Pharmacogenomics of Alzheimer’s and Parkinson’s diseases

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Abstract

Neurodegenerative disorders (NDDs) (Alzheimer’s disease, Parkinson’s disease) represent major problems of health in developed countries, with important psychosocial burden for families and high cost for the society. NDDs share some common pathogenic mechanisms such as age-related decline, multiple genetic defects distributed across the genome, deposits of abnormal proteins in the brain, and diverse environmental risk factors. Patients with NDDs currently receive polypharmacy with a high risk for drug-drug interactions and severe adverse drug events. Pharmacogenomics accounts for 60-90% variability in drug pharmacokinetics and pharmacodynamics. Major determinants of the pharmacogenomic outcome include pathogenic, mechanistic, metabolic, transporter and pleiotropic genes. The expression of these genes is under regulatory control of the epigenetic machinery. Approximately, 80% of the Caucasian population is deficient in the metabolism of drugs due to polymorphisms in metabolic genes; consequently, less than 40% of patients respond appropriately to conventional drugs. The implementation of pharmacogenomic procedures in the clinical practice may help to optimize therapeutics in NDDs.

Key Words:
Alzheimer’s disease, Parkinson’s disease, Neurodegenerative disorders, Pharmacogenomics, Pharamacoepigenetics, Drugs, APOE, CYPs.
1. Introduction

The most relevant neurodegenerative disorders (NDDs) in developed countries are Alzheimer’s disease (AD) and Parkinson’s disease (PD), though over 50 different NDDs can affect the population. Dementia and PD are among the top 15 conditions with the highest increase in disease burden. About 45-50 million people suffer dementia (75 million in 2030; 145 million in 2050; 7.7 million new cases/year)[1].

The prevalence of PD ranges from 3.58 per 100,000 to 12,500 per 100,000, with an annual incidence ranging from 1.5 per 100,000 to 346 per 100,000 in different countries [2]. PD may coexist with dementia and depression in over 25% of the cases.

Cost-effectiveness of interventions in most brain disorders ranges between US$100 and US$2,000 per healthy life year gained. However, drug effectiveness is lower than 30% in most neuropsychiatric disorders [3].

AD and PD, as many other NDDs, share in common some features, including (i) polygenic/complex defects in conjunction with epigenetic changes, cerebrovascular dysfunction and environmental risk factors; (ii) age-related onset, with an increase in prevalence in parallel with age; (iii) a progressive neuronal degeneration which starts in early periods of life, while their clinical manifestation occurs decades later; (iv) conformational changes in proteins responsible for the abnormal deposits of neurotoxic byproducts; (v) lack of specific biomarkers for a predictive diagnosis and/or early detection; and (vi) no curative treatments [4].

The practical application of pharmacogenomic procedures for optimizing therapeutics is still in its infancy, and pharmacogenetic-guided therapy faces many barriers to full integration into clinical practice [5]. However, physicians are more accurate in their pharmacological prescriptions when they know the pharmacoegenetic profile of their patients [6].

2. Genetic determinants of the pharmacogenomic outcome

Pharmacogenetics accounts for 60-90% variability in pharmacokinetics and pharmacodynamics. Different categories of genes are involved in the pharmacogenetic cascade responsible for drug efficacy and safety, including the following: (i) Pathogenic genes associated with disease pathogenesis (Tables 1-2); (ii) mechanistic genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) metabolic genes associated with drug metabolism (Tables 3-4): (a) phase I reaction enzymes: alcohol dehydrogenases, aldehyde dehydrogenases, aldo-keto reductases, amine oxidases, carbonyl reductases, cytidine deaminase, cytochrome P450 family, cytochrome b5 reductase, dihydropirimidine dehydrogenase, esterases, epoxidases, flavin-containing monooxygenases, glutathione reductase/peroxidases, short-chain dehydrogenases/reductases, superoxide dismutases, and xanthine dehydrogenase; and (b): phase II reaction enzymes: amino acid transferases, dehydrogenases, esterases, glucuronosyl transferases, glutathione transferases, methyl transferases, N-acetyl transferases, thioltransferase, and sulfotransferases; (iv) transporter genes associated with drug transporters, including 49 ABC transporter genes and the multidrug resistance associated proteins which belong to the ABCC family integrated by 13 members, as well as other genes encoding transporter proteins of the solute carrier superfamily (SLC) and solute carrier organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions [7-11].
3. Pharmacoepigenetics

Pharmacogenomics alone does not predict all phenotypic variation in drug response [12,13]. The genes involved in the pharmacogenomic network are under the regulatory control of the epigenetic machinery, this configuring the novel pharmacoepigenomic apparatus [12-16]. Epigenetics involves heritable alterations of gene expression, chromatin organization, and microRNA (miRNA) regulation without changes in DNA sequence. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and miRNAs are among the major regulatory elements that control metabolic pathways at the molecular level, regulating gene expression transcriptionally and post-transcriptionally [17,18]. Methylation varies spatially across the genome with a majority of the methylated sites mapping to intragenic regions [19]. About 70% of CpG dinucleotides within the human genome are methylated. DNA may be subjected to epigenetic modifications related to disease development, environmental exposure, drug treatment and aging [12,15]. Epigenetic regulation is responsible for the tissue-specific expression of genes involved in pharmacogenetic processes, and epigenetics plays a key role in the development of drug efficacy, safety and resistance. [20].

4. Alzheimer's disease

Genomic, epigenomic, cerebrovascular, metabolic and environmental factors are potentially involved in the pathogenesis of AD [21]. The age- and sex-related syndromic profile of AD reflects, at least, a tetravalent phenotype: (i) a neuropathological component (classic hallmarks: senile plaques, neurofibrillary tangles, neuritic desarborization, neuronal loss); (ii) a neurobehavioral component: cognitive deterioration, behavioral changes, functional decline; (iii) an age-related biological component (direct-, indirect-, and un-related biochemical, hematological and metabolic phenotypes); (iv) gender-related phenotypes; and (v) concomitant age-related disorders [21-23]. The pharmacological treatment of these concomitant pathologies adds complexity and risks to the multifactorial therapeutic intervention in patients with dementia.

4.1. Treatments

AD patients may take many different drugs/day for the treatment of dementia-related symptoms, including memory deterioration, behavioral changes, and functional decline, or for the treatment of concomitant pathologies. The co-administration of several drugs may cause side-effects and adverse drug reactions in over 60% of AD patients, who in 2-10% of the cases require hospitalization. The principal causes of these iatrogenic effects are the inappropriate combination of drugs, and the genomic background of the patient, responsible for his/her pharmacogenomic outcome.

During the past 10 years, over 6,000 different compounds have been studied as potential candidate drugs for the treatment of AD [1,7,24]. In addition to the FDA-approved drugs since 1993 (tacrine, donepezil, rivastigmine, galantamine, memantine)(Table 3), most candidate strategies fall into 6 major categories: (i) novel cholinesterase inhibitors and neurotransmitter regulators, (ii) anti-Aβ treatments (APP regulators, Aβ breakers, active and passive immunotherapy with vaccines and antibodies, β- and γ-secretase inhibitors or modulators), (iii) anti-tau treatments, (iv) pleiotropic products (most of them of natural origin), (v) epigenetic intervention, and (vi) combination therapies [1,7,9,25].

During the past 15 years no new drugs have been approved for the treatment of AD and the available drugs are not cost-effective [26]. Therefore, the pharmacogenetics of AD is very limited, circumscribed to cholinesterase inhibitors and memantine (Table 3), remaining stuck in a primitive stage of underdevelopment due to the lack of novel therapeutic options. Although
many studies on the pharmacogenetics of AD have been published since the early 2000’s [27], many of them are redundant and contradictory, focusing mainly on the APOE gene and, to a lesser extent, on some CYP family genes and other minor genes [28].

4.2. Pharmacogenomics

4.2.1. Pathogenic genes

Several pathogenic genes (Table 1) may contribute to AD neuropathology [29,30]. Mendelian mutations affect genes directly linked to AD, including mutations in the amyloid beta precursor protein (APP) gene (21q21) (AD1), presenilin 1 (PSEN1) gene (14q24.3)(AD3), and presenilin 2 (PSEN2) gene (1q31-q42) (AD4)[61]. Mendelian mutations are very rare in AD (1:1000). However, multiple polymorphic risk variants can increase neuronal vulnerability to premature death. There are at least 695 genes potentially associated with AD, of which the most relevant one is APOE (19q13.2). The Apolipoprotein E (APOE) gene (AD2) is the most prevalent as a risk factor for AD, especially in those subjects harboring the APOE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia [29]. Although the APP, PSEN1, PSEN2 and MAPT genes are considered major pathogenic genes for AD and classic tauopathies [30], mutations in these genes represent less than 5% of the AD population and, consequently, their influence on AD pharmacogenetics associated with conventional anti-dementia drugs is quantitatively negligible.

