In the aging human brain, multiple comorbid pathologies are the rule, not the exception, particularly for those who die after age 80 with cognitive impairment. While the amyloid plaques and tau neurofibrillary tangles of Alzheimer’s disease remain highly prevalent and strongly associated with cognitive impairment in this age-group, it has become increasingly apparent that there is another proteinopathy at play. TDP-43 is a DNA-binding protein that regulates many aspects of protein production and was first associated with neurodegenerative disease when it was identified as a major constituent of the pathologic inclusions in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD). More recently TDP-43 proteinopathy has been described in the brains of people over age 80 years without FTLD or ALS, but often with comorbid AD pathology. These individuals, usually diagnosed with AD clinically, at autopsy lack the degree of AD neuropathologic change expected based on the clinical picture, but do have TDP-43 pathology in the hippocampus and other mesial temporal structures. Until recently there was no consensus-based nomenclature for this pathology, but it is now referred to as Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). The presence of pathological TDP-43 in these cases suggests a novel disease mechanism in older adults with neurodegenerative disease and the increased awareness of this pathology has sparked new research focused on understanding the interactions between multiple pathologic proteins in the aging brain and ways to intervene.