Pharmacogenomics of Cognitive Dysfunction and Neuropsychiatric Disorders in Dementia

Ramon Cacabelos

EuroEspes Biomedical Research Center, International Center of Neuroscience and Genomic Medicine, 15165 Bergondo, Corunna, Spain; rcacabelos@euroespes.com

Received: 12 March 2020; Accepted: 21 April 2020; Published: 26 April 2020

Abstract: Symptomatic interventions for patients with dementia involve anti-dementia drugs to improve cognition, psychotropic drugs for the treatment of behavioral disorders (BDs), and different categories of drugs for concomitant disorders. Demented patients may take >6–10 drugs/day with the consequent risk for drug–drug interactions and adverse drug reactions (ADRs >80%) which accelerate cognitive decline. The pharmacoepigenetic machinery is integrated by pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes redundantly and promiscuously regulated by epigenetic mechanisms. CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 geno-phenotypes are involved in the metabolism of over 90% of drugs currently used in patients with dementia, and only 20% of the population is an extensive metabolizer for this tetragenic cluster. ADRs associated with anti-dementia drugs, antipsychotics, antidepressants, anxiolytics, hypnotics, sedatives, and antiepileptic drugs can be minimized by means of pharmacogenetic screening prior to treatment. These drugs are substrates, inhibitors, or inducers of 58, 37, and 42 enzyme/protein gene products, respectively, and are transported by 40 different protein transporters. APOE is the reference gene in most pharmacogenetic studies. APOE-3 carriers are the best responders and APOE-4 carriers are the worst responders; likewise, CYP2D6-normal metabolizers are the best responders and CYP2D6-poor metabolizers are the worst responders. The incorporation of pharmacogenomic strategies for a personalized treatment in dementia is an effective option to optimize limited therapeutic resources and to reduce unwanted side-effects.

Keywords: alzheimer’s disease; anxiety; behavioral disorders; depression; epilepsy; neuropsychiatric disorders; personalized medicine; pharmacogenomics; psychosis; sleep disorders

1. Introduction

Alzheimer’s disease (AD) is the most prevalent form of dementia (>50%), followed by vascular (VD), mixed dementia (MXD) (30–40%), and other modalities of neurodegenerative disorders (NDDs) (Lewy body dementia (LBD), frontotemporal dementia (FTD), prion dementia, Pick’s dementia, Parkinson–dementia complex (PDC); and comorbid FTD-amyotrophic lateral sclerosis) (5–10%). MXD shows the highest prevalence (>50%) in patients over 70–75 years of age. Genomic defects (Table 1), epigenetic aberrations, cerebrovascular dysfunction, and multiple environmental factors are the major risk factors that precipitate pathogenic cascades leading to the clinical phenotype of dementia which is characterized by progressive cognitive deterioration, behavioral changes, functional decline, and classical neuropathological hallmarks (extracellular Aβ deposition in senile plaques, intracellular neurofibrillary tangles with hyperphosphorylated tau, dendritic desarborization, and neuronal loss) [1–6]. The main focus of pharmacological research over the past 50 years has been the identification of cognitive enhancers; however, no US Food and Drug Administration (FDA)-approved drugs for AD have been reported for the past two decades [7]. Behavioral disorders (BDs) (psychotic, depressive, anxiety, sleep disorders, and inappropriate sexual behaviors) are common (10–90%) in...
patients with dementia and tend to increase in parallel with the cognitive deterioration [8–14]. BDs increase the risk of institutionalization, impair daily functioning, reduce quality of life, and accelerate cognitive deterioration [15,16]. BDs also increase the costs of dementia (e.g., LBD and VD) [17].

Table 1. Prevalent Alzheimer’s disease-related pathogenic genes.

| Gene Symbol | Gene Name | Gene ID | OMIM # | Locus | dbSNP ID | Risk Allele | MAF |
|-------------|-----------|---------|--------|-------|----------|-------------|-----|
| ABCA7       | ATP binding cassette subfamily A member | 10347   | 605414 | 19p13.3 | rs3764650 | G          | 0.20 (G) |
| APOE        | Apolipoprotein E | 348     | 107741 | 19q13.32 | rs429358; rs7412 | *4 | 0.15 (C); 0.08 (T) |
| APP         | Amyloid beta precursor protein | 351     | 104760 | 21q21.3 | 52 SNPs | <0.01 |
| BIN1        | Bridging integrator 1 | 274     | 601248 | 2p14.3 | rs744373 | C          | 0.36 (C) |
| BUB3        | Chromosome 9 open reading frame 72 | 9184    | 603719 | 10q26.13 | rs4908270 | T          | 0.10 (T) |
| C9orf72     | CD2 associated protein | 203228  | 614260 | 9p21.2 | rs3849942 | T          | 0.22 (T) |
| CD2AP       | CD23 molecule Cluster | 23607   | 604241 | 6p12.3 | rs9349407 | C          | 0.25 (C) |
| CD33        | CD93 molecule Cluster | 945     | 159590 | 19q13.41 | rs3865444 | T          | 0.01 (T) |
| CLU         | Complement C3b/C4b receptor 1 | 1191    | 185430 | 8p11.1 | rs1136000 | T          | 0.38 (T) |
| CPZ         | Complement C3b/C4b receptor 1 | 8532    | 603105 | 4p16.1 | rs7436874 | C          | 0.36 (C) |
| CR1         | Disrupted in schizophrenia 1 Ectonucleotide pyrophosphatase/phosphodiesterase 1 | 185430  | 120620 | 1q21.2 | rs3818361 | T          | 0.25 (T) |
| DISC1       | Lipoma HMGIC fusion partner | 27185   | 605210 | 1q42.2 | rs1685202 | G          | 0.03 (G) |
| ENPP1       | Ectonucleotide pyrophosphatase/phosphodiesterase 1 | 5167    | 173335 | 6q23.2 | rs7767170 | T          | 0.02 (T) |
| EXO1        | Exonuclease 1 Laminin subunit alpha 3 | 9156    | 606063 | 1p22.3 | rs1776148 | A          | 0.27 (A) |
| LAMA3       | Lipoma HMGIC fusion partner | 64231   | 605654 | 11q12.2 | rs11082762 | A          | 0.47 (A) |
| LHFP        | Membrane spanning 4-domains A4E | 10186   | 606710 | 13q13.3-q14.11 | rs7995844 | G          | 0.35 (G) |
| MAPT        | Membrane spanning 4-domains A6A | 4137    | 157140 | 1q21.3 | 15 SNPs | <0.01 |
| MS4A4E      | Membrane spanning 4-domains A4E | 643680  | 608401 | 8p21.1 | rs670139 | A          | 0.38 (A) |
| MS4A6A      | Membrane spanning 4-domains A6A | 64231   | 606548 | 11q12.2 | rs61932 | A          | 0.45 (A) |
| NLRP4       | NLR family pyrin domain containing 4 | 147945  | 609645 | 19q13.43 | rs12462372 | A          | 0.08 (A) |
| NTNG1       | Netrin G1 Phosphatidylinositol binding clathrin assembly protein Piwi like | 3909    | 608085 | 18q11.2 | rs1180905 | T          | 0.32 (T) |
| PICALM      | TBC1 domain family member 5 | 8301    | 603025 | 11q14.2 | rs3851179 | A          | 0.31 (A) |
| PIWIL2      | RNA-mediated gene silencing 2 Presenilin 1 | 55124   | 610312 | 8p21.3 | rs426653 | G          | 0.47 (G) |
| PSEN1       | RNA-mediated gene silencing 2 Presenilin 2 | 5663    | 104311 | 14q24.2 | 241 SNPs | <0.01 |
| PSEN2       | Serine/threonine kinase 3 | 5664    | 600759 | 14q24.2 | 43 SNPs | <0.01 |
| STK36       | Syntaxin 17 | 27148   | 607652 | 2q35 | rs2303565 | C          | 0.33 (C) |
| STX17       | Serotonin transporter 1 | 55014   | 604204 | 9q31.1 | rs1997368 | G          | 0.32 (G) |
| SUN1        | Serotonin transporter 1 | 256979  | 607723 | 7p12.3 | rs2708909 | G          | 0.39 (G) |
| TBC1D5      | USP6 N-terminal like Zinc finger | 9279    | 615740 | 3p24.3 | rs10510480 | C          | 0.11 (C) |
| USP6NL      | USP6 N-terminal like Zinc finger | 9712    | 605405 | 10p14 | rs3847437 | T          | 0.04 (T) |
| ZSWIM7      | SWIM-type containing 7 | 125150  | 614535 | 17p12 | rs10491104 | T          | 0.41 (T) |
There is not a prototypical pattern of BDs in different dementia types; however, BDs tend to be more prevalent in FTD, in cases where the compromise of frontotemporal regions is more relevant [18–20], and in cases with mild traumatic brain injury (TBI) [21] where DNA damage-induced cellular senescence pathways have been identified [22]. Apathy, depression, dysphoria, agitation, aggression, hallucinations, and delusions are frequent distressing symptoms in dementia [14]. A current behavioral phenotype is the hyperactivity–impulsivity–irritability–disinhibition–aggression–agitation complex, with a difficult set of symptoms to manage, causing an important psychological burden for caregivers and hospital staff [23]. Some neuropsychiatric disorders may increase the risk for late-onset dementia, and dementia may increase the risk for delayed-onset BDs in specific cases [24].

The primary causes of BDs in dementia are unclear. APP, MAPT, APOE, and other variants in pathogenic genes (Table 1) as well as the presence of schizophrenia- and/or depression-related SNPs [25–27], together with additional metabolic disorders [28], cerebrovascular risk or consolidated vascular damage [4,29–31], premorbid personality [32], and inappropriate management may contribute to BDs in AD. BDs partially correlate with conventional biomarkers of dementia [33,34]; however, agitation/aggression correlates with AD cerebrospinal fluid (CSF) biomarkers, and depression is inversely associated with core AD CSF pathology (low A\(\beta\)42, high Tau, and high pTau) [35,36]. Over 50% of AD patients show comorbidities (TDP-43 and Lewy bodies) which associate with frontotemporal lobar degeneration and LBD. Some of these comorbidities might explain BDs in dementia. TDP-43 is associated with aberrant psychomotor activity, and Lewy bodies are associated with anxiety, irritability, sleep disorders, and appetite anomalies [37]. In FTD, C9orf72 hexanucleotide repeat expansion with more than 80 G4C2 repeats has been associated with high frequency of psychotic symptoms [38]. Limbic-predominant age-related TDP-43 encephalopathy with high pTau burden might also predispose to more severe cognitive deterioration and BDs [39].

Most BDs in dementia are susceptible to pharmacological intervention, and though some studies suggest that psychotropic medication does not accelerate cognitive decline [40], most studies indicate that inappropriate treatments and consequent adverse drug reactions (ADRs) are frequent and deleterious [41–43]. Current ADRs in the elderly population are associated with benzodiazepines, neuroleptics, antidepressants, and antihypertensives. These drugs may cause falls; delirium and excess mortality increase with polypharmacy; over-infections are frequent in patients with inappropriate use of broad-spectrum antibiotics; increased risk of stroke is observed in patients with dementia treated with antipsychotics; nonsteroidal anti-inflammatory drugs may cause hypertensive crises, bleeding, and cerebrovascular problems; and other ADRs have been extensively reported worldwide [43–46].

To palliate preventable ADRs, drug information resources have been developed. Some of them are designed for analyzing drug interactions, and others are useful to help physicians for an appropriate drug prescription [47–51]. However, few resources incorporate pharmacogenomics (PGx) as a practical tool for clinical use [45,52–56].

About 80% variability in drug pharmacokinetics and pharmacodynamics is attributed to PGx factors [56,57]. Rare variants contribute to approximately 30–40% of functional variability in 146 pharmagenes with clinical relevance. Over 240 pharmagenes are potentially associated with ADRs, and over 400 genes and their products influence drug efficacy and safety [53,54]. Furthermore, the pharmacological outcome is highly influenced by components of the PGx machinery, the chemical properties of each drug, and other diverse factors (e.g., compliance, nutrition, metabolic conditions, and concomitant drugs) [58,59].

The present review explores available information for personalized treatment of dementia in the areas of cognition and BDs based on PGx principles.

### 2. The Pharmacogenomic Machinery

The pharmacogenomic machinery is composed by a network of gene clusters coding for proteins and enzymes responsible for drug targeting and processing as well as critical components of the epigenetic machinery that regulate gene expression [60,61]. The pharmagenes involved in the
pharmacogenomic response to drugs can be classified into five major categories: (i) Pathogenic genes (Table 1) which are associated with disease pathogenesis [62]; (ii) mechanistic genes coding for components of enzymes, receptor subunits, transmitters, and messengers associated with the mechanism of action of drugs; (iii) metabolic genes of different categories that encode phase I–II reaction enzymes responsible for drug metabolism. Phase-I reaction enzymes include (in alphabetical order) alcohol dehydrogenases, aldehyde dehydrogenases, aldo-keto reductases, amine oxidases, carbonyl reductases, cytidine deaminases, cytochrome P450 family (CYPs) of mono-oxygenases, cytochrome b5 reductase, dihydroxyprmidine dehydrogenase, esterases, epoxidases, flavin-containing monoxygenases, glutathione reductase/peroxidases, peptidases, prostaglandin endoperoxide synthases, short-chain dehydrogenases, reductases, superoxide dismutases, and xanthine dehydrogenase. The most relevant Phase-II reaction enzymes include the following: amino acid transferases, dehydrogenases, esterases, glucuronosyl transferases, glutathione transferases, methyl transferases, N-acetyl transferases, thioltransferase, and sulfotransferases; (iv) transporter genes coding for drug transporters. The most relevant categories of transporters include the following: ATPase (P-type subfamily), V-type (vacuolar H+-ATPase subunit), and ATPase (F-type subfamily); ATP-binding cassette transporters (subfamily A) (ABC1), subfamily B (MDR/TAP), subfamily C (CFTR/MRP), subfamily D (ALD), subfamily E (OABP), subfamily F (GCN20), and subfamily G (WHITE); and solute carriers (high-affinity glutamate and neutral amino acid transporter family) (SLC); and (v) pleiotropic genes which encode proteins and enzymes involved in a great variety of metabolic cascades and metabolomic networks [6,43,56,61–63].

The expression or repression of all these genes and their products are regulated in a redundant and promiscuous fashion by the epigenetic machinery (DNA methylation/demethylation, histone/chromatin remodeling, and miRNA regulation), configuring the pharmacoepigenetic apparatus. The same enzyme/protein/transporter can process a multitude of drugs, and the same drug can be processed by a vast array of gene products in an orchestrated manner to operate as a security system against xenobiotic intruders [61–67].

A vast array of polymorphic variants in over 600 defective human genes are potentially involved in AD pathogenesis and drug response. The presence of the ε4 allele in the APOE gene is the most important risk factor among top pathogenic genes (Table 1) [1]. However, many other SNPs in diverse genes may contribute to AD-related neurodegeneration and premature neuronal death, including genes encoding components of the pharmacogenetic machinery. Polymorphic variants in ABC and SLC transporters may affect AD pathogenesis and response to drugs [3,63,68–73]. SNPs in genes encoding transporter proteins may affect brain penetrance and accessibility to neuronal/glial targets, drug metabolism, and drug resistance [70,74,75].

Mutations in ABC transporters affect pathogenesis and therapeutics in AD. The ABCB1 transporter protein (P-gp1) and other transporters of this category are located on endothelial cells lining brain vasculature. They play important roles in limiting the movement of substances into and enhancing their efflux from the brain. ABCB1 is a very active drug transporter in the brain. It is estimated that over 1270 drugs are directly or indirectly processed via the ABCB1 transporter protein P-gp. Approximately, 490 drugs are substrates, 618 are inhibitors, and 182 are inducers [55]. In Caucasians and African-Americans, 116 and 127 polymorphic sites, respectively, have been identified with a minor allele frequency greater than 5%. ABCB1 C1236T in exon 12, G2677T/A in exon 21, and C3435T in exon 26 are common variants. The ABCB1*13 haplotype involves 3 intronic SNPs (in intron 9, 13, and 14) and the 1236, 2677, and 3435 (TTT) SNPs. The ABCB1 C1236T, G2677T/A, and C3435T variants participate in the P-gp1 function at the blood–brain barrier (BBB). AD patients carrying T in C1236T, G2677T, and C3435T have exhibited higher binding potential values than T noncarriers. ABCB1 variants might be potential biomarkers and might contribute to the progression of Aβ deposition in AD brains [76,77]. ABCB1 transports Aβ from the brain into the blood stream, and the cholesterol transporter ABCA1 neutralizes Aβ aggregation in an APOE-dependent manner, facilitating Aβ elimination from the brain [78]. Other ABCs have shown potential association with AD [79]. The ABCA7 (G allele) rs115550680 SNP has been
associated with AD in Europeans, with a comparable effect to that of the APOE-ε4 SNP rs429358 [80]. The ABCA7 SNP rs200538373, with altered ABCA7 exon 41 splicing, also shows association with AD risk [81]. ABCA7 methylation might be a biomarker of AD [82]. In AD, ABCA7 mRNA expression is higher than in controls, correlating with disease progression and cognitive decline. Alterations in lipid metabolism associated with APOE-ε4 and several SNPs in ABCA7 (rs3764650, rs3752246, and rs4147929) and loss-of-function mutations are pathogenic and PGx-dysfunctional in AD [83–85]. An intronic variable number tandem repeat (VNTR) in the ABCA7 locus shows strong association with AD [86]. ABCA7 variants cause accumulation of amyloid peptides and BBB dysfunction. ABCA7 defects decrease APOE secretion and cholesterol exchange across the BBB [87]. Cholesterol-related genes such as ABCG2 mRNA expression has been observed in AD. Methylation of specific CpG islands in the ABCA2 (rs2230805 and rs2230806) and ABCA1 (rs2282649), which affect lipid metabolism and membrane trafficking, may also be pathogenic and PGx-disruptive [63,88]. Soluble low-density lipoprotein receptor-related protein-1 (sLRP1), soluble receptor of advanced glycation end products (sRAGE), and transport proteins participate in the clearance of plasma Aβ in an APOE-dependent manner [89].

