazine is widely used across Europe, as it is in North America and in Australia, and off-label anti-psychotic drugs are also regularly prescribed by physicians across the globe, which may be more effective or better tolerated than existing treatments that are specifically licensed for HD; much more work is needed to compare all these drugs head to head.[11-13]

Tetrabenazine and deutetrabenazine are also the only two drugs with positive randomized controlled trials. In the TETRA study, tetrabenazine had a mean effect of -3.5 units in the UHDRS total maximal chorea score (range: 0, absent chorea, to 28, marked/prolonged chorea in 7 different body segments); while in the FIRST-HD study, deutetrabenazine had a mean effect of -2.5 units in the same score, both against a placebo intervention[14 15].

Sung and colleagues evaluated physician perception of benefit in real-world clinical practice. An analogous measurement of global effect may be inferred from the results generated in clinical trials: in the absence of a placebo group, we can assess the mean change from baseline in the active arms of these trials (-5 and -4.4 units in the UHDRS total maximal chorea score for TETRA and FIRST-HD, respectively). Even after accounting for the placebo effect, these results were considered by the participants and the clinicians in these trials to be relevant, and led to the approval of these drugs[14 15].

In line with prior evidence, Sung and colleagues confirmed that the most frequent reasons why clinicians decide to treat chorea have to do with social and family embarrassment, impact of functional ability and quality of life, and risk of injuries[10 11]. Still, there is uncertainty as to whether the available interventions have a beneficial impact on these underlying factors, as opposed to the visible movement disorder per

se[16 17]. The picture drawn by the survey about the safety profile of tetrabenazine is very much in line with data from the TETRA study[14].

An important question remains to be answered: will real-world use of deutetrabenazine produce a different perception of benefit? Little is known about how tetrabenazine and deutetrabenazine compare to each other. No head-to-head evaluation has been performed or is planned, and indirect treatment comparisons have controversial results[18-20]. Based on the FIRST-HD study results, we anticipate that deutetrabenazine will likely produce similar perception to what was detected in this survey.

Nonetheless, we affirm Sung and colleagues' core finding that the symptomatic interventions available for people with Huntington's disease are limited, leaving significant unmet need. Even though targeted interventions to modify the underlying pathology appear to be closer than ever[21 22], there will always be a need for efficacious, safe, tolerable and evidence-based symptomatic treatments.

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