APOEε4 genotype confers 12-15 times risk of developing Alzheimer's disease (AD) at an earlier age than their APOEε3 counterparts. Recently, we showed using molecular modeling and biochemical assays that, in competition with the Transcriptional Factor EB (TFEB), ApoE4 but not ApoE3, or ApoE2 binds specifically and avidly to Coordinated Lysosomal Expression And Regulation (CLEAR) motifs, hindering the production of autophagy proteins crucial for the completion of lysosomal autophagy of aggregates, leading to pronounced aggregate burden. Therapeutically, targeting a small molecule drug, an FDA-approved drug, that specifically binds to ApoE4 and inhibits the interaction with CLEAR DNA motifs would free up CLEAR site for interaction with TFEB to mount the response and transcribe proteins required for lysosomal autophagy of aggregates. Toward this, we propose to virtually screen FDA-approved drugs that bind avidly and specifically to ApoE4, followed by experimental validations of top drugs as potential drug candidates for repurposing against ApoE4.