The ATP-binding cassette transporter ABCA2 is an endolysosomal membrane protein with pleiotropic activities and a critical role in mediating sphingolipids and cholesterol trafficking [90]. ABCA1 (rs2230805 and rs2230806) and ABCA2 variants are associated with AD [91,92]. Upregulation of ABCA2 mRNA expression has been observed in AD. Methylation of specific CpG islands in the ABCA2 gene negatively associates with AD risk. ABCA2 mRNA expression might also be used to differentially diagnose mild cognitive impairment (MCI) from other forms of dementia (i.e., Huntington’s disease) but not AD from MCI [93].

ABCG2 is a transporter of large, hydrophobic, charged molecules and different toxic compounds. Dysfunctional ABCG2 variants may affect absorption, distribution, accumulation, effectiveness, and toxicity of xenobiotic compounds and drugs [94]. ABCG2 is upregulated in AD brains and is involved in Aβ transport. The ABCG2-C421A variant (rs2231142) (ABCG2 C/C genotype) is associated with AD. Interaction of the ABCG2 C/C genotype with the APOE ε4 allele may increase AD risk [95].

Aβ alters BBB ABC efflux transporters and BBB permeability; specifically, ABCB1, ABCC5, and ABCG2; pregnane X receptor (PXR); and constitutive androstane receptor (CAR) transcription factors are inhibited by Aβ in brain endothelial cells [96].

Transporters encoded by genes of the solute carrier superfamily (SLC) and solute carrier organic (SLCO) transporter family are also important for AD pharmacogenomics. The human solute carrier (SLC) superfamily of transporters includes several hundred membrane-bound proteins with roles in physiological, pathological, and PGx processes. Over 200,000 exonic single-nucleotide variants (SNVs) have been identified, 99.8% of which are present in <1% of analyzed alleles. In the individual genome, there are about 29.7 variants with putative functional effects, and in specific populations, interethnic variability shows over 80% deleterious SLC variants [97].

In addition to APP, PSEN1, and PSEN2 mutations, SNPs in membrane proteins that alter the transmembrane trafficking of products also influence pathogenesis and PGx. One example of this may be SORL1. SORL1 (LR11) gene variants are associated with AD. SORL1 encodes a type 1 transmembrane 250-kDa protein (sorLA) that belongs to both the low-density lipoprotein receptor (LDLR) family and the vacuolar protein sorting 10 (VPS10) domain receptor family, acting as a sorting receptor for APP. SorLA, which interacts with ApoE and Tau, is a central regulator of trafficking and processing of APP and of Aβ destruction [98]. Another example might be the sarco/endo粗plasmic reticulum (SR/ER) calcium (Ca\(^{2+}\))-ATPase (SERCA) pump, an integral endoplasmic reticulum protein which has been associated with neuropsychiatric disorders (NPDs) and NDDs [99]. Translocation of substances across the mitochondrial membranes is required for cellular survival and efficient functioning. Major components of this translocation machinery are the translocase of the outer (TOMM) and inner mitochondrial membrane (TIMM) complexes. Mutations in the TIMM8A (DDP) and DNAJC19 (TIMM14) genes are pathogenic for Mohr–Tranebjaerg syndrome and dilated
cardiomyopathy syndrome, and polymorphisms in the TOMM40 gene are associated with AD and other NDDs [100].

Transient receptor potential melastatin 2 (TRPM2) is a Ca$^{2+}$-permeable nonselective cation channel of the TRP ion channel family. TRPM2 dysfunction linked to aberrant intracellular Ca$^{2+}$ accumulation and neuronal death has been implicated in AD. TRPM2 is involved in the induction of N-methyl-D-aspartate (NMDA) receptor-dependent long-term depression, a form of synaptic plasticity at glutamate synapses [101].

Drug transporter expression is altered at the BBB and peripheral tissues in AD. Intestinal expression of multidrug resistance-associated protein 2 (Mrp2), monocarboxylate transporter 1 (Mct1), and UDP-glucuronosyltransferase (Ugt) and liver expression of Cyp51a1 and Cyp2c29 have been found altered in AD transgenic models [102].

3. CNS Drugs

According to data available in the World Guide for Drug Use and Pharmacogenomics [55] and the EuroPharmaGenics (EPG) database [56] concerning central nervous system (CNS) drugs (Figure 1), the best-known genes of the pharmacogenetic machinery involved in the processing of antiepileptic, antidepressant, anxiolytic, hypnotic, sedative, antiparkinsonian, and antipsychotic drugs are mechanistic and metabolic genes, and poorly investigated genes are those involved in pathogenic mechanisms, transporters, and pleiotropic genes (Figure 1). Globally, 74% pathogenic, 97% mechanistic, 94% metabolic, 68% transporter, and 40% pleiotropic genes have so far been associated with CNS drug efficacy and safety [103].

CNS drugs can act as substrates, inhibitors, or inducers of enzymes encoded by metabolic genes (Figure 2). Among the 307 most frequently used CNS drugs, antiepileptics represent 14.66%, antiparkinsonians represent 10.42%, antipsychotics represent 21.82%, anxiolytics represent 11.40%, hypnotics and sedatives represent 21.17%, antidepressants represent 20.53%, and anti-dementia drugs represent 1%–2% (Figure 1 and Table 2). About 90% of these drugs use CYP enzymes as major metabolic pathways. CNS drugs are substrates, inhibitors, or inducers of 58, 37, and 42 enzyme/protein gene products, respectively, and are transported by 40 different protein transporters (Figure 3). CNS drugs are major substrates of CYP3A4 (71%), CYP3A5 (37%), CYP2D6 (60%), CYP2C19 (45%), and CYP1A2 enzymes (44%); inhibitors of CYP3A4 (22%), CYP2D6 (23%), CYP2C19 (20%), CYP1A2 (17%), and CYP2C9 (15%); and inducers of CYP2C9 (9%), CYP2D6 (7%), CYP3A4 (5%), CYP1A2 (4.5%), CYP2A6 (4.5%), and CYP2B6 (3.7%). Major transporters of CNS drugs are ABCB1 (29%), SLCA1 (20%), SLC6A4 (20%), CLCNs (15%), SLC6A3 (12%), and SLC6A2 (11%) (Figure 3) [103].

Approximately 80% of patients are deficient metabolizers for the tetrategic cluster integrated by CYP2D6, 2C19, 2C9, and 3A4/4 variants which encode enzymes responsible for the metabolism of 60–80% of drugs of current use, showing ontogenic-, age-, sex-, circadian- and ethnic-related differences. CYP geno-phenotypes differentiate extensive (EM; normal, NM), intermediate (IM), poor (PM), or ultra-rapid metabolizers (UM) with great geographic and ethnic variability worldwide [4,43,63].

The integration of CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 variants into tetragenic haplotypes yields 156 geno-phenotypes. H3 (1/1-1/1-1/3-3) (20.87%) is the most frequent haplotype, representing full extensive metabolizers. Only 17 haplotypes exhibit a frequency higher than 1% in the Caucasian population. According to this, it is very likely that about 80% of individuals are deficient for the biotransformation of current drugs metabolized via CYP2D6-2C9-2C19-3A4 enzymes [4,43,63].
Figure 1. Pharmacogenetic machinery-related pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes of antiepileptics, antidepressants, anxiolytics, and antipsychotics.

Figure 2. Substrates of antiepileptics, antipsychotics, anxiolytics, and antidepressants.
Four acetylcholinesterase inhibitors have been approved for the treatment of AD. Tacrine was introduced in 1993 and discontinued years later due to hepatotoxicity; Donepezil was introduced in 1996; Galantamine was introduced in 2001; and Rivastigmine was introduced in 2002. Memantine, an NMDA partial antagonist, was approved by the FDA in 2003 [104,105]. Over the past decade, the most prevalent pharmacological categories currently investigated as candidate strategies for the treatment of AD included neurotransmitter enhancers (11.38%), anti-Amyloid agents (13.30%), multi-target drugs (2.45%), anti-Tau agents (2.03%), and diverse natural products (25.58%). Some novel drugs (8.13%), novel targets (5.66%), revised old drugs (11.77%), anti-inflammatory drugs (1.20%), neuroprotective peptides (1.25%), stem cell therapy (1.85%), nanocarriers/nanotherapeutics (1.52%), and others (combination treatments, cognitive enhancers/nootropics, neurotrophic factors, polyunsaturated fatty acids, hormone therapy, epigenetic drugs, RNAi gene silencing, miRNAs, and gene therapy) (<1% each) have also been investigated in exploratory studies for the treatment of AD [6]. However, no new drugs have been FDA-approved for the past 20 years. Consequently, most PGx studies concentrate on acetylcholinesterase inhibitors (AChEIs) (Donepezil, Galantamine, and Rivastigmine), Memantine, and combination treatments [2,3,106–108].

APOE gene variation is associated with major pathogenic events in AD [109,110], and APOE has been used as a reference gene in many clinical trials as a PGx marker, followed by metabolic genes (CYP geno-phenotypes) [1,2,4,56,106,107,111–118]. APOE-4 carriers exhibit differential phenotypic patterns of acetylcholinesterase and butyrylcholinesterase activities as well as CYP enzyme activities with strong influence in PGx outcomes [119]. SNP variation in CYP2D6, acetylcholinesterase, butyrylcholinesterase, choline acetyltransferase, and paraoxonase is associated with better clinical response to AChEIs [120].

4.1. Donepezil

Donepezil is the most prescribed AChEI for the treatment of AD worldwide [107,121]. Donepezil is a major substrate of CYP2D6, CYP3A4, ACHE, and UGTs; inhibits ACHE and BCHE; and is transported by ABCB1 [120,122] (Table 2). Several CYP2D6 variants may modify donepezil efficacy and safety in AD [55], and APOE and CYP2D6 variants are determinant in the effects of donepezil. APOE-4 carriers tend to be the worst responders, and APOE-3 carriers are the best responders to donepezil.

Figure 3. Substrates, inhibitors, inducers, and transporters of 307 CNS drugs (antidepressants, anxiolitics, hypnotics, sedatives, antipsychotics, antiepiletics, antiparkinsonian, and anti-dementia drugs).
in either monotherapy or drug combination regimes; CYP2D6-EMs are the best responders, and CYP2D6-PMs are the worst responders [1,2,4,56,106,111–118]. CYP2D6 geno-phenotypes influence donepezil clearance. CYP2D6-PMs show a 32% slower elimination, and CYP2D6-UMs show a 67% faster elimination [123]. AD carriers of the common variant rs1080985 of CYP2D6 show poor response to donepezil [122,124]. In Chinese patients, CYP2D6-EMs and PMs show a similar response to donepezil; however, EMs are better responders than UMs. Patients harboring the rs1080985 G allele are poor responders to donepezil, and the worst responders accumulate in carriers of the bigenic APOE-ε4/rs1080985-G genotype [125]. The mutated CYP2D6 allele *2A is more frequent in responder than in nonresponder patients (75.38% vs. 43.48%). In Italian patients, 67% of the cases were responders, in whom abnormal enzymes accumulate, and 33% were nonresponders [126]. In Chinese and Thai AD cases, carriers of the mutant CYP2D6*10 allele responded better (58% responders) than carriers of the wild-type CYP2D6*1 allele [127]. The CYP2D6*10 variant strongly affects steady-state plasma concentration of donepezil and therapeutic outcome in Asian populations [128]. A recent study in China showed that CYP2D6*10 carriers treated with donepezil/galantamine have less side effects and that CYP2D6*10 carriers respond better to ChEIs [129].

Lower plasma donepezil concentration-to-dose ratios and better clinical response to donepezil have been reported in patients homozygous for the TT/T genotype in the ABCB1 haplotypes 1236C/2677G/3435C (46%) and 1236T/2677T/3435T (41%) [130]. There is also a better response to donepezil in ABCA1 rs2230806 GG carriers than in AA or AG carriers [131].

APOE-ε4/BCHE-K* carriers show an earlier age of onset, an accelerated cognitive decline, and a differential response to donepezil therapy [132]. Donepezil is not recommended in BCHE-K and APOE-4 carriers [133].

Donepezil is also used for the treatment of BDs in AD, LBD, and other dementia types [14,107,134]. Some reports indicate that AChEIs may also be beneficial in vascular dementia and cardiovascular disorders [135]. Donepezil might also ameliorate oxaliplatin-induced peripheral neuropathy [136] and confer protection against induced seizures in a mouse model (Scn1a+/−) of Dravet syndrome, an encephalopathy caused by de novo loss-of-function mutations in the SCN1A gene [137].

Table 2. Pharmacogenetics of conventional anti-dementia drugs.

| Drug                  | Properties                                      | Pharmacogenetics                                      |
|-----------------------|-------------------------------------------------|-------------------------------------------------------|
| **Donepezil Hydrochloride** | Aricept, 120011-70-3, Donepezil HCl, BNAG, E-2020, E2020 | **Pathogenic genes:** APOE, CHAT  
**Mechanistic genes:** CHAT, CHAT, BCHE  
**Metabolic genes:** Substrate: CYP2D6 (major), CYP3A4 (major), UGTs, CHES  
**Inhibitor:** ACH, BCHE  
**Transporter genes:** ABCB1 |
| **IUPAC Name:**       | 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride | **Effect:** Nootropic agent, cholinesterase inhibitor, parasympathomimetic effect |
| **Molecular Formula:**| C22H22ClN |                                                                       |
| **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 |                                                                       |
| Drug                | Properties                                                                 | Pharmacogenetics                                                                 |
|---------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Galantamine hydrobromide** | **Name:** Galantamine hydrobromide | **Pathogenic genes:** APOE, APP  
**Mechanistic genes:** ACHE, BCHE, CHRNA4, CHRN2B  
**Metabolic genes:** Substrate: CYP2D6 (major), CYP3A4 (major), UGT1A1  
**Inhibitor:** ACHE, BCHE  |
| **Memantine Hydrochloride** | **Name:** Memantine Hydrochloride,  
41100-52-1, Namenda, Memantine HCL, Axura, 3,5-Dimethyl-1-adamantanamine hydrochloride,  
3,5-dimethyladamantan-1-amine hydrochloride | **Pathogenic genes:** APOE, MAPT, PSEN1  
**Mechanistic genes:** CHRFAM7A, DLGAP1, FOS, GRIN2A, GRIN2B, GRIN3A, HOMER1, HTR3A  
**Metabolic genes:** Inhibitor: CYP1A2 (weak), CYP2A6 (weak), CYP2B6 (strong), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP3A4 (weak), NR1H2  
**Transporter genes:** NR1H2  
**Pleiotropic genes:** APOE, MAPT, MT-TK, PSEN1  |
| **Rivastigmine tartrate** | **Name:** Rivastigmine tartrate,  
129101-54-8, SDZ-ENA 713, Rivastigmine hydrogentartrate, Rivastigmine Hydrogen Tartrate, ENA 713, ENA-713 | **Pathogenic genes:** APOE, APP  
**Mechanistic genes:** ACHE, BCHE, CHAT, CHRNA4, CHRN2B  
**Metabolic genes:** Inhibitor: ACHE, BCHE  
**Pleiotropic genes:** APOE, MAPT  |
| Drug                        | Name: Tacrine Hydrochloride, Tacrine HCl, 1684-40-8, Hydroxaminacrine, tacrine HCl, 9-AMINO-1,2,3,4-TETRAHYDROACRIDINE HYDROCHLORIDE, Tenakrin | Properties                                                                 | Pharmacogenetics                                                                 |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| IUPAC Name:                 | 1,2,3,4-tetrahydroacridin-9-amine hydrochloride                                                                                           |                                                                                 | Pathogenic genes: APOE, Mechanistic genes: ACHE, BCHE, CHRNA4, CHRNA2, Metabolic genes: Substrate: CYP1A2 (major), CYP2D6 (minor), CYP3A4 (major), Inhibitor: ACHE, BCHE, CYP1A2 (weak), Transporter genes: SCN1A, Pleiotropic genes: APOE, CES1, GSTM1, GSTT1, LEPR, MTHFR |
| Molecular Formula:          | C_{12}H_{15}ClN_{2}                                                                                                                         |                                                                                 |                                                                                 |
| Molecular Weight:           | 234.7246 g/mol                                                                                                                              |                                                                                 |                                                                                 |
| Category:                   | Cholinesterase inhibitor                                                                                                                   |                                                                                 |                                                                                 |
| Mechanism:                  | Elevates acetylcholine in cerebral cortex by slowing degradation of acetylcholine                                                          |                                                                                 |                                                                                 |
| Effect:                     | Nootropic agent, cholinesterase inhibitor, Parasympathomimetic effect                                                                      |                                                                                 |                                                                                 |

**Table 2. Cont.**

**Mechanism:** Binds preferentially to NMDA receptor-operated calcium channels; May act by blocking actions of glutamate at NMDA receptors; Elevates acetylcholine in cerebral cortex by slowing degradation of acetylcholine