4.2.2. APOE

To date, the most influential gene in AD pharmacogenetics is the APOE gene [7,9,31]. Multiple studies over the past two decades have demonstrated that APOE variants may affect the therapeutic response to anti-dementia drugs [7,9,23,31,32](Fig. 1). In over 100 clinical trials for dementia, APOE has been used as the only gene of reference for the pharmacogenomics of AD. Several studies indicate that the presence of the APOE-4 allele differentially affects the quality and extent of drug responsiveness in AD patients treated with cholinergic enhancers, neuroprotective compounds, endogenous nucleotides, immunotrophins, neurotrophic factors, combination therapies and other drug categories [7,9,33](Fig. 1); however, controversial results are frequently found due to methodological problems, study design, and patient recruitment in clinical trials. The major conclusion in most studies is that APOE-4 carriers are the worst responders to conventional treatments [7,9,23,31,33](Fig. 1).

Adjacent to the APOE locus (19q13.2) and in linkage disequilibrium with APOE is the TOMM40 gene. A poly T repeat in an intronic polymorphism (rs10524523) (intron 6) in the TOMM40 gene, which encodes an outer mitochondrial membrane translocase involved in the transport of Aβ and other proteins into mitochondria, has been implicated in AD [34]. There are 3 allele groups for rs10524523 (‘523’), based on the number of ‘T’-residues: 'Short' (S, T ≤ 19), 'Long' (L, 20 ≤ T ≤ 29) and 'Very Long' (VL, T ≥ 30)[35]. Longer lengths of rs10524523 are associated with a higher risk for late-onset AD (LOAD)[34,35]. Intronic poly T (rs10524523) within this region affects expression of the APOE and TOMM40 genes in the brain of patients with LOAD. S/VL and VL/VL are the only TOMM40 poly T genotypes which interact with all major APOE genotypes; in contrast, the APOE-4/4-TOMM40-L/L association is unique, representing approximately 30% of APOE-4/4 carriers [8]. The first pharmacogenetic study of the APOE-TOMM40 region in AD patients receiving a multifactorial treatment revealed that: (i) APOE-4 carriers are the worst responders and APOE-3 carriers are the best responders to conventional treatments; (ii) TOMM40 poly T-S/S carriers are the best responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment (Fig. 1); (iii) patients harboring a large (L) number of poly T repeats in intron 6 of the TOMM40 gene (L/L or S/L genotypes) in haplotypes associated with APOE-4 are the worst responders to treatment; (iv)
patients with short (S) TOMM40 poly T variants (S/S genotype), and to a lesser extent S/VL and VL/VL carriers, in haplotypes with APOE-3 are the best responders to treatment; and (v) in 100% of the cases, the L/L genotype is exclusively associated with the APOE-4/4 genotype, and this haplotype (4/4-L/L) is probably responsible for early onset of the disease, a faster cognitive decline, and a poor response to different treatments [8-10](Fig. 1).

The construction of a pentagenic haplotype integrating all possible variants of the APOE+APOB+EPOC3+CETP+LPL genes yields 111 haplotypes (H) with differential basal cholesterol (CHO) levels [36]. About 75% of these haplotypes in the AD population have a frequency below 1%, 10% have a frequency between 1% and 2%, 8% have a frequency between 2% and 5%, and only 4% of the haplotypes are present in more than 5% of AD patients. All these haplotypes influence the response of CHO to lipid-lowering drugs in AD cases or in dyslipidemic patients [36].

4.2.3. Metabolic genes

Over 80% of AD patients are deficient metabolizers for the CYP2D6/2C19/2C9/3A4 tetragenic cluster [23,36]. 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 [7,31,37]. The distribution and frequency of CYPs genotypes are very similar in the general population and in AD; however, the condition of extensive (EM), intermediate (IM), poor (PM) or Ultra-Rapid metabolizer (UM) is determinant for drug efficacy and safety when treating AD patients with anti-dementia drugs or with drugs for concomitant disorders [11,36]. Tetragenic haplotypes integrating CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 variants yield 156 genotypes. The most frequent haplotype is H3 (1/1-1/1-1/1-3/3)(20.87%), representing full extensive metabolizers, and only 17 haplotypes exhibit a frequency higher than 1% in the Caucasian population. This indicates that 80% of individuals are deficient for the biotransformation of current drugs which are metabolized via CYP2D6-2C9-2C19-3A4 enzymes [36].

Cytochrome P450 46A1 (CYP46A1)(cholesterol 24-hydroxylase), that controls cholesterol elimination from the brain and is involved in higher activities of the CNS, has been proposed as a potential target for AD treatment [38]. Genes encoding Phase-II reaction enzymes have also been found to be associated with AD risk. For instance, associations of GSTM1 and GSTT1 null deletion and GSTP1 313 A/G variants with risk of AD have been found [39]. These variants may affect the efficiency of glutathione S-transferases (GSTs) in drug metabolism, especially in APOE4 carriers [39].

4.2.4. Transporters

Polymorphic variants in genes encoding transporter proteins may affect drug metabolism, brain penetration and accessibility to neuronal/glial targets, and drug resistance [40]. Of special importance in AD are the ABC and SLC family genes [41]. ABC genes (ABCB1, ABCC1, ABCG2), and other genes of this family encode proteins which are essential for drug metabolism and transport. Mutations in ABC transporters influence pathogenesis and therapeutics of brain disorders [41]. 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 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 [11]. The ABCB1 C1236T, G2677T/A and C3435T SNPs influence blood-brain barrier (BBB) P-glycoprotein
function. AD patients with one or more T in C1236T, G2677T and C3435T have significantly higher binding potential values than patients without a T. Genetic variations in ABCB1 might contribute to the progression of Aβ deposition in the brain [42] and some ABCB1 SNPs (C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26) and inferred haplotypes might represent novel biomarkers of AD [43]. ABCB1 directly transports Aβ from the brain into the blood circulation, whereas the cholesterol transporter ABCA1 neutralizes Aβ aggregation capacity in an APOE-dependent manner, facilitating subsequent Aβ elimination from the brain [44].

Some other ABCs have shown potential association with AD [41]. Both common and rare SNPs within ABCA7 have been associated with AD. The G allele of the ABCA7 rs115550680 SNP is associated with AD in Europeans. The effect size for the SNP in ABCA7 was comparable with that of the APOE ε4-determining SNP rs429358 [45]. The ABCA7 SNP rs200538373 is associated with altered ABCA7 exon 41 splicing and AD risk [46].

ABCG2 is involved in Aβ transport and is up-regulated in AD brains. The ABCG2 gene (C421A; rs2231142) (ABCG2 C/C genotype) is associated with AD and the ABCG2 C/C genotype and the APOE e4 allele may exert an interactive effect on AD risk [47].

Also of importance for AD pharmacogenomics are transporters encoded by genes of the solute carrier superfamily (SLC) and solute carrier organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, [41].

### 4.2.5. Anti-Dementia Drugs

Most anti-dementia drugs are metabolized via CYP enzymes. Donepezil is a major substrate of CYP2D6, CYP3A4, ACHE, and UGTs, inhibits ACHE and BCHE, and is transported by ABCB1 [7,11,21,28,31,48] (Table 3). CYP2D6 variants affect donepezil efficacy and safety in AD. The common variant rs1080985 of CYP2D6 is associated with poor response to donepezil [48]. A higher frequency of mutated CYP2D6 allele *2A was found in responder than in non-responder patients [49]. In contrast, other studies revealed that CYP2D6-PMs and UMs tend to be poor responders to conventional doses of donepezil as compared to EMs and IMs [7,11,21,28,50].

The effects of galantamine are potentially influenced by APOE, APP, ACHE, BCHE, CHRNA4, CHRNA7, CHRN2B variants. This drug is a major substrate of CYP2D6, CYP3A4, and UGT1A1, and an inhibitor of ACHE and BCHE [11,50,51](Table 3). Major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization [53].

