Other recent pharmacogenetic studies with pathogenic or mechanistic genes indicate that the response to AChEIs is associated with 2 SNPs in the intronic region of *CHAT* rs2177370 and rs3793790.[94] The *CHRNA7* T allele (rs6494223) is also associated with a better response to AChEIs and there is further confirmation that *APOE-4* carriers are the worst responders to conventional AChEIs.[95]

5.3.2 CYPs

Over 70% of AD patients are deficient metabolizers for the *CYP2D6*/*2C19*/*2C9* trigenic cluster; and for the *CYP2D6*/*2C19*/*2C9*/*3A4* tetragenic cluster, more than 80% of the patients exhibit a deficient metabolizer geno-phenotype.[6] These four *CYP* genes encode enzymes responsible for the metabolism of 60–80% of drugs of current use, showing ontogenic-, age-, sex-, circadian- and ethnic-related differences.[10,11,66,96] According to the database of the World Guide for Drug Use and Pharmacogenomics,[23] 982 drugs are CYP2D6-related: 371 drugs are substrates, over 300 drugs are inhibitors, and 18 drugs are CYP2D6 inducers. Over 600 drugs are *CYP2C9*-related, 311 acting as substrates (177 are major substrates, 134 are minor substrates), 375 as inhibitors (92 weak, 181 moderate, and 102 strong inhibitors), and 41 as inducers of the CYP2C9 enzyme.[23] Nearly 500 drugs are CYP2C19-related, 281 acting as substrates (151 are major substrates, 130 are minor substrates), 263 as inhibitors (72 weak, 127 moderate, and 64 strong inhibitors), and 23 as inducers of the CYP2C19 enzyme.[23] The CYP3A4/5 enzyme metabolizes over 1900 drugs, 1033 acting as substrates (897 are major substrates, 136 are minor substrates), 696 as inhibitors (118 weak, 437 moderate, and 141 strong inhibitors), and 241 as inducers of the CYP3A4 enzyme.[23]

In healthy subjects, CYP2D6 extensive metabolizers (EMs) account for 55.71% of the population, whereas intermediate metabolizers (IMs) account for 34.7%, poor metabolizers (PMs) 2.28%, and ultra-rapid metabolizers (UMs) 7.31%.[11,18] In AD, EMs, IMs, PMs, and UMs are 56.38%, 27.66%, 7.45%, and 8.51%, respectively. There is an accumulation of AD-related genes of risk in PMs and UMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to a combination therapy with AChEIs, neuroprotectants, and vasoactive substances. The pharmacogenetic response in AD appears to be dependent upon the networking activity of genes involved in drug metabolism and genes involved in AD pathogenesis.[10,11,17,53,66,67,97,98] By phenotypes, in the control population, CYP2C9-PMs represent 7.04%, IMs 32.39%, and EMs 60.56%. In AD, PMs, IMs, and EMs are 6.45%, 37.64%, and 55.91%, respectively.[11,23] The frequencies of the 3 major *CYP2C19* geno-phenotypes in the control population are: *CYP2C19-*1*/**1*-EMs 68.54%, *CYP2C19-*1*/**2*-IMs 30.05%, and *CYP2C19-*2*/**2*-PMs 1.41%. EMs, IMs, and PMs account for 69.89%, 30.11%, and 0%, respectively, in AD.[11,23] Concerning *CYP3A4*/*5* polymorphisms in AD, 82.75% of the cases are EMs (*CYP3A5*3*/**3*), 15.88% are IMs (*CYP3A5*1*/**3*), and 1.37% are UMs (*CYP3A5*1*/**1*).[11]