**Effect:** Nootropic agent, cholinesterase inhibitor, Parasympathomimetic effect

**AADAC:** arylacetamide deacetylase; **AANAT:** aralkylamine N-acetyltransferase; **ABAT:** 4-aminobutyrate aminotransferase; **ABCB1:** ATP-binding cassette, sub-family B (MDR/TAP), member 1; **ABCB11:** ATP-binding cassette, sub-family B (MDR/TAP), member 1; **ABCCL:** ATP-binding cassette, sub-family C (CFTR/MRP), member 1; **ABCC2:** ATP-binding cassette, sub-family C (CFTR/MRP), member 2; **ABCC3:** ATP-binding cassette, sub-family C (CFTR/MRP), member 3; **ABCC4:** ATP-binding cassette, sub-family C (CFTR/MRP), member 4; **ABCC6:** ATP-binding cassette, sub-family C (CFTR/MRP), member 6; **ABCC8:** ATP-binding cassette, sub-family C (CFTR/MRP), member 8; **ABCG2:** ATP-binding cassette, sub-family G (WHITE), member 2 (Jouvin blood group); **ACACA:** acetyl-CoA carboxylase alpha; **ACADS:** acyl-CoA dehydrogenase short/branched chain; **ACHE:** acetylcholinesterase (Yt blood group); **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; **ACSM20:** acyl-CoA synthetase medium-chain family member 2B; **ACSM4:** acyl-CoA synthetase medium-chain family, member 3; **ACDY1:** adenylyl cyclase 1 (brain); **ADH1A:** alcohol dehydrogenase 1A (class I), alpha polypeptide; **ADH1B:** alcohol dehydrogenase 1B (class I), beta polypeptide; **ADH1C:** alcohol dehydrogenase 1C (class I), gamma polypeptide; **ADH4:** alcohol dehydrogenase 4 (class II), pi polypeptide; **ADH5:** alcohol dehydrogenase 5 (class III), chi polypeptide; **ADH6:** alcohol dehydrogenase 6 (class V); **ADH7:** alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; **ADH8:** alcohol dehydrogenases; **ADHFE1:** alcohol dehydrogenase, iron containing, 1; **ADIPOQ:** adiponectin, C1Q and collagen domain containing; **ADRA1A:** adrenoceptor alpha 1A; **ADRA1B:** adrenoreceptor alpha 1B; **ADRA1D:** adrenoceptor alpha 1D; **ADRA1S:** alpha 1-adrenergic receptor family; **ADRA2A:** adrenoreceptor alpha 2A; **ADRA2B:** adrenoreceptor alpha 2B; **ADRA2C:** adrenoreceptor alpha 2C; **ADRA2S:** alpha 2-adrenergic receptor family; **ADRA3:** alpha-beta-adrenergic receptor family; **ADRB1:** adrenoreceptor beta 1; **ADRB2:** adrenoreceptor beta 2; **ADRB3:** adrenoreceptor beta 3; **ADRB5:** beta-adrenergic receptor family; **ADRs:** adrenoceptors; **AGXT:** alanine-glyoxylate aminotransferase; **AHR:** aryl hydrocarbon receptor; **AKR1A1:** aldo-keto reductase family 1, member A1 (aldehyde reductase); **AKR1B1:** aldo-keto reductase family 1, member B1 (aldo reductase); **AKR1C1:** aldo-keto reductase family 1, member C1; **AKR1D1:** aldo-keto reductase family 1, member D1; **ALB:** albumin; **ALDH1A1:** aldehyde dehydrogenase 1 family, member A1; **ALDH1A2:** aldehyde dehydrogenase 1 family, 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; **ANKK1:** ankyrin repeat and kinase domain containing 1; **AOX1:** aldehyde oxidase 1; **APOA1:** apolipoprotein A-I; **APOA5:** apolipoprotein A-V; **APOC3:** apolipoprotein C-III; **APOD:** apolipoprotein D; **APOE:** apolipoprotein E; **APP:** amyloid beta (A4) precursor;
protein; AQP1: aquaporin-1; ASMT: arsanic (+3 oxidation state) methyltransferase; ASMT: acetylserotonin O-methyltransferase; BAAI: bile acid CoA: amino acid N-acyltransferase (glycine N-choloyltransferase); BCHE: butyrylcholinesterase; BCL2: B-cell CLL/lymphoma 2; BCL2L1: BCL2-like 1; BDNF: brain-derived neurotropic factor; BLK: BLK proto-oncogene, Src family tyrosine kinase; CA1: carbonic anhydrase 1; CA2: carbonic anhydrase 2; CA3: carbonic anhydrase 3; CA4: carbonic anhydrase 4; CA7: carbonic anhydrase 7; CA12: carbonic anhydrase 12; CA14: carbonic anhydrase 14; CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit; CACNs: calcium channel, voltage-dependent family; CALM1: calmodulin 1 (phosphorylation kinase, delta); CALMs: calmodulins; CALY: Calcyon neuron specific vesicular protein; CASR: calcium-sensing receptor; CAT: catalase; CB1R: carbonyl reductase 1; CB3R: carbonyl reductase 3; CB4R: carbonyl reductase 4; CBS: cystathionine-beta-synthase; CCB1L: cysteine conjugate-beta lyase, cytoplasmic; CCND1: cyclin D1; CD4: cytidine deaminase; CEL: carboxyl ester lipase; CELF4: CUGBP, Elav-like family member 4; CERKL: ceramide kinase-like; CES1: carboxylesterase 1; CES1P1: carboxylesterase 1 pseudogene 1; CES2: carboxylesterase 2; CES3: carboxylesterase 3; CES5A: carboxylesterase 5A; CFTR: cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7); CHRM1: cholinergic receptor, muscarinic 1; CHRM2: cholinergic receptor, muscarinic 2; CHRM3: cholinergic receptor, muscarinic 3; CHRM4: cholinergic receptor, muscarinic 4; CHRM5: cholinergic receptor, muscarinic 5; CHRM5s: cholinergic receptor family; CHRNA2: cholinergic receptor nicotinic alpha 2 subunit; CHRNA3: Cholinergic receptor nicotinic alpha 3 subunit; CHRNA4: cholinergic receptor, nicotinic, alpha 4 (neuronal); CHRNA7: cholinergic receptor, nicotinic, alpha 7 (neuronal); CHRNA8: nicotinic cholinergic receptors, alpha type; CHRN2B: cholinergic receptor, nicotinic, beta 2 (neuronal); CHRN4: cholinergic receptor nicotinic beta 4 subunit; CHRN5: nicotinic cholinergic receptor family; 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-acetylglucosaminie-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; CKS1B: CDC2 protein kinase regulatory subunit 1B; CLCNs: voltage-sensitive chloride channel family; CNR1: cannabinoid receptor 1 (brain); CNTF: ciliary neurotrophic factor; COMT: Catechol-O-methyltransferase; CREB1: cAMP responsive element binding protein 1; CRHR1: corticotropin releasing hormone receptor 1; CRHR2: corticotropin releasing hormone receptor 2; CXCR2: chemokine (C-X-C motif) receptor 2; CXCR5: cholecystokinin b5 receptor 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; CYP2F2: cytochrome P450, family 2, subfamily F, 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; CYP3A4/5: cytochrome P450, family 3, subfamily A, polypeptide 4/5; 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; CYP3A4: cytochrome P450, family 3, subfamily A; 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 E, 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 1; **CYP11B2**: 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 1; **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, polypeptide 1; **CYP27A1**: cytochrome P450, family 27, subfamily A, polypeptide 1; **CYP27B1**: cytochrome P450, family 27, subfamily B, polypeptide 1; **CYP39A1**: cytochrome P450, family 39, subfamily A, polypeptide 1; **CYP4A11**: cytochrome P450, family 46, subfamily A, polypeptide 1; **CYP51A1**: cytochrome P450, family 51, subfamily A, polypeptide 1; **DAO**: D-amino-acid oxidase; **DCC**: dopa decarboxylase (aromatic L-amino acid decarboxylase); **DDOST**: dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit (non-catalytic); **DHRS1**: dehydrogenase/reductase (SDR family) member 1; **DHRS2**: dehydrogenase/reductase (SDR family) member 2; **DHRS3**: dehydrogenase/reductase (SDR family) member 3; **DHRS4**: dehydrogenase/reductase (SDR family) member 4; **DHRS5**: dehydrogenase/reductase (SDR family) member 7; **DHRS9**: dehydrogenase/reductase (SDR family) member 9; **DHRS12**: dehydrogenase/reductase (SDR family) member 12; **DHRS13**: dehydrogenase/reductase (SDR family) X-linked; **DIO2**: deiodinase, iodothyronine, type II; **DLGAP1**: discs, large (Drosophila) homolog-associated protein 1; **DPEF1**: dipeptidase 1 (renal); **DPP4**: dipeptidyl-peptidase 4; **DPYD**: dihydropyrimidine dehydrogenase; **DRD1**: dopamine receptor D1; **DRD2**: dopamine receptor D2; **DRD3**: dopamine receptor D3; **DRD4**: dopamine receptor D4; **DRD5**: dopamine receptor D5; **DRDs**: dopamine receptors; **DTNB1**: dystrobrevin binding protein 1; **EPHX1**: Epoxide hydrolase 1, microsomal ( xenobiotic); **EPHX2**: epoxide hydrolase 2, microsomal ( xenobiotic); **ESD**: esterase D; **FABP1**: fatty acid binding protein 1, liver; **FGB**: fibrinogen beta chain; **FKBP5**: binding protein 5; **FMO1**: flavin containing monoxygenase 1; **FMO2**: flavin containing monoxygenase 2; **FMO3**: flavin containing monoxygenase 3; **FMO4**: flavin containing monoxygenase 4; **FMO5**: flavin containing monoxygenase 5; **FMO6P**: flavin containing monoxygenase 6 pseudogene; **FMOs**: flavin containing monoxygenases; **FOS**: FBJ murine osteosarcoma viral oncogene homolog; **GABBRs**: gamma-aminobutyric acid (GABA) A receptors, beta; **GABRA1**: gamma-aminobutyric acid (GABA) A receptor, alpha 1; **GABRA2**: gamma-aminobutyric acid (GABA) A receptor, alpha 2; **GABRA3**: gamma-aminobutyric acid (GABA) A receptor, alpha 3; **GABRA4**: gamma-aminobutyric acid (GABA) A receptor, alpha 4; **GABRA5**: gamma-aminobutyric acid (GABA) A receptor, alpha 5; **GABRA6**: gamma-aminobutyric acid (GABA) A receptor, alpha 6; **GABRAs**: gamma-aminobutyric acid (GABA) A receptors; **GABRB1**: gamma-aminobutyric acid type A receptor beta1 subunit; **GABRB2**: gamma-aminobutyric acid type A receptor beta2 subunit; **GABRB3**: gamma-aminobutyric acid (GABA) A receptor, beta 3; **GABRB4**: gamma-aminobutyric acid (GABA) A receptors, beta subtype; **GABRD**: gamma-aminobutyric acid (GABA) A receptor, delta; **GABRE**: gamma-aminobutyric acid (GABA) A receptor, epsilon; **GABRG1**: gamma-aminobutyric acid type A receptor gamma1 subunit; **GABRG2**: gamma-aminobutyric acid (GABA) A receptor, gamma 2; **GABRG3**: gamma-aminobutyric acid type A receptor pi subunit; **GABRGs**: gamma-aminobutyric acid (GABA) A receptors, gamma subtype; **GABRP**: gamma-aminobutyric acid (GABA) A receptor, pi; **GABRQ**: gamma-aminobutyric acid (GABA) A receptor, theta; **GABRS**: gamma-aminobutyric acid type A receptor rho1 subunit; **GABRR2**: gamma-aminobutyric acid type A receptor rho2 subunit; **GABRR3**: gamma-aminobutyric acid type A receptor rho3 subunit; **GABRs**: gamma-aminobutyric acid (GABA) receptors; **GAL3ST1**: galactose-3-O-sulfotransferase 1; **GAMT**: guanidinoacetate N-methyltransferase; **GFRA2**: GDNF family receptor alpha 2; **GHI**: growth hormone 1; **GLRs**: glycine receptors; **GLRX**: glutaredoxin (thioltransferase); **GLYAT**: glycinine-N-acyltransferase; **GNAS**: GNAS complex locus; **GNB3**: guanine nucleotide binding protein (G protein), beta polypeptide 3; **GNMT**: glycine N-methyltransferase; **GPX1**: glutathione peroxidase 1; **GPR35**: G protein-coupled receptor 35; **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; **GRI1A**: glutamate receptor, ionotropic, AMPA 1; **GRI2A**: glutamate receptor, ionotropic, AMPA 2; **GRI3A**: glutamate
Int. J. Mol. Sci. 2020, 21, 3059

receptor, ionotropic, AMPA 3; GRIA4: glutamate receptor, ionotropic, AMPA 4; GRIAs: ionotropic glutamate receptors; GRIK2: glutamate receptor, ionotropic, kainate 2; GRIK4: glutamate receptor, ionotropic, kainate 4; GRK5: G protein-coupled receptor kinase 5; GRIN1: glutamate ionotropic receptor NMDA type subunit 1; GRIN2A: glutamate receptor, ionotropic, N-methyl D-aspartate 2A; GRIN2B: glutamate receptor, ionotropic, N-methyl D-aspartate 2B; GRIN2C: glutamate receptor, ionotropic, N-methyl D-aspartate 2C; GRIN2D: glutamate ionotropic receptor NMDA type subunit 2D; GRIN3A: glutamate ionotropic receptor NMDA type subunit 3A; GRIN3B: glutamate receptor, ionotropic, N-methyl-D-aspartate 3B; GRM3: glutamate receptor, metabotropic 3; GSKB3: glycogen synthase kinase 3 beta; 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; GSTs: glutathione S-transferases; GSTT1: glutathione S-transferase theta 1; GSTT2: glutathione S-transferase theta 2; GSTZ1: glutathione S-transferase zeta 1; GZMA: granzyme A (granzyme 1, cytototoxic T-lymphocyte-associated serine esterase 3; GZMB: granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1); HRH1: histamine receptor H1; HRH2: histamine receptor H2; HRH4: histamine receptor H4; HRHs: histamine receptor family; HSD11B1: hydroxysteroid (11-beta) dehydrogenase 1; HSD17B10: hydroxysteroid (11-beta) dehydrogenase 10; HSD17B11: hydroxysteroid (17-beta) dehydrogenase 11; HSD17B14: hydroxysteroid (17-beta) dehydrogenase 14; HTR1A: 5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled; HTR1B: 5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled; HTR1D: 5-hydroxytryptamine (serotonin) receptor 1D, G protein-coupled; HTR1E: 5-hydroxytryptamine (serotonin) receptor 1E, G protein-coupled; HTR1F: 5-hydroxytryptamine (serotonin) receptor 1F, G protein-coupled; HTR1s: 5-hydroxytryptamine (serotonin) receptors, family 1; HTR2A: 5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled; HTR2B: 5-hydroxytryptamine (serotonin) receptor 2B, G protein-coupled; HTR2C: 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled; HTR2s: 5-hydroxytryptamine (serotonin) receptors, family 2; HTR3: histone H3; HTR3A: 5-hydroxytryptamine (serotonin) receptor 3A, ionotropic; HTR3B: 5-hydroxytryptamine (serotonin) receptor 3B, ionotropic; HTR3C: 5-hydroxytryptamine (serotonin) receptor 3C, ionotropic; HTR5A: 5-hydroxytryptamine (serotonin) receptor 5A, G protein-coupled; HTR6: 5-hydroxytryptamine (serotonin) receptor 6, G protein-coupled; HTR7: 5-hydroxytryptamine (serotonin) receptor 7, adenylate cyclase-coupled; HTRs: 5-hydroxytryptamine (serotonin) receptors; HTT: huntingtin; ICAM1: intercellular adhesion molecule 1; IDO1: indoleamine 2,3-dioxygenase 1; IFNA1: interferon, alpha 1; IGF1: insulin-like growth factor 1 (somatomedin C); IL1B: interleukin 1, beta; IL1RN: interleukin 1 receptor antagonist; IL6: interleukin 6; IL12B: interleukin 12B; INMT: indolethylamine N-methyltransferase; ITGB3: integrin, beta 3 (platelet glycoprotein Illa, antigen CD61); KCNE1: potassium channel, voltage gated subfamily E regulatory beta subunit 1; KCNE2: potassium channel, voltage gated subfamily E regulatory beta subunit 2; KCN2: potassium channel, voltage gated eaq related subfamily H, member 2; KCN6: potassium channel, voltage gated eaq related subfamily H, member 6; KCNJ11: potassium channel, inwardly rectifying subfamily J member 11; KCNKs: potassium channel, subfamily K; KCNQ1: potassium channel, voltage gated KQT-like subfamily Q, member 1; KRAS: Kirsten rat sarcoma viral oncogene homolog; LEP: leptin; LEPR: leptin receptor; LIPC: lipase, hepatic; LPL: lipoprotein lipase; MAO: monoamine oxidase; MAOA: Monoamine oxidase A; MAOB: monoamine oxidase B; MCHR1: Melanin concentrating hormone receptor 1; MET: MET proto-oncogene, receptor tyrosine kinase; METAP1: Methionyl aminopeptidase 1; MGST1: Microsomal glutathione S-transferase 1; MGST2: Microsomal glutathione S-transferase 1; MGST3: Microsomal glutathione S-transferase 3; MTRN1A: melatonin receptor 1A; MTRN1B: melatonin receptor 1B; NAAA20: N(alpha)-acyltransferase 20, Naf catalytic subunit; NAT1: N-acetyltransferase 1 (arylamine N-acetyltransferase); NAT2: N-acetyltransferase 2 (arylamine N-acetyltransferase); NDUFs: NADH dehydrogenase (ubiquinone) family; NNMT: nicotinamide N-methyltransferase; Npas3: neuronal PAS domain
protein 3; NPPA: natriuretic peptide A; NPY: neuropeptide Y; NQO1: NAD(P)H dehydrogenase, quinone 1; NQO2: NAD(P)H dehydrogenase, quinone 2; NR1I2: nuclear receptor subfamily 1, group I, member 2; NR1I3: nuclear receptor subfamily 1, group I, member 3; NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor); NRG3: neuregulin 3; NRXN1: neurexin 1; NTRK1: neurotrophic tyrosine kinase, receptor, type 1; NTRK2: neurotrophic tyrosine kinase, receptor, type 2; NUBPL: nucleotide binding protein-like; NUDT9P1: nudix (nucleoside diphosphate linked moiety X)-type motif 9 pseudogene 1; OGDH: Oxoglutarate dehydrogenase; ORM1: orosomucoid 1; ORM2: orosomucoid 2; PALLD: alladin, cytoskeletal associated protein; PARK2: parkin RBR E3 ubiquitin protein ligase; PD1E1: phosphodiesterase 1C, calmodulin-dependent 70kDa; PDE5A: phosphodiesterase 5A, cGMP-specific; PNMT: Phenylethanolamine N-methyltransferase; POMC: proopiomelanocortin; PON1: Paraoxonase 1; PON2: Paraoxonase 2; PON3: Paraoxonase 3; POR: P450 (cytochrome) oxidoreductase; PPARA: Peroxisome proliferator activated receptor alpha; PPARD: Peroxisome proliferator activated receptor delta; PPARG: Peroxisome proliferator activated receptor gamma; PPARGC1A: peroxisome proliferator-activated receptor gamma, coactivator 1 alpha; PRKAB1: protein kinase, AMP-activated, beta 1 non-catalytic subunit; PRKCSH: protein kinase C substrate 80K-H; PRL: prolactin; PRLH: prolactin releasing hormone; PSEN1: presenilin 1; PSEN2: presenilin 2; PSMD9: proteasome (prosome, macropain) 265 subunit, non-ATPase, 9; PTGES: Prostaglandin E synthase; PTGSI: Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase); PTGS2: Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase); RB1: retinoblastoma 1; RGS2: regulator of G-protein signaling 2; RGS4: regulator of G-protein signaling 4; RGS7: regulator of G-protein signaling 7; RRAS2: related RAS viral (r-ras) oncogene homolog 2; RXRA: retinoid X receptor, alpha; SAT1: spermidine/spermine N1-acetyltransferase 1; SCL6A4: solute carrier family 6 (neurotransmitter transporter), member 4; SCN1A: sodium channel, voltage gated, type I alpha subunit; SCN3A: Sodium voltage-gated channel alpha subunit 3; SCN5A: sodium channel, voltage gated, type V alpha subunit; SCNA: synuclein, alpha (non A4 component of amyloid precursor); SCN1B: sodium voltage-gated channel beta subunit 1; SCN5: sodium channels, voltage gated; SIGMAR1: sigma non-opioid intracellular receptor 1; SLC6A2: solute carrier family 6 (neurotransmitter transporter), member 2; SLC6A3: solute carrier family 6 (neurotransmitter transporter), member 3; SLC6A4: solute carrier family 6 (neurotransmitter transporter), member 4; SLC10A1: solute carrier family 10 (sodium/bile acid cotransporter), member 1; SLC16A1: solute carrier family 16 member 1; SLC18A2: solute carrier family 18 member 2; SLC22A1: solute carrier family 22 (organic cation transporter), member 1; SLC22A2: solute carrier family 22 (organic cation transporter), member 2; SLC22A3: solute carrier family 22 (organic cation transporter), member 3; SLC22A4: solute carrier family 22 member 4; SLC22A5: solute carrier family 22 member 5; SLC22A6: solute carrier family 22 member 6; SLC22A7: solute carrier family 22 member 7; SLC22A8: solute carrier family 22 member 8; SLC01B1: solute carrier organic anion transporter family, member 1B1; SLC01B3: solute carrier organic anion transporter family, member 1B3; SLC01C1: Solute carrier organic anion transporter family member 1C1; SLC02A1: Solute carrier organic anion transporter family member 2A1; SLC02B1: solute carrier organic anion transporter family, member 2B1; SLC03A1: solute carrier organic anion transporter family, member 3A1; SMOX: spermine oxidase; SOD1: Superoxide dismutase 1, soluble; SOD2: superoxide dismutase 2, mitochondrial; SPG7: spastic paraplegia 7 (pure and complicated autosomal recessive); STAT3: signal transducer and activator of transcription 3 (acute-phase response factor); SULT1A1: sulfotransferase family, cytosolic, 1A, phenol-prefering, member 1; SULT1A2: sulfotransferase family, cytosolic, 1A, phenol-prefering, member 2; SULT1A3: sulfotransferase family, cytosolic, 1A, phenol-prefering, member 3; SULT1B1: sulfotransferase family, cytosolic, 1B, member 1; SULT1C1: sulfotransferase family, cytosolic, 1C, member 1; SULT1C2: sulfotransferase family, cytosolic, 1C, member 2; SULT1C3: sulfotransferase family, cytosolic, 1C, member 3; SULT1C4: sulfotransferase family, cytosolic, 1C, member 4; SULT1E1: sulfotransferase family 1E, estrogen-prefering, member 1; SULT2A1: sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preffering, member 1; SULT2B1: sulfotransferase family, cytosolic, 2B, member 1; SULT4A1: sulfotransferase family 4A, member 1; SULT6B1: sulfotransferase family, cytosolic, 6B, member 1; TXB2I: T-box 21; TRXAS1: thromboxane A synthase 1 (platelet); TDO2: tryptophan 2,3-dioxygenase; TGFBI: transforming growth factor, beta 1; TMEM163: transmembrane protein 163; TNC: tumor necrosis factor; TNFRSF1A: tumor necrosis factor receptor superfamily, member 1A; TNF: tumor necrosis factor; TPR: translocator protein (18kDa); TST: thiopurine S-methyltransferase; TSG6: thiopurine S-methyltransferase; UCHL1: ubiquitin carboxyl-terminal esterase L1
4.2. Galantamine