Galantamine is extensively metabolized by the enzymes CYP2D6 and CYP3A and is a substrate of the P-gp. CYP2D6 variants are determinant for galantamine pharmacokinetics. CYP2D6-PMs exhibit higher dose-adjusted galantamine plasma concentrations than heterozygous and homozygous CYP2D6-EMs [53]; however, these pharmacokinetic changes might not substantially affect pharmacodynamics [54]. The co-administration of galantamine with paroxetine (a CYP2D6 strong inhibitor), ketoconazole (a CYP3A4 strong inhibitor) and erythromycin increases its bioavailability [55].

APOE, APP, CHAT, ACHE, BCHE, CHRNA4, CHRN2B and MAPT variants may affect rivastigmine pharmacokinetics and pharmacodynamics, but CYP enzymes are not involved in the metabolism of rivastigmine [11,50,56]. UGT2B7-PMs show higher rivastigmine levels with a poor response to treatment [57].

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 [11,50,58]. 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 [59]. 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 [60].

5. Parkinson’s disease

Associated with different potentially pathogenic risk factors (toxins, drugs, pesticides, brain microtrauma, focal cerebrovascular damage, genomic defects), PD neuropathology is characterized by a selective loss of dopaminergic neurons in the substantia nigra pars compacta and Lewy body deposition, with widespread involvement of other CNS structures and peripheral tissues [61,62]. PD is a form of α-synucleinopathy with Lewy bodies deposited in midbrain. Descriptive phenomena to explain in part this neuropathological phenotype include the following: (i) genomic factors, (ii) epigenetic changes, (iii) toxic factors, (iv) oxidative stress anomalies, (v) neuroimmune/neuroinflammatory reactions, (vi) hypoxic-ischemic conditions, (vii) metabolic deficiencies, and (viii) ubiquitin-proteasome system dysfunction [62].

5.1. Pathogenomics

Mutations in a series of primary genes are known to cause autosomal dominant and recessive forms of PD [62-65]. Mutations in some genes (e.g., SNCA, PARK2, PINK1, PARK7, LRRK2, BST1, MAPT) might be causative in familial forms of PD whereas diverse genetic defects in other loci might represent susceptibility loci associated with sporadic PD without family history [62]. Mendelian variants with high penetrance explain less than 10% of familial PD [140]. In a recent meta-analysis of PD GWAS with over 7 million variants, 26 loci have shown significant association with PD. Significant associations at different loci (DLG2, SIPA1L2, STK39, VPS13C, RIT2, BST1, PARK16) have been found in Asians vs Europeans, together with allelic heterogeneity at LRRK2 and at 6 other loci including MAPT and GBA-SYT11 [66]. Some other candidate genes have been recently reported to be associated with PD in different cohorts (i.e., RAD51B, DYRK1A, CHCHD2, VPS35, RAB39B, TMEM230) [62](Table 3).

5.2. Anti-Parkinsonian drugs

Classical therapeutic interventions for the symptomatic treatment of psychomotor dysfunction in PD include pharmacotherapy, deep brain stimulation, and physiotherapy [150]. In addition to dopamine precursors (L-DOPA), other symptomatic treatments for PD include dopamine agonists (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine), monoamine oxidase (MAO) inhibitors (selegiline, rasagiline), and catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone) [11,62,68](Table 4). The initial complication of long-term L-DOPA therapy is the “wearing-off” phenomenon [69], together with motor fluctuations and dyskinesia, which develop during the use of both L-DOPA and dopamine agonists [70]. PD patients under long-term treatment with L-DOPA and/or conventional antiparkinsonian drugs experience a hyperdopaminemic status which might be responsible for (i) the clinical improvement of PD cardinal symptoms in the short term, (ii) the “wearing-off” phenomenon, (iii) motor fluctuations and dyskinesia, (iv) systemic complications (gastrointestinal disorders, cardiovascular problems, hormonal dysregulation), and (v) neuropsychiatric disorders (depression, anxiety, toxic psychosis) [62].

5.3. Pharmacogenomics
In recent years, novel evidence has demonstrated the impact of pharmacogenetics on anti-PD drug efficacy and safety [71,72] (Table 4). In the particular case of L-DOPA, the ANKK1, BDNF, LRRK2, and PARK2 genes are pathogenic players potentially involved in its effects. The CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, and OPRM1 genes are mechanistic genes whose products influence L-DOPA efficacy and safety. L-DOPA is a substrate of enzymes encoded by the COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DBH, DDC, G6PD, MAOB, TH, UGT1A1, and UGT1A9 genes responsible for its metabolism. SLC6A3 is the major transporter of L-DOPA; and ACE, ACHE, and APOE are pleiotropic players in L-DOPA efficacy and safety [11] (Table 4). ADORA2A SNPs and HOMER1 variants may be associated with L-DOPA-induced dyskinesia and psychotic symptoms [73]. A haplotype integrating -141CIn/Del, rs2283265, rs1076560, C957T, TaqIA, and rs2734849 polymorphisms at the DRD2/ANKK1 gene region might also be associated with L-DOPA-induced motor dysfunction [74]. SLC6A3 is a genetic modifier of the treatment response to L-DOPA in PD [75]. The multi-drug resistance gene (MDR1) C1236T polymorphism may also influence PD pharmacotherapy [76] as well as SNPs in genes encoding the dopamine transporter (DAT; SLC6A3) and the vesicular monoamine transporter 2 (VMAT2; SLC18A2) [77]. Other categories of anti-PD drugs exhibit specific pharmacogenetic profiles (Table 4).

Recent studies with E-PodoFavalin-15999 (Atremorine®), a novel biopharmaceutical compound, obtained by means of non-denaturing biotechnological procedures from structural components of Viciafaba L., for the prevention and treatment of PD [62,71,78], show further demonstration that pharmacogenetics is determinant in dopaminergic neuroprotection, L-DOPA-induced dopamine response, and safety [62,77]. Preclinical studies (in vitro) revealed that Atremorine is a powerful neuroprotectant in (i) cell cultures of human neuroblastoma SH-SYSY cells; (ii) hippocampal slices in conditions of oxygen and glucose deprivation; and (iii) striatal slices under conditions of neurotoxicity induced by 6-OHDA [79]. In vivo studies showed that Atremorine (i) protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration; (ii) inhibits MPTP-induced microglia activation and neurotoxicity in the substantia nigra; and (iii) improves motor function in mice with MPTP-induced neurodegeneration [62,71,78,80].

Atremorine enhances dopaminergic neurotransmission and increases plasma dopamine levels by 200-500-fold. However, although the dopaminergic surge induced by Atremorine is proportional to basal DA levels in PD patients, its real potency and pharmacodynamic and pharmacokinetic properties are highly influenced by genetic and pharmacogenetic factors [62,71] (Fig. 2). The condition of EM, IM, PM, or UM associated with different CYP variants, and the inheritance of the APOE-4 allele as well, influence the Atremorine-induced dopamine response in PD patients [71].

According to the information available, it seems reasonable to assume that the personalized treatment of PD patients requires the implementation of pharmacogenetic procedures in order to optimize therapeutics (improving efficacy and safety) [11,62].

6. Future Trends

Conventional drugs for NDDs are not cost-effective in the long-term, their pharmacodynamic properties are very limited, and none of them is devoid of side effects [26]. Less than 20% of patients with NDDs show a moderate response, roughly indicating that 60-80% of their cost is a waste of pharmacoeconomic resources. Furthermore, these drugs represent a pharmacological burden for surviving neurons which are forced to overwork under critical conditions; but they do not protect neurons against a premature death. Multifactorial treatments, with about 50% of good responders, only show a clear benefit during the initial phases of treatment; thereafter, cognitive decline and/or psychomotor function, depending on the NDD, progress with a minimum effect of the pharmacological regime [8,9]. In addition, the therapeutic response to conventional drugs is genotype-dependent, but routine pharmacogenetic studies are scarcely...
performed; and over 90% of AD patients are simultaneously receiving different types of drugs for concomitant disorders with a high risk of drug-drug interactions and ADRs. In the particular case of AD, over the past 15 years no new drugs have been approved by the FDA or other Regulatory Agencies worldwide [1,10]. This alarming situation should help governmental authorities, the pharmaceutical industry, the scientific community, and the public to understand and accept that the strategies used so far to fight against dementia in developed countries for the past 50 years have been a calamitous failure. The situation with PD is different; however, most anti-PD drugs are symptomatic, but not neuroprotective and/or anti-pathogenic. A highly important issue to take into consideration in future preventive programs for NDDs is the impact that cardiovascular disorders and cerebrovascular damage associated with vascular risk factors such as hypertension, lipid metabolism disorders, or diabetes may have on neurodegeneration, accelerating disease progression. Consequently, a profound revision of pathogenic mechanisms, environmental risk factors, preventive strategies, early diagnosis, and affective treatments is urgently required. In this context, several considerations have been proposed to achieve a more mature profile of NDD pharmacogenomics: (i) a better characterization of the roles played in drug efficacy and safety by genes involved in the pharmacogenomic network is necessary; (ii) since most genes are under the influence of the epigenetic machinery, pharmacoprogenomics is becoming an attractive field which deserves special attention, and some epigenetic drugs might also be helpful in selected cases, although most epigenetic drugs at this moment pose technical problems (bioavailability, toxicity, brain penetration); (iii) drug-drug interactions represent a problematic issue in over 80% of patients (most patients require a multifactorial treatment with different drugs); (iv) since the neurodegenerative process underlying NDD neuropathology starts 20-30 years before the onset of the disease, novel therapeutics should be addressed to prevent premature neuronal death (symptomatic drugs have proven to be poorly effective); (v) specific biomarkers for AD and PD are necessary in 3 different contexts: predictive markers before disease onset, early diagnosis in initial stages, and drug monitoring (in both preventive and/or therapeutic strategies); and (vi) educational programs are necessary for physicians to be aware of the usefulness of pharmacogenomics to prescribe more accurately, avoid adverse reactions and optimize the limited therapeutic resources available for the treatment of NDDs.

