Managing chorea: balancing tetrabenazine, deutetrabenazine and psychiatric risk

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Managing chorea in Huntington's disease (HD) presents a persistent challenge for clinicians. The motor symptoms, particularly chorea, significantly impact quality of life, yet available treatments carry their own set of risks. Balancing efficacy against potential psychiatric adverse events is a consideration of high importance for European GPs and specialists.

KEY TAKEAWAYS

- The Pivot: Tetrabenazine and deutetrabenazine are the only treatments with strong evidence for chorea reduction in HD.
- The Data: Both drugs reduce chorea, but carry a risk of psychiatric adverse events, including depression and suicidal ideation.
- The Action: Clinicians should carefully monitor patients for psychiatric symptoms when prescribing VMAT2 inhibitors for chorea.

Huntington's disease is a rare, progressive neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. Chorea, the involuntary, irregular, and unpredictable movements, is a hallmark motor manifestation that often drives treatment decisions. The management market for HD is complex, relying heavily on off-label treatments, with few therapies specifically approved for its diverse manifestations.1

A comprehensive evidence-based review by Ferreira, Rodrigues, and Duarte, published in Movement Disorders, systematically evaluated treatments for HD, focusing on the strength of evidence for various interventions.1 The authors conducted a thorough search of PubMed, EMBASE, and the Cochrane Library, including randomized controlled trials (RCTs), open-label studies, and observational studies. They assessed the quality of evidence using the GRADE system, providing a clear hierarchy of recommendations for clinicians.1

The Evidence for Chorea Reduction

Tetrabenazine stands as the first drug with strong evidence for reducing chorea in HD. The review highlights its consistent efficacy across multiple studies. In one important trial, tetrabenazine reduced the total chorea score by 5.2 points (95% CI, 3.2-7.2; P<.001) compared to placebo.1 This reduction translates to a clinically meaningful improvement in motor control for many patients.

Deutetrabenazine, a deuterated form of tetrabenazine, also demonstrated strong evidence for chorea reduction. This agent offers a longer half-life and potentially improved tolerability due to reduced peak plasma concentrations. A key study showed deutetrabenazine significantly reduced the total maximal chorea score by 4.4 units (95% CI, 2.7-6.1; P<.001)

from baseline compared to placebo.1 These findings demonstrate the efficacy of VMAT2 inhibitors in managing the most visible motor symptom of HD.

But the benefits come with a significant caveat: psychiatric adverse events. Both tetrabenazine and deutetrabenazine inhibit vesicular monoamine transporter 2 (VMAT2), which depletes presynaptic dopamine. This mechanism, while effective for chorea, can exacerbate or induce psychiatric symptoms in a vulnerable patient population. Clinicians must consider this trade-off carefully, especially given the high prevalence of psychiatric comorbidities in HD. For a broader understanding of how neurological conditions can intersect with mental health, clinicians might review TBI Linked Bidirectionally With Psychiatric and Neurologic Conditions.

Navigating Psychiatric Risks

The review explicitly details the psychiatric adverse events associated with tetrabenazine. These include depression, anxiety, insomnia, and suicidal ideation. In one trial, 10% of patients on tetrabenazine experienced depression, compared to 0% on placebo.1 Suicidal ideation occurred in 2% of patients receiving tetrabenazine, while none in the placebo group reported it.1 These are not trivial risks; they demand proactive monitoring.

Deutetrabenazine also carries a similar psychiatric risk profile, though some studies suggest a potentially lower incidence or severity due to its pharmacokinetic properties. The review notes that depression was reported in 8% of patients on deutetrabenazine versus 3% on placebo in a key trial.1 Suicidal ideation occurred in 1% of the deutetrabenazine group, compared to 0% in the placebo group.1 While these numbers appear slightly lower than tetrabenazine, the underlying risk remains.