Galantamine is a major substrate of CYP2D6, CYP3A4, ABCB1, and UGT1A1 and an inhibitor of ACHE and BCHE. APOE, APP, ACHE, BCHE, CHRNA4, CHRNA7, and CHRNB2 variants may also affect galantamine efficacy and safety \[120,138–141\]. Galantamine is mainly metabolized by CYP2D6 and CYP3A4 enzymes. Major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization \[142\]. Galantamine is a substrate of ABCB1. CYP2D6 variants are major determinants of galantamine pharmacokinetics, with CYP2D6-PMs presenting 45% and 61% higher dose-adjusted galantamine plasma concentrations than heterozygous and homozygous CYP2D6-EMs \[120,143\]; however, these pharmacokinetic changes might not substantially affect pharmacodynamics \[144\]. The coadministration of galantamine with CYP2D6 and CYP3A4 strong inhibitors increases its bioavailability \[48,145\].

Some recent studies show promising results with galantamine in cases of drug abuse (opioids, cocaine, and cannabis) \[147,148\] and TBI \[149\]. In combination with CDP-Choline, memantine, and antipsychotics, galantamine might be useful in schizophrenia \[150,151\].

4.3. Rivastigmine

Rivastigmine is a dual inhibitor of acetylcholinesterase (AChE; EC 3.1.1.7) and butyrylcholinesterase (BuChE; EC 3.1.1.8) in AD \[152,153\]. APOE, APP, CHAT, ACHE, BCHE, CHRNA4, CHRNA7, and MAPT variants may affect rivastigmine pharmacokinetics and pharmacodynamics. CYP enzymes are not involved in the metabolism of rivastigmine \[120,138,145,154\]. UGT2B7-PMs show higher rivastigmine levels with a poor response to treatment \[155\]. In combination treatments with memantine, carriers of CYP2D6*3, UGT2B7, and UGT1A9*5 variants show differential responses to treatment. Two SNPs on the intronic region of CHAT (rs2177370 and rs3793790) \[156\] and CHRNA7 variants may influence the response to AChEIs \[157\]. Two SNPs, one intronic marker in PRKCE-rs6720975 and an intergenic NBEA-rs17798800 marker, might also contribute to differential therapeutic response to AChEIs \[158\]. Females with the BChE-wt/wt show a better benefit with rivastigmine than males, and BChE-K* male carriers show a faster cognitive decline than females \[159\]. AD patients harboring the BChE K-variant (rs1803274), causing a reduced enzyme activity, show low clinical response to rivastigmine. The K-variant (p. A539T) and other SNPs located outside the coding sequence in 5'UTR (rs1126680) and/or intron 2 (rs55781031) of the BChE gene are responsible for reduced enzyme activity and poor response to rivastigmine \[160\]. Rivastigmine may be useful in VD and Parkinson’s disease \[161,162\] and in combination with low-dose quetiapine can improve psychotic symptoms in LBD \[163\].
4.4. Memantine

Memantine is an N-Methyl-D-Aspartate (NMDA) receptor antagonist which binds preferentially to NMDA receptor-operated cation channels [108]. Memantine inhibits the actions of glutamate via NMDA receptors and antagonizes GRIN2A, GRIN2B, GRIN3A, HTR3A, and CHRFAM7A. APOE, PSEN1, and MAPT are pathogenic genes which might influence the effects of memantine in AD, and variants in some mechanistic genes (GRIN2A, GRIN2B, GRIN3A, HTR3A, CHRFAM7A, c-Fos, Homer1b, and PSD-95) may also modify its therapeutic effects. CYP2B6 and CYP2D6 are strongly inhibited by memantine. In contrast, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 are weakly inhibited [55,120,164,165]. Studies in human liver microsomes show that memantine inhibits CYP2B6 and CYP2D6; decreases CYP2A6 and CYP2C19; and has no effect on CYP1A2, CYP2E1, CYP2C9, or CYP3A4 [166]. The coadministration of CYP2B6 substrates decreases memantine metabolism by 65%. NR1I2 rs1523130 is the only genetic covariate for memantine clearance in clinical studies. NR1I2 rs1523130 CT/TT carriers show a slower memantine elimination than carriers of the CC genotype [165]. NMDA receptors are glutamate receptors with Mg2+-mediated voltage-dependence effects in synaptic plasticity. Mutations in NMDA receptor subunits are present in NDDs. Patients with severe epileptic encephalopathy harbor the missense variant GluN2AN615K (GRIN2A C1845A), which affects NMDA receptor channel blockers, including memantine [167].

Memantine can be used alone or in combination with AChEIs in AD [168,169]. Proteomic studies in the hippocampus and the cerebral cortex of AD-related transgenic mice (3× Tg-AD) treated with memantine revealed alterations in the expression of 233 and 342 proteins, respectively [170]. In APP23 transgenic mice with cerebral amyloid angiopathy (CAA), memantine reduces cerebrovascular Aβ and hemosiderin deposits by enhancing Aβ-cleaving IDE expression [171]. Memantine is useful for the treatment of both cognitive deterioration and BDs in AD and other forms of dementia [172,173]. AD patients treated with memantine plus citalopram show improvement in BDs [174]; in combination with antipsychotics, it may improve verbal memory, learning, verbal letter fluency, and working memory with no effect on psychotic symptoms in patients with chronic schizophrenia [175,176]; at a dose of 20 mg/day, it may be effective in patients with obsessive-compulsive disorder [177]; at 10 mg/day, it may be helpful in migraine [178]; and, in combination with naltrexone, it enhances the efficacy of naltrexone in reducing alcohol drinking and craving [179]. Memantine might also be useful in the treatment of punctate and dynamic allodynia by the blockade of the microglia Kir2.1 channel to suppress microglia activation [180], and in combination with dextromethorphan, it may be beneficial in neuropathic pain [181].

4.5. Multifactorial Treatments

Most studies in which AD patients are treated with multifactorial combinations reveal that APOE-3/3 carriers are the best responders and that APOE-4/4 carriers are the worst responders. Concerning CYP-related PGx outcomes, CYP2D6-EMS are the best responders, CYP2D6-PMs are the worst responders, and CYP2D6-IMs and UMs show an intermediate response [1–3,56,71,106,112,115,116,118] (Figures 4–6).

In linkage disequilibrium with and adjacent to the APOE locus (19q13.2) is the TOMM40 gene, which encodes an outer mitochondrial membrane translocase involved in the transport of Aβ and other proteins into mitochondria. A poly T repeat in an intronic polymorphism (rs10524523) (intron 6) in the TOMM40 gene has been implicated in AD pathogenesis and PGx. The number of “T”-residues in the rs10524523 (“523”) locus differentiates 3 allele groups: “short” (S, T ≤ 19), “long” (L, 20 ≤ T ≤ 29), and “very long” (VL, T ≥ 30). rs10524523 L variants are associated with a higher risk for late-onset AD (LOAD). APOE-TOMM40 interactions affect the risk of AD and the response to drugs. The S/L and VL/VL TOMM40 poly T genotypes interact with all APOE genotypes; however, the APOE-4/4-TOMM40-L/L association is unique, accounting for 30% of APOE-4/4 carriers. TOMM40 poly T-S/S carriers are the best responders, VL/VL and S/L carriers are intermediate responders, and L/L carriers are the worst responders to treatment. TOMM40-L/L and S/L carriers in haplotypes with APOE-4 are the worst responders to treatment. TOMM40-S/S carriers and, to a lesser extent,
TOMM40-S/VL and TOMM40-VL/VL carriers in haplotypes with APOE-3 are the best responders to treatment. The TOMM40-L/L genotype is exclusively associated with the APOE-4/4 genotype in 100% of the cases, and this haplotype (4/4-L/L) might be responsible for premature neurodegeneration and consequent early onset of the disease, a faster cognitive deterioration, and a limited response to conventional treatments [4,116] (Figure 5).

| APOE Genotypes | Number (Frequency) |
|-----------------|--------------------|
| APOE-2/3        | 76 (8.26%)         |
| APOE-2/4        | 18 (1.96%)         |
| APOE-3/3        | 474 (51.52%)       |
| APOE-3/4        | 304 (33.04%)       |
| APOE-4/4        | 48 (5.22%)         |

Figure 4. APOE-related responder/nonresponder rate in patients with Alzheimer’s disease treated with a multifactorial/combination treatment for one year. Responders: Final Mini-Mental State Examination (MMSE) score > basal MMSE score. NonResponders: Final MMSE score < basal MMSE score. Data Source: Cacabelos et al., 2014.

Epigenetic factors are important in AD pathogenesis and response to treatment [5,26,57,61,65,71]. Sirtuin variants may alter the epigenetic machinery, contributing to AD pathogenesis. The SIRT2-C/T genotype (rs10410544) (30.92%) has been associated with AD susceptibility in the APOEε4-negative population (SIRT2-C/C, 34.72%; SIRT2-T/T 14.36%). SIRT2-APOE bigenic clusters yield 18 haplotypes that influence the PGx outcome. APOE-3/4 and APOE-4/4 genotypes accumulate in SIRT2-T/T > SIRT2-C/T > SIRT2-C/C carriers, and SIRT2-T/T and SIRT2-C/T genotypes accumulate in APOE-4/4 carriers. SIRT2-C/T carriers tend to be the best responders, SIRT2-T/T carriers are intermediate responders, and SIRT2-C/C carriers are the worst responders to a multifactorial treatment. PGx outcomes related to APOE-SIRT2 bigenic clusters show that 33CC carriers respond better than 33TT and 34CT carriers, whereas 24CC and 44CC carriers are the worst responders. SIRT2-C/T-CYP2D6-EMS are the best responders [5].
residues in the rs10524523 ("523") locus differentiates 3 allele groups: "short" (S, T) in the other proteins into mitochondria. A poly T repeat in an intronic polymorphism (rs10524523) (intron β) which encodes an outer mitochondrial membrane translocase involved in the transport of A receptors (DRD1 and DRD2), calcium-related channels (CACNA1H and CACNA1B), and solute receptors (HTR2A and HTR2C), GABAergic receptors (GABRA1 and GABRB2), dopaminergic genes, and serotonergic genes. SCZ genes include glutaminergic receptors (GRIA1, GRIN2, GRIK4, and GRM5), serotonergic genes, and glutamatergic genes.

5. Pharmacogenomics of Neuropsychiatric Disorders

5.1. Psychotic Disorders

Over 500 genes are potentially associated with psychosis and schizophrenia (SCZ) [25]. Several genes have been implicated in AD pathogenesis and PGx. The number of "T"-genotypes accumulate in APOE ε4 carriers. TOMM40 variants are associated with a higher risk for AD and the response to drugs. Interactions affect the risk of AD and the response to drugs. Sirtuin variants may alter the epigenetic machinery, contributing to AD pathogenesis. The SIRT2-C/T genotype (rs10410544) (50.92%) has been associated with AD susceptibility in the TOMM40 locus (19q13.2) is the "short" (S, T) in the other proteins into mitochondria. A poly T repeat in an intronic polymorphism (rs10524523) (intron β) which encodes an outer mitochondrial membrane translocase involved in the transport of A receptors (DRD1 and DRD2), calcium-related channels (CACNA1H and CACNA1B), and solute receptors (HTR2A and HTR2C), GABAergic receptors (GABRA1 and GABRB2), dopaminergic genes, and serotonergic genes. SCZ genes include glutaminergic receptors (GRIA1, GRIN2, GRIK4, and GRM5), serotonergic genes, and glutamatergic genes.

Figure 5. TOMM40-related responder/nonresponder rate in patients with Alzheimer’s disease treated with a multifactorial/combination treatment for one year. Responders: Final MMSE score > basal MMSE score. Nonresponders: Final MMSE score < basal MMSE score. Data Source: Cacabelos et al., 2014.

| TOMM40 Genotypes | Number (Frequency) |
|------------------|--------------------|
| TOMM40-S/S       | 169 (18.37%)       |
| TOMM40-S/L       | 72 (7.83%)         |
| TOMM40-S/VL      | 357 (38.80%)       |
| TOMM40-L/L       | 14 (1.52%)         |
| TOMM40-L/VL      | 66 (7.17%)         |
| TOMM40-VL/VL     | 242 (26.31%)       |

Figure 6. CYP2D6-related responder/nonresponder rate in patients with Alzheimer’s disease treated with a multifactorial/combination treatment for one year. Responders: Final MMSE score > basal MMSE score. Nonresponders: Final MMSE score < basal MMSE score. Data Source: Cacabelos et al., 2019.

| CYP2D6-Phenotype                 | Number (Frequency) |
|----------------------------------|--------------------|
| CYP2D6-EM (Extensive Metabolizer) | 311 (59.46%)       |
| CYP2D6-IM (Intermediate Metabolizer) | 152 (29.06%)       |
| CYP2D6-PM (Poor Metabolizer)     | 28 (5.36%)         |
| CYP2D6-UM (Ultra-Rapid Metabolizer) | 32 (6.12%)         |
5. Pharmacogenomics of Neuropsychiatric Disorders

5.1. Psychotic Disorders

Psychotic symptoms (hallucinations and delusions) are strongly related to AD-associated cognitive dysfunction, gradually progressing in parallel with disease severity [182]. In addition, symptoms of personality changes, paranoia, hallucinations, cravings, agitation, and changes in appetite may represent a prodromal noncognitive phenotype of risk for dementia [183].

Over 500 genes are potentially associated with psychosis and schizophrenia (SCZ) [25]. Several BDs in dementia incorporate SCZ genes. Major biological pathways and mechanisms associated with SCZ genes include glutaminergic receptors (GRIA1, GRIN2, GRIK4, and GRM5), serotonergic receptors (HTR2A and HTR2C), GABAergic receptors (GABRA1 and GABRB2), dopaminergic receptors (DRD1 and DRD2), calcium-related channels (CACNA1H and CACNA1B), and solute carrier transporters (SLC1A1 and SLC6A2) [184]. Aberrant motor behavior is strongly associated with the APOE-4/4 genotype and the presence of both Lewy bodies and cerebral amyloid angiopathy [185].