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**Competing Interests**

The author is President of EuroEspes, S.A., owner of the Atremorine® Patent.

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References


**LEGEND TO FIGURES**

Figure 1. APOE- and TOMM40-related therapeutic response to a multifactorial treatment in patients with Alzheimer’s disease.

AD patients received a combination treatment for 1 year: CDP-choline (500 mg/day, p.o.)(choline donor and intermediate metabolite in DNA synthesis and repair), Piracetam (1600 mg/day, p.o.)(nootropic drug), Sarilipin (E-SAR-94010)(250 mg, t.i.d.)(nutraceutical with lipid-lowering effects and anti-atherosclerotic properties), and Animon Complex® (2 capsules/day)(a nutraceutical compound integrated by a purified extract of Chenopodium quinoa (250 mg), ferrous sulphate (38.1 mg equivalent to 14 mg of iron), folic acid (200 µg), and vitamin B12 (1 µg) per capsule (RGS: 26.06671/C))[8].

Figure 2. CYP2D6- and CYP2C9-related Atremorine-induced dopamine response in patients with Parkinson’s disease.

Basal (DAb) and Atremorine-induced dopamine response (DAT) in CYP2D6 extensive (EM), Intermediate (IM), Poor (PM) and Ultra-rapid metabolizers (UM)(left panel) and in CYP2C9 extensive (EM), Intermediate (IM), and Poor metabolizers (PM)(right panel).

Dopamine levels: One hour after oral administration of Atremorine (5 g in a single dose)[71].
<table>
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<td>rs429358; rs7412</td>
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<td>C9ORF72</td>
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<td>CD2AP</td>
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<td>rs9349407</td>
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<td>CD33</td>
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<td>19q13.41</td>
<td>rs3865444</td>
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<td>rs7767170</td>
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<td>1q4.2</td>
<td>rs1776148</td>
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<td>rs11082762</td>
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<td>rs7995844</td>
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<td>8p21.1</td>
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<td>rs11803905</td>
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<td>PICALM</td>
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| **Donepezil hydrochloride**   | **Name:** Donepezil hydrochloride, Aricept, 120011-70-3, Donepezil HCl, BNAG, E-2020, E2020  
**IUPAC Name:** 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one;hydrochloride  
**Molecular Formula:** C\textsubscript{24}H\textsubscript{30}ClNO\textsubscript{3}  
**Molecular Weight:** 415.9529 g/mol  
**Category:** Cholinesterase inhibitor  
**Mechanism:** Centrally active, reversible acetylcholinesterase inhibitor; increases the acetylcholine available for synaptic transmission in the CNS  
**Effect:** Nootropic agent, cholinesterase inhibitor, parasympathomimetic effect  
| **Pathogenic genes:** APOE, CHAT  
**Mechanistic genes:** CHAT, ACHE, BCHE  
**Drug metabolism-related genes:**  
- **Substrate:** CYP2D6 (major), CYP3A4 (major), UGTs, ACHE  
- **Inhibitor:** ACHE, BCHE  
**Transporter genes:** ABCB1 |
| **Galantamine hydrobromide**  | **Name:** Galantamine hydrobromide, Galanthamine hydrobromide, 1953-04-4, Nivalin, Razadyne, UNII-MJ4PTD2VVW, Nivaline  
**IUPAC Name:** (1S,12S,14R)-9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca-6,8,10(17),15-tetraen-14-ol  
**Molecular Formula:** C\textsubscript{17}H\textsubscript{22}BrNO\textsubscript{3}  
**Molecular Weight:** 368.26548 g/mol  
**Category:** Cholinesterase inhibitor  
**Mechanism:** Reversible and competitive acetylcholinesterase inhibition leading to an increased concentration of acetylcholine at cholinergic synapses; modulates nicotinic acetylcholine receptor; may increase glutamate and serotonin levels  
**Effect:** Nootropic agent, cholinesterase inhibitor, parasympathomimetic effect  
| **Pathogenic genes:** APOE, APP  
**Mechanistic genes:** ACHE, BCHE, CHRNA4, CHRNA7, CHRN8B  
**Drug metabolism-related genes:**  
- **Substrate:** CYP2D6 (major), CYP3A4 (major), UGT1A1  
- **Inhibitor:** ACHE, BCHE |
| Name: Memantine Hydrochloride, 41100-52-1, Namenda, Memantine HCL, Axura, 3,5-Dimethyl-1-adamantanamine hydrochloride, 3,5-dimethyldadamantan-1-amine hydrochloride | Pathogenic genes: APOE, MAPT, PSEN1  
Mechanistic genes: CHRFAM7A, DLGAP1, FOS, GRIN2A, GRIN2B, GRIN3A, HOMER1, HTR3A  
Drug metabolism-related genes:  
-Inhibitor: CYP1A2 (weak), CYP2A6 (weak), CYP2B6 (strong), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (strong), CYP2E1 (weak), CYP3A4 (weak), NR1I2  
Transporter genes: NR1I2  
Pleiotropic genes: APOE, MAPT, MT-TK, PSEN1 |
|---|---|
| IUPAC Name: 3,5-dimethyladamantan-1-amine hydrochloride  
Molecular Formula: C_{12}H_{22}ClN  
Molecular Weight: 215.76278 g/mol  
Category: N-Methyl-D-Aspartate receptor antagonist  
Mechanism: Binds preferentially to NMDA receptor-operated cation channels; may act by blocking actions of glutamate, mediated in part by NMDA receptors  
Effect: Dopamine agent, antiparkinson agent, excitatory amino acid antagonist, antidyskinetic |
| Name: Rivastigmine tartrate, 129101-54-8, SDZ-ENA 713, Rivastigmine hydrogentartrate, Rivastigmine Hydrogen Tartrate, ENA 713, ENA-713 | Pathogenic genes: APOE, APP, CHAT  
Mechanistic genes: ACHE, BCHE, CHAT, CHRNA4, CHRN2B  
Drug metabolism-related genes:  
-Inhibitor: ACHE, BCHE  
Pleiotropic genes: APOE, MAPT |
| IUPAC Name: (2R,3R)-2,3-dihydroxybutanedioic acid;[3-[(1S)-1-(dimethylamino)ethyl]phenyl] N-ethyl-N-methylcarbamate  
Molecular Formula: C_{18}H_{28}N_{2}O_{8}  
Molecular Weight: 400.42352 g/mol  
Category: Cholinesterase inhibitor  
Mechanism: Increases acetylcholine in CNS through reversible inhibition of its hydrolysis by cholinesterase  
Effect: Neuroprotective agent, cholinesterase inhibitor, cholinergic agent |

