hepatotoxicity). Tacrine is a major substrate of CYP1A2 and CYP3A4, a minor substrate of CYP2D6, and is transported *via* SCN1A and ABCB4. Tacrine is an inhibitor of ACHE, BCHE, and CYP1A2.[23] Both tacrine and some tacrine-hybrids may cause an induction of *CYP1A1*, *2B1* and *3A2* expression.[122] Tacrine is associated with transaminase elevation in up to 50% of patients. The mechanism of tacrine-induced liver damage is influenced by genetic factors. The strongest association was found between alanine aminotransferase levels and three *ABCB4* SNPs.[123]

Memantine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist which binds preferentially to NMDA receptor-operated cation channels; it may act by blocking actions of glutamate, mediated in part by NMDA receptors, and is also an antagonist of GRIN2A, GRIN2B, GRIN3A, HTR3A and CHRFAM7A. Several pathogenic (*APOE*, *PSEN1*, *MAPT*) and mechanistic gene variants (*GRIN2A*, *GRIN2B*, *GRIN3A*, *HTR3A*, *CHRFAM7A*, *c-Fos*, *Homer1b* and *PSD-95*) may influence its therapeutic effects. Memantine is a strong inhibitor of CYP2B6 and CYP2D6, and a weak inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4.[23,100,124] In human liver microsomes (HLM), memantine inhibits CYP2B6 and CYP2D6 activities, decreases CYP2A6 and CYP2C19 activities, and has no effect on CYP1A2, CYP2E1, CYP2C9, or CYP3A4 activities.[125] The co-administration of memantine with CYP2B6 substrates elicits a 65% decrease in its metabolism. In clinical studies, *NR1I2* rs1523130 was identified as the unique significant genetic covariate for memantine clearance, with carriers of the *NR1I2* rs1523130 CT/TT genotypes presenting a 16% slower memantine elimination than carriers of the CC genotype.[126]

5.3.3 Transporters

Polymorphic variants in genes encoding transporter proteins may affect drug metabolism, brain penetrance and accessibility to neuronal/glial targets, and drug resistance.[23,127–129] Of special importance in AD are the ABC and SLC family genes.[129] ABC genes (*ABCB1*, *ABCC1*, *ABCG2*), and other genes of this family encode proteins that are essential for drug metabolism and transport. Mutations in ABC transporters influence pathogenesis and therapeutics of brain disorders.[129,130] The multidrug efflux transporters (P-gp1/MDR1, multidrug-resistance associated protein 4 (MRP4), breast cancer resistance protein (BCRP)), are located on endothelial cells lining brain vasculature and play important roles in limiting the movement of substances into and enhancing their efflux from the brain.

ABCB1 is one of the most important drug transporters in the brain. Over 1270 drugs have been reported to be associated with the Abcb1 transporter protein (P-gp), of which 490 are substrates, 618 are inhibitors, 182 are inducers, and 269 additional compounds which belong to different pharmacological categories of products with potential Abcb1 interaction.[23] The *ABCB1* gene has 116 polymorphic sites in Caucasians and 127 in African–Americans, with a minor allele frequency greater than 5%. Common variants are