Antipsychotics are drugs of current use (>50%) to treat BDs in dementia with limited efficacy in aggressive behaviors and psychotic symptoms. These drugs increase mortality and risk of psychomotor disorders and cerebrovascular events. Neuroleptics are prescribed for long periods of time in combination with antidepressants and anti-dementia drugs [186,187].

Antipsychotics (Table 3) are associated with the PGx activity of less than 100 pharmagenes. The different pharmacological categories of antipsychotics (phenothiazines with aliphatic side-chain, piperazine-related phenothiazines, piperidine phenothiazines, butyrophenones, indole derivatives, thioanthenes, diphenylbutylpiperidines, diazepines, oxazepines, thiazepines, benzamides, and other neuroleptics) are substrates, inhibitors, or inducers of 32, 16, and 3 enzyme/protein gene products, respectively, and are transported by at least 14 different protein transporters. CYP enzymes participate in the metabolism of 90% of antipsychotics. These drugs are major substrates of CYP3A4 (75%), CYP2D6 (72%), CYP1A2 (46%), CYP2C19 (22%), and UGT1A4 (33%); inhibitors of CYP2D6 (50%), CYP3A4 (42%), ABCB1 (29%), CYP1A2 (25%), CYP2C19 (21%), and CYP2C9 (15%); and inducers of GSTM1, MAOB, and SLC03A1 with low affinity (<5%). About 50% of antipsychotics are transported by ABCB1. Other transporters responsible for the influx-efflux of neuroleptics are KCNH2 (22%); KCNE1 and KCNE2 (18%); KCNQ1 (18%); and SLC6A2, SLC6A4, and SCN5A (11%). Haloperidol is associated with 31 pharmagenes, Olanzapine is associated with 28, and Thioridazine is associated with 27 [55,103].

The dopamine transporter (SLC6A3) gene has been the focus of attention for years in the PGx of antipsychotic drugs. The study of 6 SNPs (rs2652511 (T-844C) and rs2975226 (T-71A) in the 5′-regulatory region, rs2963238 (A1491C) in intron 1, a 30-bp VNTR in intron 8, rs27072 and the 40-bp VNTR in the 3′-region) showed association of allele and genotype frequencies with response to clozapine [188].

Major ADRs with antipsychotics are extrapyramidal symptoms, tardive dyskinesia, antipsychotic-induced weight gain, and clozapine-induced agranulocytosis. Antipsychotic-induced extrapyramidal symptoms are associated with DRD2, SLC18A2, HTR2A, GRIK3, and SLC6A3 VNTR and COMT Val158Met polymorphisms [189,190]. SNPs in ADORA1, ADORA2A, and ADORA3 have been associated with psychopathological symptoms, extrapyramidal symptoms, akathisia, and tardive dyskinesia [191]. RGS2*T*T(rs2746073), RGS2*C*C (rs4606), and RGS2*A*A (rs2746071) are associated with high risk for extrapyramidal symptoms in Russian patients treated with haloperidol [192]. Several SNPs in genes of the mTOR pathway (AKT1, rs1130214; FCHSD1, rs456998; Raptor, rs7211818; and DDIT4, rs1053639) have also been associated with extrapyramidal disorders in Spanish patients under antipsychotic treatment [193].

Tardive dyskinesia (TD) is an involuntary movement disorder that occurs in over 20% of patients after chronic treatment with antipsychotics. Disrupted in schizophrenia 1 (DISC1) gene variants, SNP variation in several CYPs, especially CYP2D6, and in HSPG2, CNR1, DPPE, LC18A2, MTNR1A, PIP5K2A, DRD2, DRD3, VMAT2, HSPG2, HTR2A, HTR2C, and SOD2 variants influence TD [194–196].
An intron-1 SNP (rs6977820) of the DPP6 (dipeptidyl peptidase-like protein-6) gene has been associated with TD in Japanese patients. DPP6 is an auxiliary subunit of Kv4 that regulates the activity of dopaminergic neurons. Decreased expression of DPP6 in the brain can be reversed by haloperidol treatment [197]. Another SNP (rs2445142) in the HSPG2 (heparan sulfate proteoglycan 2) gene has been associated with TD in both Japanese and Caucasian populations [198]. Carriers of the CNR1-rs806374 (T>C) CC genotype are more likely to develop TD and severe motor dysfunction than TT or TC among Caucasians. Cannabinoid receptor 1 (CNR1) activators inhibit movement, and this effect is prevented by rimonabant and selective CNR1 antagonists [199]. A number of SNPs in the SLC18A2 gene that encodes VMAT2 (vesicular monoamine transporter 2) may affect TD, including the rs2015586 marker (with deleterious effects) and the rs363224 marker (with protective effects in carriers of the low-expression AA genotype) [200]. Two VMAT2 inhibitors, Valbenazine and Deutetrabenazine, have been approved for treating TD [201–203].

Hyperprolactinemia is a common ADR in users of neuroleptic drugs. Risperidone-induced prolactin response is associated with 3 UGT1A1 SNPs (UGT1A1*80c.-364C>T, UGT1A1*93 c.-3156G>A, and UGT1A1 c.-2950A>G) [204].

Antipsychotic-induced weight gain occurs in over 30–40% of patients with SCZ. All antipsychotics are associated with weight gain in antipsychotic-naïve and first-episode patients; however, weight gain is greatest in patients treated with the second-generation antipsychotics clozapine and olanzapine. The proportion of patients with body weight gain (>7% baseline) is >20% for clozapine and olanzapine. The proportion of patients with body weight gain (>7% baseline) is >30% for quetiapine, and 45% for aripiprazole [205]. This ADR is caused by different genotypes: Pharmacological properties of the drug, pharmacogenetic factors, environmental factors, and ethnicity [206].

### Table 3. Pharmacological profile and pharmacogenetics of selected antipsychotics.

| Name: Aripiprazole; Abilify; Abilat; Abilify Discmelt; OPC-1459 | Pathogenic genes: DRD2, DRD3, HTR1A, HTR2A, HTR2C | Mechanistic genes: ADRA1A, ADRA2A, ADRA2B, ADRA2C, ADRA2D, DRD2, DRD3, DRD4, HRHs, HTR1A, HTR2A, HTR2B, HTR2C, HTR7 |
|-----------------------------|-----------------------------------------------|-----------------------------------------------|
| IUPAC Name: 7-[4-[4-(2,3-dichlorophenyl)] piperazin-1-yl]butoxy]-1,2,3,4-tetrahydroquinolin-2-one | Drug Name: C25H27Cl2N3O2 | Metabolic genes: CYP2D6 (major), CYP3A4 (major), CYP3A5 |
| Molecular Formula: 448.38538 g/mol | Molecular Weight: | Transporter genes: ABCB1 |
| Mechanism: Partial agonist at the D2 and 5-HT1A receptors, and as an antagonist at the 5-HT2A receptor | Effect: Antipsychotic agent; H1-receptor antagonist; Serotonergic agonist | |

| Name: Asenapine maleate; Saphris; Org5222 maleate; 85650-56-2; Org 5222 maleate; Org-5222 maleate | Pathogenic genes: ADRA2A, DRD1, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, HTR7 | Mechanistic genes: ADRA1A, ADRA2A, ADRA2B, ADRA2C, ADRA2D, DRD2, DRD3, DRD4, HRH1, HRH2, HTR1A, HTR1B, HTR2A, HTR2B, HTR2C, HTR5A, HTR6, HTR7 |
|-----------------------------|-----------------------------------------------|-----------------------------------------------|
| IUPAC Name: (ZZ)-but-2-enedioic acid, 17-chloro-4-methyl-13-oxa-4-azatetracyclo[12.4.0.0^6.10^7.12]octadeca-1(14),7,9,11,15,17-hexaene | Drug Name: C21H20ClNO5 | Metabolic genes: CYP2D6 (minor), CYP3A4 (minor), UGT1A1 |
| Molecular Formula: 401.8402 g/mol | Molecular Weight: | Inhibitor: CYP2D6 (weak) |
| Mechanism: Its main activity is associated to combination of antagonistic actions at D2 and 5-HT2A receptors | Effect: Antipsychotic agent; Dopaminergic antagonist; Serotonergic antagonist; Alpha-adrenergenic antagonist; Beta-adrenergic antagonist | |
Antipsychotics are associated with weight gain in antipsychotic-naïve and first-episode patients; 3156G>A, prolactin response is associated with 3
Hyperprolactinemia is a common ADR in users of neuroleptic drugs. Risperidone-induced

**Table 3.**

| Drug       | Atypical Antipsychotics | Pharmacogenetics |
|------------|-------------------------|------------------|
| **Name:**  | Clozapine; Leponex; Fazaclo; Iprox; CLOZARIL; Clozapin | Pathogenic genes: ADRA2A, DRD1, DRD2, DRD3, DRD4, DTNBPI, HTR2A, LPL, NRXN1, TNF |
| **IUPAC Name:** | 6-chloro-10-(4-methylpiperazin-1-yl)-2,9-diazatricyclo[9.4.0.0³,7]pentadeca-(15),3,5,7,9,11,13-heptaene | Mechanistic genes: ADRA5s, CHRM5s, DRD1, DRD2, DRD3, DRD4, HRH1, HTR1F, HTR2A, HTR2C, HTR3A, HTR6, NRXN1 |
| **Molecular Formula:** | C16H9ClN4 | **Metabolic genes:** |
| **Molecular Weight:** | 326.8236 g/mol | **Substrate:** CYP1A2 (major), CYP2A6 (minor), CYP2C8 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (minor), CYP3A4/5 (major), FMO3, UGT1A1, UGT1A3, UGT1A4 |
| **Mechanism:** | It shows serotonergic, adrenergic, and cholinergic neurotransmitter systems in addition to more selective, regionally specific effects on the mesolimbic dopaminergic system. It also displays antagonistic activity at H1-receptors | **Inhibitor:** CYP1A2 (weak), CYP2C9 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (weak) |
| **Effect:** | Dopaminergic antagonist; Serotonergic antagonist; Histamine antagonist; Muscarinic antagonist; GABA antagonist; GABA modulator; Antipsychotic agent | Transporter genes: ABCB1, SLC03A1 |
| **Name:**  | Iloperidone; Zomaril; 133454-47-4; Fanapt; Fanapta; HP 873 | **Pleiotropic genes:** APOA5, APOC3, AP0D, CNR1, FAR1, GNB3, GSK3B, LPL, RGS2, TNF |
| **IUPAC Name:** | 1-(4-[3-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyphenyl)ethyl-1-one | **Mechanistic genes:** ADRA1A, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, DRD1, DRD2, DRD3, DRD4, DRD5, GFRα2, GRIA4, HRH1, HTR1A, HTR2A, HTR2C, HTR6, HTR7, NPA53, NUDT9P1, TNR, XKR4 |
| **Molecular Formula:** | C21H20ClNO5 | **Metabolic genes:** |
| **Molecular Weight:** | 426.480583 g/mol | **Substrate:** CYP1A2, CYP2E1, CYP2D6 (major), CYP3A4 (major) |
| **Mechanism:** | It has mixed D2/5-HT2 antagonist activity. It exhibits high affinity for 5-HT2A, D2, and D1 receptors, low to moderate affinity for D1, D4, H1, 5-HT1A, 5-HT6, 5HT7, and ADRα1/α2C receptors, and no affinity for muscarinic receptors. It has low affinity for histamine H1 receptors | Transporter genes: SLC6A2, SLC03A1 |
| **Effect:** | Antipsychotic agent; Dopaminergic antagonist; Serotonergic antagonist; Antidepressant effects; Anxiolytic activity; Reduction of risk for weight gain; Cognitive Function Improved | **Pleiotropic genes:** ADRB2, CELF4, CEK5, DRD5, HTR1F, NPA53, NRG3, NUBP1, PALLD |
| **Name:**  | Olanzapine; Zyproxa; 132539-06-1; Zyproxa Zydis; Olarnek; Symbyax | Pathogenic genes: COMT, DRD1, DRD2, DRD3, GRM3, HTR2A, HTR2C, LPL |
| **IUPAC Name:** | 5-methyl-8-(4-methylpiperazin-1-yl)-4-thia-2,9-diazatricyclo[8.4.0.0³,7]tetradeca-(14),3(7),5,8,10,12-hexaene | Mechanistic genes: ABC8B1, ADRA1A, ADRA2B, AHR, BDNF, CHRM1, CHRM2, CHRM3, CHRM5, COMT, DRD1, DRD2, DRD3, DRD4, GABRs, GNR2B, GRN1B, HHR1, HTR2A, HTR2C, HTR3A, HTR6, LEP, RGS2, RGS7, SLC6A4, STAT3, TMEM163 |
| **Molecular Formula:** | C17H20N4S | **Metabolic genes:** |
| **Molecular Weight:** | 312.4325 g/mol | **Substrate:** COMT, CYP1A2 (major), CYP2C9, CYP2D6 (major), CYP3A43, CYP3A45, FMO1, FMO3, GSTM3, TPM1, UGT1A1, UGT1A4, UGT2B10 |
| **Mechanism:** | It displays potent antagonism of serotonin 5-HT2A and 5-HT2C, dopamine D1,4, histamine H1 and α1-adrenergic receptors. It shows moderate antagonism of 5-HT3 and muscarinic M3 receptors, and weak binding to GABA-A, BZD, and β-adrenergic receptors. | **Inhibitor:** ABC8B1, CYP1A2 (weak), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP3A4 (weak) |
| **Effect:** | Antipsychotic agent; GABA modulator; Muscarinic antagonist; Serotonin uptake inhibitor; Dopaminergic antagonist; Serotonergic antagonist; Histamine antagonist; Antiemetic activity | **Inducer:** GSTM1, MAOB, SLC03A1 |
| **Transporter genes:** | KCNH2, SLC6A2, SLC6A4, SLC03A1 |
| **Pleiotropic genes:** | APOA5, APOC3, GNB3, LEP, LEP, LPL |
Table 3. Cont.

| Drug                     | Properties                                                                 | Pharmacogenetics                                                                 |
|--------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Name: Paliperidone**    | Paliperidone; Paliperidone; 9-Hydroxyrisperidone; Invega; 144598-75-4;     | Pathogenic genes: ADRA2A, DRD2, HTR2A                                             |
|                          | 9-OH-risperidone; Invega Sustenna                                          | Mechanistic genes: ADRA1A, ADRA1B, ADRA2A, BDNF, DRD2, HRH1, HTR1A, HTR2A,       |
|                          |                                                                           | HTR2C                                                                           |
|                          |                                                                           | Metabolic genes:                                                               |
|                          |                                                                           | Substrate: ABCB1, CYP2D6 (minor), CYP3A45 (major), UGIs                        |
|                          |                                                                           | Inhibitor: ABCB1, SLC6A2                                                      |
|                          |                                                                           | Transporter genes: ABCB1, KCNE1, KCN1, KCNQ1, SCN5A, SLC6A2                    |
|                          |                                                                           | Transporter genes: ABCB1, KCNE1, KCN1, KCNQ1, SCN5A, SLC6A2                    |
| **Name: Quetiapine Fumarate** | Quetiapine hemifumarate; Seroquel;                                        | Pathogenic genes: ADRA2A, DRD1, DRD2, HTR1A, HTR2A, RGS4                        |
|                          | Seroquel XR; UNII-2S3PL1B6UJ                                              | Mechanistic genes: ADRA1s, ADRA2s, BDNF, CHRM1, CHRM3, CHRM5, DRD1, DRD2,       |
|                          |                                                                           | DRD4, HTR1A, HTR2A, RGS4                                                       |
|                          |                                                                           | Metabolic genes:                                                               |
|                          |                                                                           | Substrate: CYP2D6 (minor), CYP3A45 (major), CYP2C19                            |
|                          |                                                                           | Inhibitor: ABCB1, SLC6A2                                                      |
|                          |                                                                           | Transporter genes: ABCB1, KCNE1, KCN1, KCNQ1, SCN5A, SLC6A2                    |
|                          |                                                                           | Transporter genes: ABCB1, KCNE1, KCN1, KCNQ1, SCN5A, SLC6A2                    |
| **Name: Risperidone**     | Risperdal; Risperidal; 106266-06-2; Risperdal Consta; Risperidone         | Pathogenic genes: ADRA2A, BDNF, COMT, DRD1, DRD2, DRD3, DRD4, GRM3, HTR2A,       |
|                          |                                                                           | HTR2C, HTR7, PON1, RGS4                                                        |
|                          |                                                                           | Mechanistic genes: ADRA1A, ADRA1B, ADRA2A, BDNF, DRD3, DRD4, FOS, HTR2A, HTR2C, |
|                          |                                                                           | HTR3A, HTR3C, HTR6, HTR7, NR1H2, STAT3                                        |
|                          |                                                                           | Metabolic genes:                                                               |
|                          |                                                                           | Substrate: COMT, CYP2D6 (major), CYP3A45 (minor)                               |
|                          |                                                                           | Inhibitor: ABCB1, CYP2D6 (weak), CYP3A4 (weak) Inducer: MAO                     |
|                          |                                                                           | Transporter genes: ABCB1, KCN1, SLC6A                                          |
|                          |                                                                           | Pleiotropic genes: APOA5, BDNF, RGS2                                             |
### Table 3. Cont.

