Tetrabenzaine, Depression and Suicide: Good News

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Tetrabenzaine, (Xenzine™, Lundbeck) a reversible inhibitor of vesicular monoamine transporter 2, is thus far the only drug approved by the FDA specifically for Huntington’s disease. The target symptom is chorea, with a mechanism of action related to its capacity to deplete monoamines [1]. Tetrabenzaine has been available since the 1950’s, and had been repeatedly shown in large case series to benefit hyperkinetic movements associated with a number of disorders, including chorea associated with HD and tardive dyskinesia, tics associated with Tourette’s syndrome, dystonia, and myoclonus [2]. While some of the same effects can be achieved with antipsychotic agents (e.g., haloperidol, olanzapine) [3], the evidence supporting the use of these agents is mixed, and antipsychotics can place patients at risk tardive dyskinesia, which is not a side effect of tetrabenzaine. Hence the FDA approval of tetrabenzaine was a major milestone.

The use of tetrabenzine by clinicians has been held back, in part, by the highly publicized potential side effects of depression and suicide, including a “Black Box” warning [4]. Indeed, as Dorsey et al note, one participant of 54 receiving tetrabenzaine in the critical Phase III tetrabenzaine trial committed suicide [5]. The prominence of the monoamine hypothesis of depression into the 1990’s provided ample theoretical justification for this concern. Empiric studies of tetrabenzaine, including the Phase III trial that proved central to its approval for HD, did not allay concerns, though evidence supporting increased depression and suicide has been mixed, and is often confounded by the risk of depression and suicide in the underlying condition for which tetrabenzaine has been applied, including HD [6, 7].

Now Dorsey and colleagues provide evidence that tetrabenzaine does not increase the rates of depression, suicidality, or suicide. Using data collected during the COHORT observational study of HD [8], they demonstrated no excess of depression, suicidality, or suicide attempts in the patients taking tetrabenzaine compared to those who did not. The authors point out a variety of limitations, most prominently inclusion of only those patients willing to enroll in COHORT, the potential that participating in the study may itself have decreased the chance of depression and suicidality, and the nonrandom selection of which patients received tetrabenzaine. In addition, “depression” and “suicidality” were defined based on answers to single questions in the UHDRS rather than on the basis of a more comprehensive examination. On the other hand, the study was comparatively large, with greater than 350 participant-years of tetrabenzaine exposure.

While not definitive, Dorsey et al provides some reassurance that the risk of depression and suicidality from tetrabenzaine may not be as great as previously feared. This is good news for the treatment of HD, and also for the off-label use of tetrabenzaine in other dyskinesias. It will be interesting to determine the effect on depression and suicidality of compounds related to...

DISCLOSURES

The author is a site investigator for a trial of NBI-98854, Neurocine, Inc and a site coinvestigator for SD-809, Auspex, Inc)

REFERENCES
