OBJECTIVE: The mechanism of neuronal degeneration in Huntington's Disease (HD) remains unknown despite the identification of the disease-causing genetic defect. With the abasence of effective treatments in ameliorating disease progression and neuronal death in HD, we propose to perform a multi-compound trial in HD transgenic mice targeted at different proposed mechanisms of pathogenesis.

RESEARCH DESIGN: We will determine if combined therapeutic regimens have cumulative beneficial effects. We will use drugs that are currently available for human clinical use, which we have shown to be independently effective in murine HD clinical trials.

METHODOLOGY: The heart of this study will be a trial using all five drugs in cohorts of R6/2 mice at the Bedford VA Medical Center that will be evaluated according to the general protocols we have established. Since we do expect at least some synergy and will need to work out which combinations are synergistic, we will also perform two 3-drug trials at Massachusetts General Hospital to begin to sort out individual effects, and continue to perform 2-drug trials at both sites as needed to determine individual synergies. It is important that these studies are performed at two sites both to provide the needed experimental capacity and from previous experience, it will be important to provide cross validation between different animals colonies and labs.

FINDINGS: We have organized and begun initial drug treatments using coenzyme Q10 at multiple dose regimens. Preliminary data shows differences in bio availability using different sources of coenzyme Q10, comparing serum and brain levels. We have initiated preclinical trials using each coenzyme Q10 compound in HD mice.

CLINICAL RELEVANCE: If efficacious, these studies may directly translate to analogous combined drug-trials in Huntington's Disease patients and for other neurological disorders.