ADH1A: Alcohol dehydrogenase 1A (class I), alpha polypeptide; AADAC: Arylacetamide deacetylase; AANAT: aralkylamine N-acetyltransferase; ACSL1: Acyl-CoA synthetase long-chain family member 1; ACSL3: Acyl-CoA synthetase long-chain family member 3; ACSL4: Acyl-CoA synthetase long-chain family member 4; ACSM1: Acyl-CoA synthetase medium-chain family member 1; ACSM2B: Acyl-CoA synthetase medium-chain family member 2B; ACSM3: Acyl-CoA synthetase medium-chain family, member 3; ADH1B: Alcohol dehydrogenase 1B (class I), beta polypeptide; ADH1C: Alcohol dehydrogenase 1C (class I), gamma polypeptide; ADH4: Alcohol dehydrogenase 4 (class II), pi polypeptide; ADHS: Alcohol dehydrogenase 5 (class III), chi polypeptide; ADH6: Alcohol dehydrogenase 6 (class V); ADH7: Alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; ADHFE1: Alcohol dehydrogenase, iron containing, 1; AGXT: Alanine-glyoxylate
Aldo-keto reductase family 1, member A1 (aldo-keto reductase); AKR1B1: Aldo-keto reductase family 1, member B1 (aldose reductase); AKR1C1: Aldo-keto reductase family 1, member C1; AKR1D1: Aldo-keto reductase family 1, member D1; ALDH1A1: Aldehyde dehydrogenase 1 family, member A1; ALDH1A2: Aldehyde dehydrogenase family 1, subfamily A2; ALDH1A3: Aldehyde dehydrogenase family 1, subfamily A3; ALDH1B1: Aldehyde dehydrogenase 1 family, member B1; ALDH2: Aldehyde dehydrogenase 2 family (mitochondrial); ALDH3A1: Aldehyde dehydrogenase 3 family, member A1; ALDH3A2: Aldehyde dehydrogenase 3 family, member A2; ALDH3B1: Aldehyde dehydrogenase 3 family, member B1; ALDH3B2: Aldehyde dehydrogenase 3 family, member B2; ALDH4A1: Aldehyde dehydrogenase 4 family, member A1; ALDH5A1: Aldehyde dehydrogenase 5 family, member A1; ALDH6A1: Aldehyde dehydrogenase 6 family, member A1; ALDH7A1: Aldehyde dehydrogenase 7 family, member A1; ALDH8A1: Aldehyde dehydrogenase 8 family, member A1; ALDH9A1: Aldehyde dehydrogenase 9 family, member A1; AOX1: Aldehyde oxidase 1; AS3MT: Arsenic (+3 oxidation state) methyltransferase; ASMT: Aconitase; BAAT: Bile acid CoA: amino acid N-acyltransferase (glycine N-cholyltransferase); CBR1: Carboxyl reductase 1; CBR3: Carboxyl reductase 3; CBR4: Carboxyl reductase 4; CCBL1: Cysteine conjugate-beta lyase, cytoplasmic; CDA: Cytidine deaminase; CEL: Carboxyl ester lipase; CES1: Carboxylesterase 1; CES1P1: Carboxylesterase 1 pseudogene 1; CES2: Carboxylesterase 2; CES3: Carboxylesterase 3; CES5A: Carboxylesterase 5A; CHST1: Carbohydrate (keratan sulfate Gal-6) sulfotransferase 1; CHST2: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2; CHST3: Carbohydrate (chondroitin 6-sulfotransferase 3; CHST4: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 4; CHST5: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 5; CHST6: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 6; CHST7: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 7; CHST8: Carbohydrate (N-acetylglucosamine-4-O) sulfotransferase 8; CHST9: Carbohydrate (N-acetylglucosamine-4-O) sulfotransferase 9; CHST10: Carbohydrate sulfotransferase 10; CHST11: Carbohydrate (chondroitin 4) sulfotransferase 11; CHST12: Carbohydrate (chondroitin 4) sulfotransferase 12; CHST13: Carbohydrate (chondroitin 4) sulfotransferase 13; COMT: Catechol-O-methyltransferase; CYB5R3: Cytochrome b5 reductase 3; CYP1A1: Cytochrome P450, family 1, subfamily A, polypeptide 1; CYP1A2: Cytochrome P450, family 1, subfamily A, polypeptide 2; CYP1B1: Cytochrome P450, family 1, subfamily B, polypeptide 1; CYP2A6: Cytochrome P450, family 2, subfamily A, polypeptide 6; CYP2A7: Cytochrome P450, family 2, subfamily A, polypeptide 7; CYP2A13: Cytochrome P450, family 2, subfamily A, polypeptide 13; CYP2B6: Cytochrome P450, family 2, subfamily B, polypeptide 6; CYP2C8: Cytochrome P450, family 2, subfamily C, polypeptide 8; CYP2C9: Cytochrome P450, family 2, subfamily C, polypeptide 9; CYP2C18: Cytochrome P450, family 2, subfamily C, polypeptide 18; CYP2C19: Cytochrome P450, family 2, subfamily C, polypeptide 19; CYP2D6: Cytochrome P450, family 2, subfamily D, polypeptide 6; CYP2D7P1: Cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1; CYP2E1: Cytochrome P450, family 2, subfamily E, polypeptide 1; CYP2F1: Cytochrome P450, family 2, subfamily F, polypeptide 1; CYP2J2: Cytochrome P450, family 2, subfamily J, polypeptide 2; CYP2R1: Cytochrome P450, family 2, subfamily R, polypeptide 1; CYP2S1: Cytochrome P450, family 2, subfamily S, polypeptide 1; CYP2W1: Cytochrome P450, family 2, subfamily W, polypeptide 1; CYP3A4: Cytochrome P450, family 3, subfamily A, polypeptide 4; CYP3A5: Cytochrome P450, family 3, subfamily A, polypeptide 5; CYP3A7: Cytochrome P450, family 3, subfamily A, polypeptide 7; CYP3A43: Cytochrome P450, family 3, subfamily A, polypeptide 43; CYP4A11: Cytochrome P450, family 4, subfamily A, polypeptide 11; CYP4A22: Cytochrome P450, family 4, subfamily A, polypeptide 22; CYP4B1: Cytochrome P450, family 4, subfamily B, polypeptide 1; CYP4F2: Cytochrome P450, family 4, subfamily F, polypeptide 2; CYP4F3: Cytochrome P450, family 4, subfamily F, polypeptide 3; CYP4F8: Cytochrome P450, family 4, subfamily F, polypeptide 8; CYP4F11: Cytochrome P450, family 4, subfamily F, polypeptide 11; CYP4F12: Cytochrome P450, family 4, subfamily F, polypeptide 12; CYP4Z1: Cytochrome P450, family 4, subfamily Z, polypeptide 1; CYP7A1: Cytochrome P450, family 7, subfamily A, polypeptide 1; CYP7B1: Cytochrome P450, family 7, subfamily B, polypeptide 1; CYP8B1: Cytochrome P450, family 8, subfamily B, polypeptide 1; CYP11A1: Cytochrome P450, family 11, subfamily A, polypeptide 1; CYP11B1: Cytochrome P450, family 11, subfamily B, polypeptide 2; CYP17A1: Cytochrome P450, family 17, subfamily A, polypeptide 1; CYP19A1: Cytochrome P450, family 19, subfamily A, polypeptide 1; CYP20A1: Cytochrome P450, family 20, subfamily A, polypeptide 1; CYP21A2: Cytochrome P450, family 21, subfamily A, polypeptide 2; CYP24A1: Cytochrome P450, family 24, subfamily A, polypeptide 1; CYP26A1: Cytochrome P450, family 26, subfamily A, polypeptide 1; CYP26B1: Cytochrome P450, family 26, subfamily B, polypeptide 1; CYP26C1: Cytochrome P450, family 26, subfamily C,
Dihydropyrimidine dehydrogenase; Glutathione peroxidase 7; dehydrogenase, quinone 2; polypeptide 1; B; Cytochrome P450, family 39, subfamily A, polypeptide 1; Glutathione S-transferase mu 2 (muscle); Flavin containing monooxygenase 4; METAP1; GSTO2; Hydroxysteroid (11β)-dehydrogenase 1; Paraoxonase 3; GSTP1; FMO6P; Dehydrogenase/reductase (SDR family) member 9; DHR5X; Dehydrogenase/reductase (SDR family) X-linked; DLGAP1; discs, large (Drosophila) homolog-associated protein 1; DPEP1: Dipeptidase 1 (renal); DYPD: Dihydropyrimidine dehydrogenase; EPHX1: Epoxide hydrolase 1, microsomal (xenobiotic); EPHX2: Epoxide hydrolase 2, microsomal (xenobiotic); ESD: Esterase D; FMO1: Flavin containing monooxygenase 1; FMO2: Flavin containing monooxygenase 2; FMO3: Flavin containing monooxygenase 3; FMO4: Flavin containing monooxygenase 4; FMO5: Flavin containing monooxygenase 5; FMO6P: Flavin containing monooxygenase 6 pseudogene; FOS: FBJ murine osteosarcoma viral oncogene homolog; GAL3ST1: Galactose-3-O-sulfotransferase 1; GAMT: Guanidinoacetate N-methyltransferase; GLRX: Glutaredoxin (thioltransferase); GLYAT: Glycine-N-acetyltransferase; GNMT: Glycine N-methyltransferase; GPX1: Glutathione peroxidase 1; GPX2: Glutathione peroxidase 2 (gastrointestinal); GPX3: Glutathione peroxidase 3 (plasma); GPX4: Glutathione peroxidase 4; GPX5: Glutathione peroxidase 5; GPX6: Glutathione peroxidase 6 (olfactory); GPX7: Glutathione peroxidase 7; GSR: Glutathione reductase; GSTA1: Glutathione S-transferase alpha 1; GSTA2: Glutathione S-transferase alpha 2; GSTA3: Glutathione S-transferase alpha 3; GSTA4: Glutathione S-transferase alpha 4; GSTA5: Glutathione S-transferase alpha 5; GSTCD: Glutathione S-transferase, C-terminal domain containing; GSTK1: Glutathione S-transferase kappa 1; GSTM1: Glutathione S-transferase mu 1; GSTM2: Glutathione S-transferase mu 2 (muscle); GSTM3: Glutathione S-transferase mu 3 (brain); GSTM4: Glutathione S-transferase mu 4; GSTM5: Glutathione S-transferase mu 5; GSTO1: Glutathione S-transferase omega 1; GSTO2: Glutathione S-transferase omega 2; GSTP1: Glutathione S-transferase pi 1; GSTT1: Glutathione S-transferase theta 1; GSTT2: Glutathione S-transferase theta 2; GSTZ1: Glutathione S-transferase zeta 1; GZMA: Granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3) GZMB: Granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1); HNMT: Histamine N-methyltransferase; HOMER1: Homer homolog 1 (Drosophila); HSD11B1: Hydroxysteroid (11beta) dehydrogenase 1; HSD17B10: Hydroxysteroid (17-beta) dehydrogenase 10; HSD17B11: Hydroxysteroid (17-beta) dehydrogenase 11; HSD17B14: Hydroxysteroid (17-beta) dehydrogenase 14; INMT: Indolethylamine N-methyltransferase; MAOA: Monoamine oxidase A; MAOB: monoamine oxidase B; METAP1: Methionyl aminopeptidase 1; MGST1: Microsomal glutathione S-transferase 1; MGST2: Microsomal glutathione S-transferase 1; MGST3: Microsomal glutathione S-transferase 3; NAA20: N(alpha)-acetyltransferase 20, NatB catalytic subunit; NAT1: N-acetyltransferase 1 (arlyamine N-acetyltransferase); NAT2: N-acetyltransferase 2 (aryamine N-acetyltransferase); NNMT: Nicotinamide N-methyltransferase; NQO1: NAD(P)H dehydrogenase, quinone 1; NQO2: NAD(P)H dehydrogenase, quinone 2; NR1I2: nuclear receptor subfamily 1, group I, member 2; PNMT: Phenylethanolamine N-methyltransferase; PON1: Paraoxonase 1; PON2: Paraoxonase 2; PON3: Paraoxonase 3; POR: P450 (cytochrome) oxidoreductase; PTGES: Prostaglandin E synthase; PTGS1: Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase); PTGS2: Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase); SAT1: Spermidine/spermine N1-acetyltransferase 1; SMOX: Spermine oxidase; SOD1: Superoxide dismutase 1, soluble; SOD2: Superoxide dismutase 2, mitochondrial; SULT1A1: Sulfoconjugase family, cytosolic, 1A, phenol-prefering, member 1; SULT1A2: Sulfoconjugase family, cytosolic, 1A, phenol-prefering, member 2; SULT1A3: Sulfoconjugase family, cytosolic, 1A, phenol-prefering, member 3; SULT1B1: Sulfoconjugase family, cytosolic, 1B, member 1; SULT1C1: Sulfoconjugase family, cytosolic, 1C, member 1; SULT1C2: Sulfoconjugase family, cytosolic, 1C, member 2; SULT1C3: Sulfoconjugase family, cytosolic, 1C, member 3; SULT1C4: Sulfoconjugase family, cytosolic, 1C, member 4; SULT1E1: Sulfoconjugase family 1E, estrogen-prefering, member 1; SULT2A1: Sulfoconjugase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-prefering, member 1; SULT2B1: Sulfoconjugase family, cytosolic, 2B, member 1; SULT4A1: Sulfoconjugase family 4A, member 1; SULT6B1: sulfoconjugase family, cytosolic, 6B, member 1; TBXAS1: Thromboxane A synthase 1 (platelet); TPMT: Thiopurine S-methyltransferase; TST: Thiopurine S-methyltransferase; UCHL1: Ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase); UCHL3:
Ubiquitin carboxyl-terminal esterase L3 (ubiquitin thiolesterase); **UGT1A1**: UDP glucuronosyltransferase 1 family, polypeptide A1; **UGT1A3**: UDP glucuronosyltransferase 1 family, polypeptide A3; **UGT1A4**: UDP glucuronosyltransferase 1 family, polypeptide A4; **UGT1A5**: UDP glucuronosyltransferase 1 family, polypeptide A5; **UGT1A6**: UDP glucuronosyltransferase 1 family, polypeptide A6; **UGT1A7**: UDP glucuronosyltransferase 1 family, polypeptide A7; **UGT1A8**: UDP glucuronosyltransferase 1 family, polypeptide A8; **UGT1A9**: UDP glucuronosyltransferase 1 family, polypeptide A9; **UGT1A10**: UDP glucuronosyltransferase 1 family, polypeptide A10; **UGT2A1**: UDP glucuronosyltransferase 2 family, polypeptide A1, complex locus; **UGT2A3**: UDP glucuronosyltransferase 2 family, polypeptide A3; **UGT2B10**: UDP glucuronosyltransferase 2 family, polypeptide A3; **UGT2B11**: UDP glucuronosyltransferase 2 family, polypeptide A10; **UGT2B15**: UDP glucuronosyltransferase 2 family, polypeptide B15; **UGT2B17**: UDP glucuronosyltransferase 2 family, polypeptide B17; **UGT2B28**: UDP glucuronosyltransferase 2 family, polypeptide B28; **UGT2B4**: UDP glucuronosyltransferase 2 family, polypeptide B4; **UGT2B7**: UDP glucuronosyltransferase 2 family, polypeptide B7; **UGT3A1**: UDP glucosyltransferase 3 family, polypeptide A1; **UGT8**: UDP glucosyltransferase 8; **XDH**: Xanthine dehydrogenase.