#### Atypical Antipsychotics

| Drug                      | Properties                              | Pharmacogenetics                  |
|---------------------------|-----------------------------------------|-----------------------------------|
| Name: Ziprasidone; Geodon; 146939-27-7; Zeldox; Ziprazidone; Ziprasidone hydrochloride | Pathogenic genes: DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, RGS4 | Mechanistic genes: ADRA1A, ADRA2A, ADRA2B, DRD2, DRD3, HTR1A, HTR1B, HTR1D, HTR2A, HTR2C |
| **IUPAC Name:** 5-(2-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl][ethyl]-6-chloro-2,3-dihydro-1H-indol-2-one | **Molecular Formula:** C21H23ClFNO2 | **Molecular Weight:** 412.93564 g/mol |
| **Mechanism:** It has high affinity for D2, D3, 5-HT2A, 5-HT1A, 5-HT2C, 5-HT1D, and α1-adrenergic, and moderate affinity for histamine H1 receptors. It functions as antagonist at D2, 5-HT2A, and 5-HT1D receptors and as agonist at 5-HT1A receptor. It moderately inhibits reuptake of serotonin and norepinephrine | **Effect:** Antipsychotic agent; Histamine antagonist; Dopaminergic antagonist; Serotonergic antagonist; Muscarinic antagonist; Serotonin–norepinephrine reuptake inhibitor |**Metabolic genes:** Substrate: AOX1 (major), CYP1A1 (minor), UGTs | **Inhibitor:** CYP2D6 (moderate), CYP3A4 (major) | **Transporter genes:** ABCB1 |
| | **Pleiotropic genes:** | **Pathogenic genes:** | **Mechanistic genes:** | **Inhibitor:** | **Transporter genes:** |
| **Typical Antipsychotics** | **Butyrophenones** | **Stilbenes** | **Phenothiazines** | **Molecular Formula:** C21H26F3N3OS | **Molecular Weight:** 437.52155 g/mol |
| Name: Bromperidol; Impronen; Bromperidol; Tesoprel; 10457-90-6; Azurene | Pathogenic genes: DRD2, HTR2A | Mechanistic genes: DRD2, HTR2A | Metabolic genes: Substrate: CYP2D6 (minor), CYP3A4 (major), UGTs | Inhibitor: CYP2D6 (moderate) | Transporter genes: ABCB1 |
| **IUPAC Name:** 4-[[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one | **Molecular Formula:** C21H23BrFNO2 | **Molecular Weight:** 420.315223 g/mol |
| **Mechanism:** Potent dopaminergic D2 antagonist. Has weak α1-adrenolytic activity. It is a moderate serotonin 5-HT2 antagonist. Has no antihistaminic or anticholinergic effects. It acts on the mesocortex, limbic system, and basal ganglia (nigrostriate pathway) | **Effect:** Antipsychotic agent; Dopamine antagonist; α1-adrenolytic activity | **Pathogenic genes:** ADRA2A, BDNF, DRD1, DRD2, DRD4, DTNBPI, GRIN2B, HTR2A | **Mechanistic genes:** ANKK1, BDNF, COMT, DRD1, DRD2, DTNBPI, GRIN2A, GRIN3B, GRIN2C, GRIN2B, SLC6A3 | **Metabolic genes:** Substrate: CYP2A6, CYP2C8 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4/5 (major), GSTP1, UGTs |
| | **Pleiotropic genes:** | **Pathogenic genes:** | **Mechanistic genes:** | **Inhibitor:** ABCB1, CYP2D6 (moderate), CYP3A4 (moderate) | **Transporter genes:** ABCB1, ABCC1, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SLC6A3 |
| **Molecular Weight:** 375.864223 g/mol | **Pathogenic genes:** | **Mechanistic genes:** | **Inhibitor:** | **Transporter genes:** |
| **Mechanism:** Haloperidol is a butyrophenone antipsychotic which blocks postsynaptic mesolimbic dopaminergic D2 and D3 receptors in brain. Depresses release of hypothalamic and hypophyseal hormones. Believed to depress reticular activating system | **Effect:** Antipsychotic agent; Serotonergic antagonist; Dopaminergic antagonist; Antiemetic; Antidyskinesia agent; Sedative effects; Hypotension | **Pathogenic genes:** ADRA2A, BDNF, DRD1, DRD2, DRD4, DTNBPI, GRIN2B, HTR2A | **Mechanistic genes:** ANKK1, BDNF, COMT, DRD1, DRD2, DTNBPI, GRIN2A, GRIN3B, GRIN2C, GRIN2B, SLC6A3 | **Metabolic genes:** Substrate: CYP2A6, CYP2C8 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4/5 (major), GSTP1, UGTs |
| | **Pleiotropic genes:** | **Pathogenic genes:** | **Mechanistic genes:** | **Inhibitor:** ABCB1, CYP2D6 (moderate), CYP3A4 (moderate) | **Transporter genes:** ABCB1, ABCC1, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SLC6A3 |
| **Typical Antipsychotics** | **Stilbenes** | | | | |
### Phenothiazines

| Drug Name | Properties | Pharmacogenetics |
|-----------|------------|------------------|
| **Name:** Chlorpromazine; Largactil; Thorazine; Contomin; Chloropromazine; Aminazine | **IUPAC Name:** [3-(2-chloro-10H-phenothiazin-10-yl)propyl]dimethylamine | **Pathogenic genes:** BDNF, DRD1, DRD2, DRD3, DRD4, HTR2A<br>**Mechanistic genes:** ADR1A, ADRA1B, CHRM1, CHRM2, DRD1, DRD2, DRD3, DRD4, HRH1, HTR1A, HTR2A, HTR2C<br>**Metabolic genes:** CYP2A6, CYP2C9, CYP2D6 (major), CYP2D6 (minor), CYP3A4 (major), CYP3A4 (minor), FM01, UGT1A3, UGT1A4<br>**Inhibitor:** CYP2A5, CYP2D6 (strong), CYP2D6 (weak), CYP3A4, DAO<br>**Transporter genes:** ABCB1, CTRT<br>**Pleiotropic genes:** ACACA, BDNF, FABP1, LEP, NPY | **Effect:** Antipsychotic agent; Dopaminergic antagonist; Antiemetic; Anticholinergic effects; Sedative effects; Antihistaminic effects; Anti-serotonergic activity; Hypotension |
| **Name:** Fluphenazine; Trifluromethazine; Fluoroamphetamine; Fluorofenazine; Fluorophenazine; Siquazaine | **IUPAC Name:** 2-(4-{3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl}piperazin-1-yl)ethan-1-ol | **Pathogenic genes:** DRD1, DRD2<br>**Mechanistic genes:** CALM1, DRD1, DRD2<br>**Metabolic genes:** CYP2B6, CYP2D6 (major)<br>**Inhibitor:** ABCB1, CYP1A2 (weak)<br>**Transporter genes:** ABCB1 | **Effect:** Antipsychotic agent; Dopaminergic antagonist; Antiemetic; Anticholinergic effects; Sedative effects |
| **Name:** Perphenazine; Trilafon; Perphenazine; Etaperazine; Perfenazine; Fentazin | **IUPAC Name:** 2-[4-3-(2-chloro-10H-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol | **Pathogenic genes:** ADR1A2, DRD1, DRD2, HTR2A, HTR2C, RGS4<br>**Mechanistic genes:** ADR1A1, ADR1A2, DRD1, DRD2, HTR2A, HTR2C, RGS4<br>**Metabolic genes:** CYP2A6, CYP2C9 (major), CYP2C9 (major), CYP2C18 (major), CYP2C19 (major), CYP2D6 (minor), CYP3A4 (major)<br>**Inhibitor:** CYP1A2 (weak), CYP2D6 (strong)<br>**Transporter genes:** ABCB1 | **Effect:** Antipsychotic agent; Antiemetic; Dopaminergic antagonist; Antiemesis |

**Table 3. Cont.**
**Table 3. Cont.**

| Drug          | Properties                                                                 | Pharmacogenetics                          |
|---------------|----------------------------------------------------------------------------|--------------------------------------------|
| **Phenothiazines** |                                                                                  |                                            |
| Name: Thioridazine; Mellari; Melleril; Thioridazin; Melleri; Sonapax | Pathogenic genes: ADRA2A, DRD1, DRD2 Mechanistic genes: ADRA1s, ADRA2s, DRD1, DRD2 Metabolic genes: Substrate: CYP1A2 (major), CYP2C19 (minor), CYP2A6, CYP2D6 (major), CYP2D2 (major), CYP3A4 (major) Inhibitor: ABCB1, CYP1A2 (weak), CYP2A6, CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (weak), KCNH Transporter genes: ABCB1, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1 Pleiotropic genes: ADRB6, CHRM2, FABP1, HRH1 |
| IUPAC Name: 10-[2-{1-methylpiperidin-2-yl}(2-methysulfanylphenothiazine) | Molecular Formula: C$_2$_1H$_8$_N$_3$_S$_2$_ Molecular Weight: 370.57454 g/mol Mechanism: Blocks postsynaptic mesolimbic dopaminergic receptors in brain. Exhibits strong α-adrenergic-blocking effect and depresses release of hypothalamic and hypophyseal hormones Effect: Antipsychotic agent; Dopaminergic antagonist; Alpha-adrenergic antagonist; H$_1$-receptor antagonist; Serotonergic antagonist |
| **Thioxanthenes** |                                                                                  |                                            |
| Name: Thioxene, Tiottiene; Cis-Thiotoxene; Navane; Thiotoxene; Navan | Pathogenic genes: DRD2, IL12B Mechanistic genes: ABCB1, ADRA1A, ADRA1B, CALMs, DRD2, HRH1 Metabolic genes: Substrate: CYP1A2 (major), UGT1A4 Inhibitor: CALMs, POR Transporter genes: ABCB1 Pleiotropic genes: IL12B |
| IUPAC Name: (9Z)-N,N-dimethyl-9-[3-[(4-methylpiperazin-1-yl)propylidene]thioxanthen-2-sulfonylamine | Molecular Formula: C$_2$_1H$_8$_N$_3$_O$_2$_S$_2$_ Molecular Weight: 443.62526 g/mol Mechanism: Elicits antipsychotic activity by postsynaptic blockade of CNS dopamine receptors resulting in inhibition of dopamine-mediated effects. Also has α-adrenergic blocking activity. Antagonistic effect on dopaminergic (D$_1$, D$_2$, D$_3$, D$_4$), histaminergic (H$_1$), serotonergic (5-HT$_1$, 5-HT$_2$), adrenergic (α$_1$ and α$_2$) and muscarinic (M$_1$ and M$_2$) receptors Effect: Antipsychotic agent; Dopamine antagonist; Antisymptomimetic properties; Anticholinergic effects; Antidepressant effects, Antiaaggressve properties; H$_1$-receptor antagonist; Serotonergic agonist |
Table 3. Cont.

| Drug | Properties | Pharmacogenetics |
|------|------------|-----------------|
| **Thioanthenes** | | |
| **Name:** Zuclopenthixol; Zuclopentixol; Clopixol; Zuclophenixolum; Acuphase; Cisordinol | | |
| **IUPAC Name:** 2-[4-[(3Z)-3-(2-chlorothioanthen-9-ylidene)propyl]piperazin-1-yl]ethanol | **Pathogenic genes:** ADRA2A, DRD1, DRD2 | |
| **Molecular Formula:** C₂₂H₂₅ClN₂OS | **Mechanistic genes:** ADRA1s, ADRA2s, CHRM6, DRD1, DRD2, HRH1, HTR2s | |
| **Molecular Weight:** 400.9647 g/mol | **Metabolic genes:** Substrate: CYP2D6 (major), CYP3A4 (major) | |
| **Mechanism:** It mainly acts by antagonism of D₁ and D₂ dopamine receptors. It also has high affinity for alpha₁-adrenergic and 5-HT₂ receptors. It has weaker histamine H₁ receptor blocking activity, and even lower affinity for muscarinic cholinergic and alpha₂-adrenergic receptors | **Pleiotropic genes:** HTR2A | |
| **Effect:** Antipsychotic agent; Dopaminergic antagonist; H₁-receptor antagonist; Serotonergic antagonist; Dopaminergic antagonist; H₁-receptor antagonist; Serotonergic antagonist; Dopaminergic antagonist; Alpha-adrenergic antagonist. | | |
| **Typical Antipsychotics, Miscellaneous** | | |
| **Name:** Loxapine Succinate; 27833-64-3; Loxapac; Loxapine succinate salt; Cloxazepin; Daxolin | **Pathogenic genes:** DRD1, DRD2, HTR2A | |
| **IUPAC Name:** butanedioic acid:3-chloro-6-[4-methylpiperazin-1-yl]benzo[1,4]benzoazepine | **Mechanistic genes:** DRD1, DRD2, HTR2A | |
| **Molecular Formula:** C₂₂H₂₅ClN₂O₃ | **Metabolic genes:** Substrate: CYP1A2 (major), CYP2D6 (major), CYP3A4 (major), FMOs, UGT1A4 | |
| **Molecular Weight:** 445.89606 g/mol | **Pleiotropic genes:** HTR2A | |
| **Mechanism:** Blocks postsynaptic mesolimbic D₁ and D₂ receptors in brain; also possesses serotonin 5-HT₂-blocking activity | | |
| **Effect:** Antipsychotic agent; Dopamine antagonist; Serotonergic antagonist | | |
| **Name:** Pimozide; Orap; Opiran; Neoperidole; Pimozidum; 2062-78-4 | | |
| **IUPAC Name:** 3-[1-[4,4-bis(4-fluorophenyl)butyl]piperidin-4-yl]-1H-benzimidazol-2-one | **Mechanistic genes:** ADRA1A, CACNs, DRD1, DRD2, KCNH2 | |
| **Molecular Formula:** C₂₉H₂₂F₂N₂O | **Metabolic genes:** Substrate: CYPIA2 (minor), CYP2D6 (minor), CYP3A4 (major) | |
| **Molecular Weight:** 461.546166 g/mol | **Inhibitor:** ABCB1, CYP2C19 (weak), CYP2D6 (strong), CYP2E1 (weak), CYP3A4 (raise), KCNH2 | |
| **Mechanism:** It is a potent centrally-acting dopamine-receptor antagonist resulting in its characteristic neuroleptic effects. Binds and inhibits the dopamine D₂ receptor in the CNS. It is an antagonist of ADR₂A | **Transporter genes:** KCNE1, KCNE2, KCNH2, KCNH3, KCNKS, KCNQ1, SCN5A | |
| **Effect:** Antipsychotic agent; H₁-receptor antagonist; Dopaminergic antagonist; Antidyskinesia agent; Serotonergic antagonist | **Pleiotropic genes:** CHRM2 | |
Over 100 permutated pathways may be involved in weight gain regulation in response to neuroleptics, and Genome-wide association studies (GWAS) analysis revealed that Peroxisome proliferator activated receptor gamma (PPARG) and Proprotein convertase, subtilisin/hexin-type 1 (PCSK1) are involved in antipsychotic-induced weight gain [207]. Genetic associations between pathogenic genes and genes involved in lipid metabolism cannot be ruled out as feasible links in body weight changes in response to psychotropic treatments. In fact, lipoprotein lipase (LPL), a key enzyme in triglyceride hydrolysis, is expressed in brain regions which are structural substrates of higher activities of the CNS (learning, memory, behavior, cognition), and SNPs in the LPL gene locus (8p22) (rs253 C allele) have been associated with SCZ [208].

Stimulation of the serotonin (5-HT)1A receptor (HTR1A) contributes to the mechanism of action of clozapine and lurasidone. rs358532 and rs6449693, tag SNPs for rs6295, may predict response to lurasidone [209]. The CYP1A2*1F/*1F genotype has been associated with clozapine-induced generalized tonic-clonic seizures in Brazilian patients [210]. The study of 6 SNPs in the tryptophan hydroxylase (TPH) gene (rs4570625, rs11178997, rs7954758, rs7305115, and rs4290270) revealed association of the rs10789491 and rs4565946 markers and the rs4570625-rs4565946 haplotype with SCZ. TPH2 variants and the rs4570625-rs4565946 G-C haplotype do not affect response to antipsychotic drugs [211].

Antipsychotic-related ADRs can be substantially reduced with the incorporation of PGx procedures into clinical practice [27,43,103].

5.2. Depressive Disorders

Depression is the second most common psychiatric symptom in AD, after apathy. The prevalence of depression in AD varies from 5% to >40% in different studies. Patients with severe AD show a higher prevalence of depression [212,213] and depressive symptoms are associated with a faster rate of memory decline [214]. There is evidence that early life depression can be a risk factor for later life dementia and that later life depression may represent a prodrome to dementia [215], with sex-specific differences [216], especially in cases with cerebral amyloidopathy (>50%) [217]. Furthermore, depressed patients with mild cognitive impairment (MCI) have worse cognitive performance and greater loss of gray-matter volume in the cerebellum and parahippocampal gyrus [218]. Low psychomotor speed has also been associated with an increased risk of developing dementia and depressive symptoms [219]. Cardiovascular risk factors may contribute to depression in patients with MCI [220]. Late-life depression (LLD) affects 15% of the elderly population. CYP2D6, SLC6A4 5-HTTLPR, and
brain-derived neurotrophic factor (BDNF) variants influence the PGx of this condition, as recently reported by the Clinical Pharmacogenetics Implementation Consortium [221].

Some studies indicate that the APOE genotype may influence the incidence of BDs and treatment in dementia [111,117], while others did not find association of APOE-4 with depression, anxiety, apathy, agitation, irritability, or sleep disturbances in cognitively impaired subjects [222]. Genome-wide association studies (GWAS) identified 31 genes located in 19 risk loci for major depressive disorder (MDD). Common and rare variants of L3MBTL2 are associated with AD. mRNA expression levels of SORCS3 and OAT are differentially expressed in AD brain tissues, and 13 MDD risk genes may interact with core AD genes such as HACE1, NEGR1, and SLC6A15 [223].

The treatment of depression in dementia can be pharmacological, with antidepressants, especially selective serotonin reuptake inhibitors as a first choice, or nonpharmacological (emotion-oriented therapies, behavioral, and cognitive-behavioral modification programs; structured activity programs; sensory-stimulation therapies; multisensory approaches; music therapy; and mindfulness-based interventions) [224]. Meta-analyses of double-blind randomized controlled trials comparing antidepressants versus placebo for depression in AD revealed inefficacy in most cases with different drugs (sertraline, mirtazapine, imipramine, fluoxetine, and clomipramine) [225].

The mechanisms underlying depression in dementia still remain unclarified [226]. About 60% of depressive patients receive an inappropriate medication according to their pharmacogenetic background [66,227,228], and community psychiatrists and pharmacists are more accurate in their psychotropic prescriptions when they know the CYP profile of their patients [228–230].