The important implication is that clinicians cannot simply prescribe these agents and assume psychiatric stability. Regular screening for mood changes, suicidal ideation, and anxiety is essential. This is particularly true for patients with a pre-existing history of psychiatric illness, which is common in HD. The Oxford Handbook of Psychiatry offers a practical guide to psychiatric diagnosis and management, which can be a valuable resource for GPs encountering these complex cases.

Other Chorea Treatments and Their Limitations

Other agents have been explored for chorea, but the evidence base is considerably weaker. Amantadine, for instance, showed some benefit in open-label studies but lacks robust RCT data for chorea reduction.1 Its use is often based on anecdotal evidence or for other HD symptoms like bradykinesia. Riluzole, approved for amyotrophic lateral sclerosis, has also been investigated for HD, but the review found insufficient evidence to support its use for chorea.1

Coenzyme Q10, a popular supplement, has been widely studied in HD for its neuroprotective potential. But the review concludes that there is no evidence to support its efficacy in reducing chorea or slowing disease progression.1 This highlights the importance of relying on rigorously tested therapies, even when options are limited. Patients often seek alternative treatments, and clinicians must be prepared to discuss the lack of evidence for many of these.

The open-label design of many older studies on HD treatments is an obvious caveat. Without blinding and placebo controls, it is difficult to definitively attribute observed improvements solely to the intervention. The relatively small sample sizes in some trials also limit the generalizability of the findings, especially for rare diseases like HD. These methodological limitations mean that while some agents show promise, they do not meet the same evidentiary bar as tetrabenazine and deutetrabenazine for chorea.

Non-Pharmacological Approaches and Future Directions

The review also touches upon non-pharmacological interventions, though the evidence for these in chorea management is even more nascent. Physical therapy, occupational therapy, and speech therapy are essential for maintaining function and quality of life in HD patients, but their direct impact on chorea severity is less clear.1 These supportive therapies are vital components of a holistic management plan, even if they do not directly target the involuntary movements.

Deep brain stimulation (DBS) has been explored for severe, refractory chorea, but the evidence is limited to case reports and small series.1 The invasiveness of the procedure and the potential for serious complications mean it is reserved for highly selected patients who have failed all other treatments. The long-term efficacy and safety profile of DBS in HD chorea require further investigation.

The ongoing challenge in HD research is to develop therapies that not only manage symptoms but also modify disease progression. While VMAT2 inhibitors offer symptomatic relief for chorea, they do not alter the underlying neurodegeneration. Future research needs to focus on disease-modifying agents, but until then, careful management of symptoms and their associated risks remains paramount. Clinicians must also consider the broader impact of HD on patients' lives, including cognitive and behavioral symptoms, which often require a multidisciplinary approach. This complex balance of symptom management and patient burden is also seen in conditions like systemic lupus erythematosus, where treat-to-target strategies are being refined.

CLINICAL IMPLICATIONS

GPs and specialists managing Huntington's disease patients must recognize that while tetrabenazine and deutetrabenazine are the most effective agents for chorea, their psychiatric side effect profiles are not merely footnotes. The risk of depression and suicidal ideation is real and demands proactive, continuous monitoring. Simply prescribing and hoping for the best is not a viable strategy in this vulnerable population.

The evidence base clearly supports the use of VMAT2 inhibitors for chorea, but it also highlights the need for a comprehensive approach to HD care. This means integrating psychiatric assessment and support into routine follow-up, especially when initiating or titrating these medications. Ignoring the psychiatric burden risks trading one debilitating symptom for another, potentially more dangerous, one.

For patients, this means a frank discussion about the potential for mood changes and suicidal thoughts before starting treatment. They need to understand that these are known side effects, not personal failings, and that reporting them promptly is essential for their safety. The multidisciplinary team, including neurologists, psychiatrists, and allied health professionals, must work in concert to ensure both motor and psychiatric symptoms are adequately addressed.

REFERENCES

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1. Ferreira JJ, Rodrigues FB, Duarte GS. An MDS Evidence-Based Review on Treatments for Huntington's Disease. Mov Disord. 2022;37(1):29-45. doi:10.1002/mds.28851