(Adapted from Cacabelos et al [6]).

### Table 4. Pharmacogenomics of anti-Parkinsonian drugs

#### Dopamine Precursors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenetics</th>
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</thead>
<tbody>
<tr>
<td><strong>Levodopa</strong></td>
<td>Name: Levodopa; 59-92-7; Levodopa; L-dopa; Dopar; Bendopa; Dopasol; 3,4-dihydroxy-L-phenylalanine; Madopar.</td>
<td>Pathogenic genes: ANKK1, BDNF, LRRK2, PARK2&lt;br&gt;Mechanistic genes: CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1&lt;br&gt;Metabolic genes Substrate: COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DBH, DDC, G6PD, MAOB, TH, UGT1A1, UGT1A9&lt;br&gt;Transporter genes: SLC22A1, SLC6A3&lt;br&gt;Pleiotropic genes: ACE, ACHE</td>
</tr>
<tr>
<td><strong>Levodopa</strong></td>
<td>IUPAC Name: L-Tyrosine-3-hydroxy Molecular Formula: C9H11NO4 Molecular Weight: 197.19 g/mol Mechanism: Levodopa circulates in the plasma to the blood-brain-barrier, where it crosses, to be converted by striatal enzymes to dopamine. Carbidiopa inhibits the peripheral plasma breakdown of levodopa by inhibiting its carboxylation, and thereby increases available levodopa at the blood-brain-barrier. Effect: Antiparkinsonian Agents. Dopamine Precursors.</td>
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</tbody>
</table>

#### Dopaminergic Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amantadine</strong></td>
<td>Name: Amantadine; 768-94-5; Amantadine; Symmetrel; PK-Merz; Amantadina.</td>
<td>Pathogenic genes: PARK2&lt;br&gt;Mechanistic genes: CCR5, CXCR4, DRD1, DRD2, GRIN3A&lt;br&gt;Metabolic genes Substrate: COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DBH, DDC, G6PD, MAOB, TH, UGT1A1, UGT1A9&lt;br&gt;Transporter genes: SLC22A1</td>
</tr>
<tr>
<td><strong>Amantadine</strong></td>
<td>IUPAC Name: Tricyclo[3.3.1.13,7]decan-1-amine, hydrochloride Molecular Formula: C10H17NHC1 Molecular Weight: 187.71 g/mol Mechanism: Antiparkinsonian activity may be due to inhibition of dopamine reuptake into presynaptic neurons or by increasing dopamine release from presynaptic fibers. Effect: Antiparkinsonian Agents; Adamantanes; Dopamine Agonists.</td>
<td></td>
</tr>
</tbody>
</table>
**Name:** Apomorphine; 58-00-4; Apomorhin; Apo-go; Apofin; Apokinon; Apokyn; Apomorfina.
**IUPAC Name:** 4H-Dibenzo[de, g]quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl-hydrochloride, hemihydrate.
**Molecular Weight:** 312.79 g/mol
**Mechanism:** Stimulates postsynaptic D₂-type receptors within the caudate putamen in the brain.
**Effect:** Antiparkinsonian Agents; Nonergot-derivative Dopamine Receptor Agonists.