Antidepressants are associated with the PGx activity of over 600 genes. The different pharmacological categories of antidepressants (nonselective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, nonselective monoamine oxidase (MAO) inhibitors, and other chemical modalities) are substrates, inhibitors, or inducers of 40, 22, and 9 enzyme/protein gene products, respectively, and are transported by 13 different protein transporters (Figures 1–3 and Table 4). Enzymes of the Cytochrome P450 (CYP) family are involved in 100% of drugs approved for the treatment of depression. Antidepressants are major substrates of CYP2D6 (86%), CYP3A4 (72%), CYP2C19 (60%), CYP1A2 (57%), CYP2C9 (34%), UGT1A4 (29%), and UGT1A3 (25%); inhibitors of CYP2D6 (69%), CYP3A4 (55%), CYP1A2 (45%), CYP2C19 (45%), CYP2C9 (34%), SLC6A4 (32%), MAOA (29%), MAOB (29%), and ABCB1 (25%); and inducers of CYP3A4 (5%), CYP1A2 (5%), CYP2B6 (5%), CYP2C9 (3%), CYP2C19 (3%), CYP2D6 (3%), and ABCB1 (3%). Major transporters of antidepressants are SLC6A4 (62%), ABCB1 (55%), and SLC6A2 (40%) (Table 4). Sertraline is associated with 31 pharmagenes, Milnacipran is associated with 31, Mirtazapine is associated with 30, Fluoxetine is associated with 28, and Imipramine is associated with 28 [55,103]. The PGx of antidepressants has become quite well known over the past 20 years, with no relevant breakthroughs in the past decade [55,66].

CYP2C19 and CYP2D6 variants affect the occurrence of ADRs in patients treated with selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, sertraline, fluvoxamine, fluoxetine, and paroxetine), including anxiety, nightmares, and panic attacks associated with CYP2D6 and electrocardiogram (ECG)-prolonged QT associated with CYP2C19 [231]. Prolonged QTc interval is prevalent in patients with moderate-severe dementia, with behavioral symptoms, with global and temporal atrophy, and with leukoaraiosis [232]. A pharmacogenetic risk score has been proposed with top-scoring SNPs (rs12248560, rs878567, and rs17710780). The HTR1A rs878567 and CYP2C19 rs12248560 variants showed association with depression severity [233]. ACE variants influence mood in AD [111]. The coadministration of ACE inhibitors and statins with antidepressants may affect therapeutic outcomes [234].
## Table 4. Pharmacological profile and pharmacogenetics of selected antidepressants.

| Drug | Monoamine Oxidase Inhibitors (MAOIs) | Properties | Pharmacogenetics |
|------|--------------------------------------|------------|-----------------|
| **Name:** Moclamine; Manerix; Moclombemid | **IUPAC Name:** 4-chloro-N-[2-(morpholin-4-yl)ethyl]benzamide | **Molecular Formula:** C₁₃H₁₇ClN₂O₂ | **Pathogenic genes:** MAOA, MAOB **Mechanistic genes:** MAOA **Metabolic genes:** CYP1A2 (weak), CYP2C9 (weak), CYP2D6 (weak), MAOA (strong), MAOB (moderate) |
| **Molecular Weight:** 268.73928 g/mol | **Category:** Monoamine oxidase A inhibitors | **Mechanism:** Involves the selective, reversible inhibition of MAO-A. This inhibition leads to a decrease in the metabolism and destruction of monoamines in the neurotransmitters. This results in an increase in the monoamines. | **Effect:** Antidepressant agent; Monoamine Oxidase inhibition. |
| **Effect:** Antidepressant activity; Monoamine Oxidase inhibition. | **IUPAC Name:** (2-phenylethyl)hydrazine | **Molecular Weight:** 234.27276 g/mol | **Pathogenic genes:** MAOA, MAOB **Mechanistic genes:** MAOA, MAOB **Metabolic genes:** COMT, MAOA, MAOB **Substrate:** CYP2C8 (moderate), CYP2D6, CYP3A4 (moderate), MAOA, MAOB |
| **Category:** Monoamine oxidase inhibitors, non-selective | **Mechanism:** Irreversible, non-selective inhibition of MAO. It causes an increase in the levels of serotonin, norepinephrine, and dopamine in the neuron | **Inhibitor:** CYP1A2 (weak), CYP2C9 (weak), CYP2D6 (weak), MAOA (strong), MAOB (moderate) |
| **Effect:** Antidepressant activity; Monoamine Oxidase inhibition. | **Name:** Rasagiline mesylate; 161735-79-1; Azilect; Rasagiline mesilate; TVP-1012; Agilect | **IUPAC Name:** (1R)-N-(prop-2-yn-1-yl)-2,3-dihydro-1H-inden-1-amine | **Pathogenic genes:** PARK2 **Mechanistic genes:** BCL2, BCL2L1, MAOB **Metabolic genes:** CYP1A2 (major), CYP2D6, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B7, UGT2B15 **Inhibitor:** MAOB |
| **Molecular Formula:** C₁₃H₁₉NO₂S | **Molecular Weight:** 267.34398 g/mol | **Category:** Monoamine oxidase B inhibitors | **Mechanism:** Potent, irreversible, selective inhibitor of brain monoamine oxidase (MAO) type B, which plays a major role in catebolism of dopamine. |
| **Effect:** Antidepressant activity; Monoamine Oxidase inhibition; Neuroprotective agent; Antiparkinsonian agent. | **Effect:** Antidepressant activity; Monoamine Oxidase inhibition; Neuroprotective agent; Antiparkinsonian agent. | **Effect:** Antidepressant activity; Monoamine Oxidase inhibition; Neuroprotective agent; Antiparkinsonian agent. |
Table 4. Cont.

| Drug                                      | Properties                                                                 | Pharmacogenetics                                      |
|-------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------|
| **Tricyclics (TCA) and other MAOIs**      |                                                                           |                                                       |
| **Name:** Selegiline; Selegiline hydrochloride; L-Deprenyl hydrochloride; 14611-52-0; Eldepryl; Selegiline Hcl; Zelapar |                                                                           |                                                       |
| **IUPAC Name:** methyl(1-phenylpropan-2-yl) (prop-2-yn-1-yl)amine |                                                                           |                                                       |
| **Molecular Formula:** C_{13}H_{18}ClN |                                                                           |                                                       |
| **Molecular Weight:** 223.74172 g/mol |                                                                           |                                                       |
| **Category:** Monoamine oxidase B inhibitors |                                                                           |                                                       |
| **Mechanism:** Selective, irreversible inhibition of MAO-B. It binds to MAO-B within the nigrostriatal pathways in the central nervous system, thus blocking microsomal metabolism of dopamine and enhancing the dopaminergic activity in the substantia nigra. It may also increase dopaminergic activity through mechanisms other than inhibition of MAO-B. At higher doses, it can also inhibit MAO-A. | Pathogenic genes: MAOA, **PARK2** Mechanistic genes: MAOA, MAOB **Metabolic genes:** Substrate: CYP1A2 (minor), CYP2A6 (minor), CYP2B6 (major), CYP2C9 (minor), CYP2C19 (major), CYP2D6 (minor), CYP2E1 (minor), CYP3A4 (minor), MAOA **Inhibitor:** CYP1A2 (weak), CYP2A6 (weak), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (weak), MAOB (strong), MAOA **Transporter genes:** SCNA |
| **Effect:** Antidepressant activity; Monoamine Oxidase inhibition Neuroprotective agent; Antiparkinsonian agent. |                                                                           |                                                       |
| **Name:** Tranlycypromine sulphate; Tylciprine; Phenylcyclopromine sulfate; DL-Tranlycypromine sulfate; EINECS 236-807-1; 1-Amino-2-phenylcyclopropane sulfate |                                                                           |                                                       |
| **IUPAC Name:** (1R)-2-phenylcyclopropan-1-amine |                                                                           |                                                       |
| **Molecular Formula:** C_{18}H_{24}N_{2}O_{4}S |                                                                           |                                                       |
| **Molecular Weight:** 364.45916 g/mol |                                                                           |                                                       |
| **Category:** Monoamine oxidase inhibitors, non-selective |                                                                           |                                                       |
| **Mechanism:** It increases endogenous concentrations of epinephrine, norepinephrine, dopamine, serotonin through inhibition of MAO responsible for breakdown of these neurotransmitters | Pathogenic genes: MAOA, NTR2, SLC6A4 Mechanistic genes: MAOA, MAOB **Metabolic genes:** Substrate: CYP2A6 (major) Inhibitor: CYP1A2 (moderate), CYP2A6 (strong), CYP2C8 (weak), CYP2C9 (weak), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (weak), MAOA, MAOB **Transporter genes:** SLC6A4 **Pleiotropic genes:** FOS, NTRK2 |                                                       |
| **Effect:** Monoamine Oxidase inhibition; Antidepressant activity; Anti-anxiety activity |                                                                           |                                                       |
Table 4. Cont.

| Drug                  | Properties                                                                 |
|-----------------------|----------------------------------------------------------------------------|
| **Name**: Amitriptyline Hydrochloride; Annoyltin; Amitriptyline HCl; 549-18-8; Tryptizol; Domical |
| **IUPAC Name**: dimethyl[3-tricyclo[9.4.0.0\(^3\)\(^8\)]pentadeca-1(15),3,5,7,11,13-hexaen-2-ylidene]propyl]amine |
| **Molecular Formula**: C\(_{18}\)H\(_{24}\)N\(_{2}\)O\(_{4}\)S |
| **Molecular Weight**: 313.86426 g/mol |
| **Category**: Tricyclics |
| **Mechanism**: Increases synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibiting their reuptake in the presynaptic neuronal membrane |
| **Effect**: Adrenergic Uptake inhibition; Antimigraine activity; Analgesic (nonnarcotic) activity; Antidepressant action |
| **Pharmacogenetics**: Pathogenic genes: ABCB1, GNB3, HTRs, NTRK2, SLC6A4, TNF Mechanic genes: ADRA1A, HTRs, NTRK1, NTRK2 Metabolic genes: Substrate: ABCB1, CYP1A2 (minor), CYP2B6 (minor), CYP2C9 (minor), CYP2C15 (minor), CYP2D6 (major), CYP3A4/5 (major), GSTPI, UGT1A3, UGT1A4, UGT2B10 Inhibitor: ABCB1, ABC22, ABCG2, CYP1A2 (moderate), CYP2C9 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak) Transporter genes: ABCB1, ABC22, ABCG2, KCNE2, KCNH2, KCNQ1, SCN5A, SLC6A4 Pleiotropic genes: FABP1, GNAS, GNB3, NTRK1, TNF |

| **Name**: Amoxapine; Asendin; Demolox; 14028-44-5; Asendis; Moxadi |
| **IUPAC Name**: 13-chloro-10-(piperazin-1-yl)-2-oxa-9-azatricyclo[9.4.0.0\(^3\)\(^8\)]pentadeca-1(15),3,5,7,9,12,14-heptaene |
| **Molecular Formula**: C\(_{20}\)H\(_{26}\)ClN\(_{3}\)O |
| **Molecular Weight**: 313.78142 g/mol |
| **Category**: Tricyclics |
| **Mechanism**: Reduces reuptake of serotonin and norepinephrine. The metabolite, 7-OH-amoxapine, has significant dopamine receptor-blocking activity |
| **Effect**: Serotonin uptake inhibition; Adrenergic uptake inhibition; Dopamine antagonism; Neurotransmitter uptake inhibition; Antidepressant action; Anti-anxiety activity |
| **Pharmacogenetics**: Pathogenic genes: GNB3, SLC6A4 Mechanic genes: ADRA1A, ADRA2A, CHRMs, DRD1, DRD2, GABRs, GABBRs, HTRs Metabolic genes: Substrate: CYP2D6 (major) Transporter genes: SLC6A2, SLC6A4 Pleiotropic genes: DRD2, GNAS, GNB3 |
Name: Desipramine Hydrochloride; Norpromin; Desipramine HCl; DMI hydrochloride; Pertofran; Pertofran

IUPAC Name: (3-{2-azatricyclo[9.4.0.0^3,8]pentadeca-1(15),3,5,7,11,13-hexaen-2-yl}(methyl)amine

Molecular Formula: C_{19}H_{25}ClN_{2}

Molecular Weight: 302.84162 g/mol

Category: Tricyclics

Mechanism: Increases the synaptic concentration of norepinephrine in the CNS by inhibition of its reuptake by the presynaptic neuronal membrane. Additional receptor effects including desensitization of adenylyl cyclase, down-regulation of β-adrenergic receptors, and down-regulation of serotonin receptors

Effect: Enzyme inhibition; Adrenergic uptake inhibition; Antidepressant action; Analgesic activity

Pathogenic genes: ABCB1, CYP2C9, CYP2D6 (major)
Mechanistic genes: ADRA1A, ADRB5, CHRMs, HTR1A, HTR1B, HTR2A, HTR3
Metabolic genes: Substrate: CYP2A6 (major), CYP2C9, CYP2B6, CYP2C19 (major), CYP2D6 (minor), CYP3A4 (major), CYP3A5 (major), UGT1A4
Inhibitor: CYP2C9 (moderate), CYP2C19 (strong), CYP2D6 (moderate), GSTP1, SLC6A4
Transporter genes: SLC6A4, SLC22A3
Pleiotropic genes: FABP1, PTGS2

Name: Clomipramine Hydrochloride; Anafranil; Clomipramine HCl; 17321-77-6; Anaphranil; 3-(3-chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N,N-dimethylpropan-1-amine hydrochloride

IUPAC Name: (3-{14-chloro-2-azatricyclo[9.4.0.0^3,8]pentadeca-1(15),3,5,7,11,13-hexaen-2-yl}(methyl)amine

Molecular Formula: C_{18}H_{23}ClN_{2}

Molecular Weight: 351.31326 g/mol

Category: Tricyclics

Mechanism: Increases the synaptic concentration of norepinephrine in the CNS by inhibition of its reuptake by the presynaptic neuronal membrane. Additional receptor effects including desensitization of adenylyl cyclase, down-regulation of β-adrenergic receptors, and down-regulation of serotonin receptors

Effect: Serotonin uptake inhibition; Antidepressant action; Anti-anxiety activity; Antiobsessional effects; Analgesic effects

Pathogenic genes: HTR2A, SLC6A4
Mechanistic genes: ADRA1s, CHRMs, CHRNs, HRH1, HTR2s, HTR3
Metabolic genes: Substrate: CYP1A2 (major), CYP2A6, CYP2B6, CYP2C19 (major), CYP2D6 (minor), CYP3A4 (major), CYP3A5 (major), UGT1A4
Inhibitor: CYP2C9 (moderate), CYP2C19 (strong), CYP2D6 (moderate), GSTP1, SLC6A4
Transporter genes: SLC6A4, SLC22A3
Pleiotropic genes: FABP1, PTGS2

| Table 4. Cont. |
|----------------|
| **Tricyclics (TCA) and other Norepinephrine uptake inhibitors** |
| **Drug** | **Properties** | **Pharmacogenetics** |
|----------------|----------------|----------------------|
| Name: Clomipramine Hydrochloride; Anafranil; Clomipramine HCl; 17321-77-6; Anaphranil; 3-(3-chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N,N-dimethylpropan-1-amine hydrochloride | IUPAC Name: (3-{14-chloro-2-azatricyclo[9.4.0.0^3,8]pentadeca-1(15),3,5,7,11,13-hexaen-2-yl}(methyl)amine | Molecular Formula: C_{18}H_{23}ClN_{2} |
| Molecular Weight: 351.31326 g/mol | Category: Tricyclics | Pathogenic genes: HTR2A, SLC6A4 |
| Mechanism: Increases the synaptic concentration of norepinephrine in the CNS by inhibition of its reuptake by the presynaptic neuronal membrane. Additional receptor effects including desensitization of adenylyl cyclase, down-regulation of β-adrenergic receptors, and down-regulation of serotonin receptors | Effect: Serotonin uptake inhibition; Antidepressant action; Anti-anxiety activity; Antiobsessional effects; Analgesic effects | Mechanistic genes: ADRA1s, CHRMs, CHRNs, HRH1, HTR2s, HTR3 |
| Metabolic genes: Substrate: CYP1A2 (major), CYP2A6, CYP2B6, CYP2C19 (major), CYP2D6 (minor), CYP3A4 (major), CYP3A5 (major), UGT1A4 | Inhibitor: CYP2C9 (moderate), CYP2C19 (strong), CYP2D6 (moderate), GSTP1, SLC6A4 | Transporter genes: SLC6A4, SLC22A3 |
| Pleiotropic genes: FABP1, PTGS2 |

| Name: Desipramine Hydrochloride; Norpromin; Desipramine HCl; DMI hydrochloride; Pertofran; Pertofran | IUPAC Name: (3-{2-azatricyclo[9.4.0.0^3,8]pentadeca-1(15),3,5,7,11,13-hexaen-2-yl}(methyl)amine | Molecular Formula: C_{19}H_{25}ClN_{2} |
| Molecular Weight: 302.84162 g/mol | Category: Tricyclics | Pathogenic genes: ABCB1, CRHR1, CRHR2, FKBP5, HTR1A, IL1B, NR3C1, NTRK2, PDE5A, SLC6A4, THX21 |
| Mechanism: Increases the synaptic concentration of norepinephrine in the CNS by inhibition of its reuptake by the presynaptic neuronal membrane. Additional receptor effects including desensitization of adenylyl cyclase, down-regulation of β-adrenergic receptors, and down-regulation of serotonin receptors | Effect: Enzyme inhibition; Adrenergic uptake inhibition; Antidepressant action; Analgesic activity | Mechanistic genes: ADcy1, ADRA1A, ADRB5, CHRMs, HTR1A, IFNA1, PDE1C, PSMD9, PRKCSH, STAT3 |
| Metabolic genes: Substrate: CYP1A2 (minor), CYP2C9, CYP2D6 (major) | Inhibitor: ABCB1, CYP2A6 (moderate), CYP2B6 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (moderate), SLC6A2, SLC22A3 | Transporter genes: ABCB1, SLC6A2, SLC6A3, SLC6A4, SLC22A3 |
| Pleiotropic genes: NTRK2, FOS |
Tricyclics (TCA) and other Norepinephrine reuptake inhibitors