**Name:** Bromocriptine; 25614-03-3; Parlodel; Pravidel; Cycloset; Corpadel; Bromol; Bromocriptina.
**IUPAC Name:** Ergotaman-3′-6′-18-trione, 2-bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-, monomethanesulfonate, (5′α).
**Molecular Weight:** 750.70 g/mol
**Mechanism:** Semisynthetic ergot alkaloid derivative and dopamine receptor (D2) agonist which activates postsynaptic dopamine receptors in the tuberoinfundibular (inhibiting pituitary prolactin secretion) and nigrostriatal pathways (enhancing coordinated motor control). Causes transient increases in growth hormone secretion in individuals with normal growth hormone concentrations. Paradoxically causes sustained suppression of growth hormone secretion in acromegaly. Dysregulation of brain serotonin activity may also occur.
**Effect:** Antiparkinsonian Agents; Ergot-derivative Dopamine Receptor Agonists.

**Name:** Cabergoline; 81409-90-7; Cabergoline; Dostinex; Cabaser; Cabergolinum; Cabaseril; Cabergolina.
**IUPAC Name:** Ergoline-8β-carboxamide, N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonil]-6-(2-propenyl)
**Molecular Weight:** 451.60 g/mol
**Mechanism:** A long-acting dopamine receptor agonist. Has high binding affinity for dopamine D₂-receptors and lesser affinity for D₁,α₂- and α₁-adrenergic, and serotonin (5-HT₁ and 5-HT₂) receptors. Reduces serum prolactin concentrations by inhibiting release of prolactin from the anterior pituitary gland (agonist activity at D₂ receptors).
**Effect:** Antiparkinsonian Agents; Ergot-derivative Dopamine Receptor Agonists.

**Name:** Lisuride; 18016-80-3; Dopergin; Arolac; Dopergine; Dipergon; Lysenyl; Lisurida.
**IUPAC Name:** 3-[(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea
**Molecular Weight:** 338.45 g/mol
**Mechanism:** Displays dopaminergic, and consequently prolacting-reducing properties. Active substance lisuride has pronounced affinity for dopamine receptors in striatum and pituitary.
**Effect:** Antiparkinsonian Agents; Ergot-derivative Dopamine Receptor Agonists. Antimigraine Agents. Miscellaneous.

**Pathogenic genes:** PARK2
**Mechanistic genes:** ADRA2A, ADRA2B, ADRA2C, CALY, DRD1, DRD2, DRD3, DRD4, DRD5, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C
**Metabolic genes**
- **Substrate:** COMT, CYP1A2 (minor), CYP2B6, CYP2C9 (minor), CYP2C19 (minor), CYP2D6, CYP3A4 (minor), CYP3A5, DDC, UGT1A1, UGT1A9
- **Inhibitor:** CYP1A2 (weak), CYP2C19 (weak), CYP3A4 (weak)

**Transporter genes:** SLC22A1, SLC6A3
**Pleiotropic genes:** ACE, AP0E

**Pathogenic genes:** BDNF, GSK3B
**Mechanistic genes:** ADRA2A, ADRA2B, ADRA2C, AKT1, BDNF, CNR1, DRD1, DRD2, DRD3, DRD4, DRD5, GSK3B, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C, HTR7
**Metabolic genes**
- **Substrate:** COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4 (major), CYP3A5, DDC, MAOB, UGT1A1, UGT1A9
- **Inhibitor:** CYP1A2 (weak), CYP3A4 (moderate)
**Ropinirole**

Name: Ropinirole; ReQuip; Ropinirol; Ropinilorum; ReQuip CR

IUPAC Name: 2-H-indol-2-one 4-[[2-(dipropylamino)ethyl]-1,3-dihydro-, monohydrochloride

Molecular Formula: C_{20}H_{29}N_2O

Molecular Weight: 296.84 g/mol

Mechanism: Has high relative in vitro specificity and full intrinsic activity at D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 and D_4 receptor subtypes. Although precise mechanism of action is unknown, it is believed to be due to stimulation of postsynaptic dopamine D_2-type receptors within caudate putamen. Mechanism of Ropinirole-induced postural hypotension is believed to be due to D_2-mediated blunting of noradrenergic response to standing and subsequent decrease in peripheral vascular resistance.

Effect: Antiparkinsonian Agents; Nonergot-derivative Dopamine Receptor Agonists.

**Mechanistic genes:** ADRA1A, ADRA1B, ADRA1D, ADRA2A, ADRA2B, ADRA2C, DRD1, DRD2, DRD3, DRD4, DRD5, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C

**Metabolic genes:**

- **Substrate:** COMT, CYP1A2 (major), CYP2B6, CYP2C19, CYP3A4 (minor), CYP3A5, DDC, UGT1A1, UGT1A9
- **Inhibitor:** CYP1A2 (moderate), CYP2B6 (moderate), CYP3A4 (moderate)

**Transporter genes:** SLC22A1, SLC6A3

**Pleiotropic genes:** ACE, APOE

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**Pramipexole**

Name: Pramipexole; 104632-26-0; Pramipexole; Pramipexol; Parmital; Mirapex; Mirapexin; Sifrol

IUPAC Name: 2,6-Benzothiazole-4,5,6,7-tetrahydro-N^2-propyl-,(S)

Molecular Formula: C_{18}H_{21}N_2S

Molecular Weight: 211.33 g/mol

Mechanism: By binding to D_3 subfamily dopamine receptor, and to D_3 and D_4 receptors, it is though that Pramipexole can stimulate dopamine activity on nerves of striatum and substantia nigra.

Effect: Antiparkinsonian Agents; Nonergot-derivative Dopamine Receptor Agonists.

**Mechanistic genes:** ADRA1A, ADRA1B, ADRA2A, ADRA2B, DRD1, DRD2, DRD3, DRD4, DRD5, GNR2A, GNR2B, HCRT, HOMER1, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C, LMO3, OPRM1

**Metabolic genes:**

- **Substrate:** COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DDC, MAOB, UGT1A1, UGT1A9

**Transporter genes:** SLC22A1, SLC6A3

**Pleiotropic genes:** ACE, APOE

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**Rotigotine**

Name: Rotigotine; 99755-59-6; Rotigotine; Rotigotina; Neupro

IUPAC Name: 1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl][2-[(2-thienyl)ethyl]amino]-6S

Molecular Formula: C_{20}H_{29}NO

Molecular Weight: 315.47 g/mol

Mechanism: A non-ergot dopamine receptor agonist with specificity for D_3, D_2, and D_1-dopamine receptors. Although precise mechanism of action is unknown, it is believed to be due to stimulation of postsynaptic dopamine D_2-type auto receptors within substantia nigra, leading to improved dopaminergic transmission in motor areas in basal ganglia, notably caudate nucleus/putamen regions.

Effect: Antiparkinsonian Agents; Nonergot-derivative Dopamine Receptor Agonists.

**Mechanistic genes:** ADRA1A, ADRA1B, ADRA1D, ADRA2A, ADRA2B, ADRA2C, DRD1, DRD2, DRD3, DRD4, DRD5, GNR2A, GNR2B, HCRT, HOMER1, LMO3, OPRM1

**Metabolic genes:**

- **Substrate:** COMT, MAOB
- **Inhibitor:** CYP1A2 (moderate), CYP2B6 (moderate), CYP3A4 (moderate)

**Transporter genes:** SLC22A1, SLC6A3

**Pleiotropic genes:** ACE, APOE
## Monoamine-Oxidase B (MOB) Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenetics</th>
</tr>
</thead>
</table>
| Selegiline | Name: Selegiline; 14611-51-9; Selegiline; Selegilina; L-Deprenalin; Emsam; Jumex; Eldepryl; Carbex  
IUPAC Name: Benzeneethanamine,Nα-dimethyl-N-2-propynyl-,hydrochloride,(R)  
Molecular Formula: C₁₇H₁₉N₂HCl  
Molecular Weight: 223.74 g/mol  
Mechanism: Potent, irreversible inhibitor of the monoamine oxidase (MAO). Plasma concentrations achieved via administration of oral dosage forms in recommended doses confer selective inhibition of the MAO type B, which plays a major role in metabolism of dopamine. Selegiline may also increase dopaminergic activity by interfering with dopamine reuptake at synapse.  
Mechanistic genes: CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1  
Metabolic genes  
Substrate: COMT, CYP1A2, CYP1A2 (minor), CYP1B1, CYP2A6 (minor), CYP2B6 (major), CYP2C8 (minor), CYP2C19 (major), CYP2D6 (minor), CYP2E1 (minor), CYP3A4 (minor), CYP3A5, CYP19A1, DDC, MAOA, MAOB, UGT1A1, UGT1A9  
Inhibitor: CYP1A2 (weak), CYP2A6 (weak), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (weak), MAOB  
Transporter genes: SLC22A1, SLC6A3  
Pleiotropic genes: ACE, APOE |
| Rasagiline | Name: Rasagiline; 136236-51-6; Azilet; Elbrux; Rasagilina; Rasax.  
IUPAC Name: 1H-Inden-1-amine,2,3-dihydro-N-2-propynyl-,(R)-methanesulfonate  
Molecular Formula: C₁₇H₁₇N₂O₃S  
Molecular Weight: 267.34 g/mol  
Mechanism: Potent, irreversible inhibitor of the monoamine oxidase (MAO) type B, which plays a major role in catabolism of dopamine. Inhibition of dopamine depletion in striatal region of brain reduces symptomatic motor deficits of Parkinson’s Disease. There is also experimental evidence of Rasagiline conferring neuroprotective effects (antioxidant, antiapoptotic), which may delay onset of symptoms and progression of neuronal deterioration.  
Mechanistic genes: BL2C, CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1  
Metabolic genes  
Substrate: COMT, CYP1A2 (major), CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DDC, MAOB, UGT1A1, UGT1A9  
Inhibitor: MAOB  
Transporter genes: SLC22A1, SLC6A3  
Pleiotropic genes: ACE, APOE |

## Catechol-O-Methyltransferase (COMT) Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenetics</th>
</tr>
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</table>
| Entacapone | Name: Entacapone; 130929-57-6; Comtan; Comtess; Entacapona.  
IUPAC Name: E-α-Cyano-N,N-diethyl-3,4-dihydroxy-5-nitrocinnamamida  
Molecular Formula: C₁₇H₁₃N₃O₄S  
Molecular Weight: 305.29 g/mol  
Mechanism: A selective inhibitor of catechol-O-methyltransferase (COMT). When entacapone is taken with levodopa, its pharmacokinetics is altered, resulting in more sustained levodopa serum levels compared to levodopa taken alone.  
Effect: Antiparkinsonian Agents. Catechol-O-methyltransferase Inhibitors. | Pathogenic genes: ANKK1, BDNF, LRRK2, PARK2  
Mechanistic genes: CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1  
Metabolic genes  
Substrate: COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DDC, MAOB, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15  
Inhibitor: COMT, CYP1A2 (weak), CYP2A6 (weak), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (weak) |

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This table summarizes the properties and pharmacogenetics of various drugs used in the treatment of Parkinson’s Disease. The table includes the name and IUPAC name of each drug, its molecular formula and weight, the mechanism of action, and the effect on the disease. The pharmacogenetics section lists the pathogenic, mechanistic, and metabolic genes associated with each drug, along with their respective substrates and inhibitors.
**ABC1**: ATP binding cassette subfamily B member 1, **ACE**: angiotensin I converting enzyme, **ACHE**: acetylcholinesterase, **ADCY7**: adenylate cyclase 7, **ADRA1A**: adrenoeceptor alpha 1A, **ADRA1B**: adrenoeceptor alpha 1B, **ADRA2D**: adrenoeceptor alpha 2D, **ADRA2C**: adrenoeceptor alpha 2C, **AKT1**: v-akt murine thymoma viral oncogene homolog 1, **ANKK1**: ankyrin repeat and kinase domain containing 1, **APOE**: apolipoprotein E, **BDNF**: brain-derived neurotrophic factor, **BLC2**: B-cell CLL/lymphoma 2, **CALY**: calycyn neuron specific vesicular protein, **CCK**: cholecystokinin, **CCKAR**: cholecystokinin A receptor, **CCKBR**: cholecystokinin B receptor, **CCK5**: C-C motif chemokine receptor 5 (gene/pseudogene), **CHAT**: choline O-acetyltransferase, **CNS1**: cannabinoid receptor 1 (brain), **COMT**: catechol-O-methyltransferase, **CREB1**: cAMP responsive element binding protein 1, **CXCR4**: C-X-C motif chemokine receptor 4, **CYP1A1**: cytochrome P450 family 1 subfamily A member 1, **CYP1A2**: cytochrome P450 family 1 subfamily A member 2, **CYP1B1**: cytochrome P450 family 1 subfamily B member 1, **CYP2A6**: cytochrome P450 family 2 subfamily A member 6, **CYP2B6**: cytochrome P450 family 2 subfamily B member 6, **CYP2C19**: cytochrome P450 family 2 subfamily C member 19, **CYP2C9**: cytochrome P450 family 2 subfamily C member 9, **CYP2D6**: cytochrome P450 family 2 subfamily D member 6, **CYP2E1**: cytochrome P450 family 2 subfamily E member 1, **CYP3A4**: cytochrome P450 family 3 subfamily A member 4, **CYP3A5**: cytochrome P450 family 3 subfamily A member 5, **CYP19A1**: cytochrome P450 family 19 subfamily A member 1, **DBH**: dopamine beta-hydroxylase, **DCC**: doppa decarboxylase, **DRD1**: dopamine receptor D1, **DRD2**: dopamine receptor D2, **DRD3**: dopamine receptor D3, **DRD4**: dopamine receptor D4, **DRD5**: dopamine receptor D5, **G6PD**: glucose-6-phosphate dehydrogenase, **GPT**: glutamic-pyruvate transaminase (alanine aminotransferase), **GRIN2A**: glutamate ionotropic receptor NMDA type subunit 2A, **GRIN2B**: glutamate ionotropic receptor NMDA type subunit 2B, **GRIN3A**: glutamate ionotropic receptor NMDA type subunit 3A, **GSK3β**: glycogen synthase kinase 3 beta, **HCRTR**: hypocretin (orexin) neuropeptide precursor, **HOMER1**: homer scaffolding protein 1, **HRH1**: histamine receptor H1, **HRH1A**: 5-hydroxytryptamine receptor 1A, **HTR1B**: 5-hydroxytryptamine receptor 1B, **HTR1D**: 5-hydroxytryptamine receptor 1D, **HTR2A**: 5-hydroxytryptamine receptor 2A, **HTR2B**: 5-hydroxytryptamine receptor 2B, **HTR2C**: 5-hydroxytryptamine receptor 2C, **HTR7**: 5-hydroxytryptamine receptor 7, **LIMD**: LIM domain only 3, **LRK2**: leucine-rich repeat kinase 2, **MAOA**: monoamine oxidase A, **MAOB**: monoamine oxidase B, **OPRM1**: opioid receptor mu 1, **PAH**: phenylalanine hydroxylase, **PDZK1**: parkin RBR E3 ubiquitin protein ligase, **SLC2A1**: solute carrier family 2 member 1, **SLC6A3**: solute carrier family 6 member 3, **SLC6A4**: solute carrier family 6 member 4, **SST**: somatostatin, **TH**: tyrosine hydroxylase, **TSPAN**: translocase protein, **UGT1A1**: UDP glucuronosyltransferase family 1 member A1, **UGT1A6**: UDP glucuronosyltransferase family 1 member A6, **UGT1A9**: UDP glucuronosyltransferase family 1 member A9, **UGT2B7**: UDP glucuronosyltransferase family 2 member B7, **UGT2B15**: UDP glucuronosyltransferase family 2 member B15.

(Adapted from Cacabelos et al [185]).