| Drug                          | Properties                                                                 | Pharmacogenetics                                                                 |
|-------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Name:** Doxepin Hydrochloride; Silenor; Adapin; Novoxapin; Toruan; Curatin | **IUPAC Name:** dimethyl(3-(9-oxatricyclo[9.4.0.0³,⁸]pentadeca-1(15),3,5,7,11,13-hexaen-2-ylidene)propyl)amine  |
| **Molecular Formula:** C₁₉H₂₅ClN₂ | **Molecular Weight:** 315.83708 g/mol | **Mechanism:** It increases the synaptic concentration of serotonin and norepinephrine in the CNS by inhibition of their reuptake by the presynaptic neuronal membrane  |
| **Effect:** Adrenergic uptake inhibition; Histamine Antagonism; Antidepressant action; Analgesic effects; Pruritus reduction | **Pathogenic genes:** ABCB1, SLC6A4  |
| **Mechanistic genes:** ADRBs, CHRMs, HRH1, HRH2, HTRs  |
| **Metabolic genes:** | **Substrate:** CYP1A1 (minor), CYP1A2 (minor), CYP2C9 (minor), CYP2C19 (major), CYP2D6 (major), CYP3A4/5 (minor), GSTP1, UGT1A3, UGT1A4 |
| **Inhibitor:** CYP2C19 (strong), CYP2D6 (moderate)  |
| **Transporter genes:** ABCB1, KCNH2, SLC6A2, SLC6A4  |
| **Name:** Imipramine Hydrochloride; Tofranil; Imipramine Hcl; 113-52-0; Chimoreptin; Feinalmin | **IUPAC Name:** (3-(2-azatricyclo[9.4.0.0³,⁸]pentadeca-1(15),3,5,7,11,13-hexaen-2-yl)propyl)dimethylamine  |
| **Molecular Formula:** C₁₉H₂₂ClNO | **Molecular Weight:** 316.8682 g/mol | **Mechanism:** It binds the sodium-dependent serotonin transporter and sodium-dependent norepinephrine transporter preventing or reducing the reuptake of norepinephrine and serotonin by nerve cells. It causes down-regulation of cerebral cortical beta-adrenergic receptors  |
| **Effect:** Adrenergic uptake inhibition; Antidepressant action; Antienuretic effects; Analgesic activity; attention enhancer | **Pathogenic genes:** ABCB1, BDNF, HTR2A, SLC6A4  |
| **Mechanistic genes:** ADRB2, DRD2, CHRMs, HTR2A, SCNs  |
| **Metabolic genes:** | **Substrate:** CYP1A2 (minor), CYP2B6 (minor), CYP2C19 (major), CYP2D6 (major), CYP3A4 (minor), CYP3A7, GSTP1, UGT1A3, UGT1A4, UGT2B10 |
| **Inhibitor:** CYP1A2 (weak), CYP2C9 (moderate), CYP2C19 (weak), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (moderate), FMO1, SLC22A2, SLC22A3  |
| **Transporter genes:** ABCB1, SLC6A2, SLC6A4, SLC22A2, SLC22A3  |
| **Pleiotropic genes:** ADRB2, BDNF, FABP1, FOS, ORMI  |
### Table 4. Cont.

| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Name:** Nortriptyline Hydrochloride; Pamelor; Allegron; Altilev; Nortrilen; 894-71-3 | | Pathogenic genes: ABCB1, GNB3, HTR1B, NR3C1, SLC6A4 |
| | IUPAC Name: methyl[3-(tricyclo[9.4.0.0³,8]pentadeca-1(15),3,5,7,11,13-hexa-2-ylidene)propyl]amine | Mechanistic genes: ADCY1, ADRA2s, ADRB1s, GNB3, HRH1, HTR2 |
| | Molecular Formula: C$_{19}$H$_{22}$ClN | Metabolic genes: |
| | Molecular Weight: 299.83768 g/mol | Substrate: CYP1A2 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4 (minor), UGTs |
| | Category: Tricyclics | Inhibitor: CYP2C8 (moderate), CYP2C9 (moderate), CYP2C19 (moderate), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (moderate) |
| | Mechanism: Inhibits the reuptake of the neurotransmitter serotonin at the neuronal membrane or acts at beta-adrenergic receptors. It has additional receptor effects including desensitization of adenyl cyclase, down-regulation of β-adrenergic receptors, and down-regulation of serotonin receptors | Transporter genes: ABCB1, SLC6A2, SLC6A4 |
| | Effect: Adrenergic uptake inhibitor; Antidepressant agent; Analgesic activity; Hypno-sedative activity | Pleiotropic genes: HTR1B |
| **Name:** Protriptyline Hydrochloride | | |
| | IUPAC Name: methyl[3-(tricyclo[9.4.0.0³,8]pentadeca-1(15),3,5,7,11,13-hexa-2-ylidene)propyl]amine | Mechanistic genes: SLC6A2, SLC6A4 |
| | Molecular Formula: C$_{19}$H$_{22}$ClN | Metabolic genes: |
| | Molecular Weight: 299.83768 g/mol | Substrate: CYP1A2 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4 (minor) |
| | Category: Tricyclics | Inhibitor: CYP1A2 (moderate), CYP2C9 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP3A4 (moderate) |
| | Mechanism: Increases synaptic concentration of serotonin and/or norepinephrine in CNS by inhibition of their reuptake by presynaptic neuronal membrane | Transporter genes: SLC6A2, SLC6A4 |
| | Effect: Adrenergic uptake inhibitor; Antidepressant agent; Analgesic activity; Anti-migraine effect | Pleiotropic genes: ADRA1A, GNAS, ITGB3 |
| **Name:** Trimipramine; Sapient; Surmontil; Beta-Methyl trimipramine, Trimiprime | | Pathogenic genes: ABCB1, SLC6A4 |
| | IUPAC Name: (3-[2-azatricyclo[9.4.0.0³,8]pentadeca-1(15),3,5,7,11,13-hexa-2-ylidene-2-methyl]propyl) dimethylamine | Mechanistic genes: SLC6A2, SLC6A4, SLC22A1, SLC22A2 |
| | Molecular Formula: C$_{20}$H$_{26}$N$_{2}$ | Metabolic genes: |
| | Molecular Weight: 294.43384 g/mol | Substrate: CYP2C19 (major), CYP2D6 (major), CYP3A4/5 (major) |
| | Category: Tricyclics | Inhibitor: ABCB1 |
| | Mechanism: Increases synaptic concentration of serotonin and/or norepinephrine in CNS by inhibition of their reuptake by presynaptic neuronal membrane | Transporter genes: SLC6A2, SLC6A4, SLC22A1, SLC22A2 |
| | Effect: Adrenergic uptake inhibition; Antidepressant action; Antihistaminic activity; Sedative effect | |
Table 4. Cont.

| Drug                        | Properties                                                                 | Pharmacogenetics                                      |
|-----------------------------|----------------------------------------------------------------------------|-------------------------------------------------------|
| **Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRI)** |                                                                            |                                                       |
| **Name: Desvenlafaxine;**   | O-Desmethylvenlafaxine; 93413-62-8; 4-(2-Dimethylamino)-1-1-(hydroxy-    | Pathogenic genes: ABCB1, SLC6A4                        |
|                             | cyclohexyl)ethyl)phenol; 4-[2-(Dimethylamino)-1-1-(hydroxy-cyclohexyl)ethyl]phenol; Desvenlafaxine (INN) | Mechanistic genes: HTR1A, SLC6A2, SLC6A3, SLC6A4   |
|                             | Molecular Formula: C_{17}H_{28}ClNO2                                        | Metabolic genes:                                      |
|                             | Molecular Weight: 263.3752 g/mol                                             | Substrate: CYP3A4 (minor), UGTs                       |
|                             | Mechanism: It is a potent and selective serotonin and norepinephrine reuptake inhibitor | Inhibitor: CYP2D6 (weak), SLC6A2, SLC6A4             |
|                             | Effect: Serotonin uptake inhibition; Norepinephrine uptake inhibition;     | Transporter genes: ABCB1, SLC6A2, SLC6A4             |
|                             | Antidepressant activity                                                     |                                                       |
| **Name: Duloxetine Hydrochloride;** | 13643-34-9; Duloxetine HCl; Cymbalta; (S)-N-Methyl-3-(naphthalen-1-    | Pathogenic genes: ABCB1, SLC6A4                        |
|                             | 1-oxy)-3-(thiophen-2-yl)propyl]amine                                         | Mechanistic genes: COMT, HTR1A, SLC6A2, SLC6A4       |
|                             | Molecular Formula: C_{18}H_{29}ClNOS                                         | Metabolic genes:                                      |
|                             | Molecular Weight: 333.8755 g/mol                                              | Substrate: CYP1A2 (major), CYP2D6 (major)             |
|                             | Mechanism: It is a selective serotonin- and norepinephrine-reuptake inhibitor and a weak inhibitor of dopamine reuptake | Inhibitor: ABCB1, CYP1A2 (moderate), CYP2B6 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP3A4 (moderate), SLC6A2, SLC6A4 |
|                             | Effect: Antidepressant activity; Anti-anxiety activity; Serotonin uptake inhibition; Norepinephrine uptake inhibition; Anti-Fibromyalgia agent; Analgesic activity; Urinary continence improvement | Transporter genes: ABCB1, SLC6A2, SLC6A4             |
| **Name: Levomilnacipran;**  | UNII-UGM0326TXX; UGMii326TXX; Fetzima; (1S,2R)-2-(aminomethyl)-N,NN-diethyl-1-phenylcyclopropane-1-carboxamide; F2695 |                                                       |
|                             | Molecular Formula: C_{15}H_{26}N_{2}O                                         |                                                       |
|                             | Molecular Weight: 246.34798 g/mol                                              |                                                       |
|                             | Mechanism: Potentiation of serotonin and norepinephrine in the central nervous system through inhibition of reuptake at serotonin and norepinephrine transporters |                                                       |
|                             | Effect: Serotonin uptake inhibition; Norepinephrine uptake inhibition;     |                                                       |
|                             | Antidepressant activity                                                       |                                                       |
### Table 4. Cont.

#### Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRI)

| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Name:** Milnacipran Hydrochloride; Toledomin; Midalcipran; Ixel; Savella; Milnacipranum | **IUPAC Name:** (1R,2S)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropene-1-carboxamide | **Pathogenic genes:** BDNF, CYP2C19 (minor), CYP2D6 (minor)  **Mechanistic genes:** ADRA2A, BDNF, SLC6A4, SLC6A6  **Metabolic genes:** **Substrate:** COMT, CYP1A2 (minor), CYP2A6 (minor), CYP2B6 (minor), CYP2C8, CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (minor), CYP2E1 (minor), CYP3A45 (minor), CYP4F2, CYP4F8  **Inhibitor:** CYP3A45 (moderate)  **Inducer:** CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A45  **Transporter genes:** SLC6A2, SLC6A4  **Pleiotropic genes:** DRD2, HTR2A, HTR2C, HTR2D, HTR2F, HTR2H, HTR6, HTR7, HTR8, MAOA, MAOB, SLC6A4, TPH1, TPH2, TH | **Mechanism:** Active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake  **Effect:** Serotonin uptake inhibition; Norepinephrine uptake inhibition; Antidepressant activity; Anti-anxiety activity; Sustained effects |

| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Name:** Venlafaxine Hydrochloride; 99300-78-4; VENLAFAXINE HCl; Effexor XR; Dobupal; Trevilor | **IUPAC Name:** 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol | **Pathogenic genes:** ABCB1, BDNF, CREB1, FKBPs, HTR1A, HTR2A, NR3C1, SLC6A3, SLC6A4, TPH2  **Mechanistic genes:** BDNF, FKBPs  **Metabolic genes:** **Substrate:** ABCB1, CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4 (major)  **Inhibitor:** ABCB1, CYP1A2 (weak), CYP2B6 (weak), CYP2D6 (weak), CYP3A4 (weak), SLC6A2, SLC6A3, SLC6A4  **Transporter genes:** ABCB1, ABC1, ABCG2, SLC6A2, SLC6A3, SLC6A4  **Pleiotropic genes:** DRD2, HTR2A, HTR2D, HTR2F, HTR2H, HTR6, HTR7, HTR8, MAOA, MAOB, SLC6A4, TPH1, TPH2, TH | **Mechanism:** Active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake  **Effect:** Serotonin uptake inhibition; Norepinephrine uptake inhibition; Antidepressant activity; Anti-anxiety activity; Sustained effects |

#### Selective Serotonin Reuptake Inhibitors (SSRI)

| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Name:** Citalopram Hydrobromide; Nitalapram; Cipram; Celexa; Celaapram; Cipripine | **IUPAC Name:** 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile | **Pathogenic genes:** ABCB1, BDNF, CREB1, CRHR1, CRHR2, FKBPs, GRIA3, GRIK2, GRIK4, GSK3β, HTR1A, HTR1B, HTR2A, MAOA, SLC6A4, TPH1, TPH2  **Mechanistic genes:** ADRs, CHRM5s, DRDs, FKBPs, GABRs, GRIK4, HRHs, HTR1A, HTR1B, HTR1D, HTR2A, SLC6A4, TPH1  **Metabolic genes:** **Substrate:** ABCB1, COMT, CYP2C19 (major), CYP2D6 (minor), CYP3A4 (major), CYP3A5  **Inhibitor:** ABCB1, CYP1A2 (weak), CYP2B6 (weak), CYP2C19 (weak), CYP2D6 (weak), MAOA, MAOB  **Transporter genes:** ABCB1, SLC6A4  **Pleiotropic genes:** BDNF | **Mechanism:** Selectively inhibits serotonin reuptake in the presynaptic neurons and has minimal effects on norepinephrine or dopamine  **Effect:** Serotonin uptake inhibition; Serotonergic neurotransmission enhancer; Antidepressive activity, Agitation reduction, Anti-Anxiety activity |
| Name                  | Molecular Formula | Molecular Weight | Mechanism                                      | Effect                                                      | Pharmacogenetics                                                                 |
|-----------------------|-------------------|------------------|------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------|
| Escitalopram oxalate; Lexapro; Cipralex; 219861-08-2; UNII-5U5DBW7L0; Esertia | C_{17}H_{23}FNO | 441.42623 g/mol | Inhibits the reuptake of serotonin with little to no effect on norepinephrine or dopamine reuptake. It has very high affinity for 5-HT1 and α - and β-adrenergic. D_{3}, H_{1}, M_{3}, and benzodiazepine receptors | Serotonin uptake inhibition; Serotonergic neurotransmission enhancer; Antidepressive activity; Anti-anxiety activity | Pathogenic genes: ABCB1, CREB1, FKBP5, GRI1A3, GRIK2, GRIK4, NR3C1, SLC6A4 |
| Fluoxetine Hydrochloride; Prozac; Fluoxetine Hcl; 59333-67-4; Sarafem; Fluctin | C_{17}H_{19}ClF_{3}NO | 345.78707 g/mol | Potentiates serotonin activity in CNS resulting from its inhibition of CNS neuronal reuptake of serotonin. | Serotonin agent; Antidepressive activity; Anti-obssesive activity; Anti-anxiety activity; Anorexigenic effects | Pathogenic genes: ABCB1, BDNF, CREB1, FKBP5, GSK3B, GSK3B, TRH1A, TRH2A, MAOA, NR3C1, NTRK2, SLC6A4, TBX21, TRH1, TRH2 |
| Fluvoxamine Maleate; Luvox; 61718-82-9; Favarin; Faverin; Flosyfrol | C_{19}H_{25}F_{3}N_{2}O_{6} | 434.40681 g/mol | Inhibits CNS neuron serotonin uptake. | Antidepressive activity; Anti-anxiety activity; Serotonin uptake inhibition. | Pathogenic genes: BDNF, HTR2A, SIGMAR1, TRH1 |
| Parietel; Prilosec; Prilosec OTC; Zegerid | C_{18}H_{26}NO_{3} | 329.3836 g/mol | Does not cause any anticholinergic effect. | | |
Table 4. Cont.

| Drug                              | Properties                                                                 | Pharmacogenetics                                      |
|-----------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------|
| **Selective Serotonin Reuptake Inhibitors (SSRI)** |                                                                           |                                                        |
| **Name:** Paroxetine; Paxil; Aropax; Paxil CR; Seroxat; Pexeva              |                                                                           | Pathogenic genes: ABCB1, CREB1, HTR1B, HTR2A, HTR3B, MAOA, SLC6A3, SLC6A4, TRH, THP1, THP2 |
| **IUPAC Name:** (3S,4R)-3-[2H-1,3-benzo[d]oxol-5-yl]oxy)methyl]-4-(4-fluorophenyl)piperidine |                                                                           | Mechanic genes: CREB1, HTR2A, HTR3A, SLC6A4, TRH, THP1, THP2 |
| **Molecular Formula:** C$_{15}$H$_{20}$FNO$_3$                              |                                                                           |                                                        |
| **Molecular Weight:** 329.365403 g/mol                                       |                                                                           |                                                        |
| **Mechanism:** It is an SSRI. Presumably acts by inhibiting serotonin reuptake from brain synapse stimulating its activity in the brain |                                                                           |                                                        |
| **Effect:** Serotonin uptake inhibition; Serotonergic neurotransmission enhancer; Antidepressant activity; Anti-anxiety activity; Anti-obssesive activity |                                                                           |                                                        |
| **Name:** Sertraline Hydrochloride; 79559-97-0; Sertraline HCl; Zolofit; Lustral; Gladem |                                                                           | Pathogenic genes: ABCB1, CREB1, GNB3, HTR1B, MAOA, SIGMAR1, SLC6A4, TRH, THP1, THP2 |
| **IUPAC Name:** (1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine |                                                                           | Mechanic genes: HTR1B, HTR1D, SIGMAR1, SLC6A2, SLC6A3, SLC6A4, TRH | Metabolic genes: 
| **Molecular Formula:** C$_{17}$H$_{18}$Cl$_{3}$N                             |                                                                           |                                                        |
| **Molecular Weight:** 342.6952 g/mol                                         |                                                                           |                                                        |
| **Mechanism:** It has selective inhibitory effects on presynaptic serotonin reuptake and only very weak effects on norepinephrine and dopamine neuronal uptake |                                                                           |                                                        |
| **Effect:** Serotonin uptake inhibition; Serotonergic neurotransmission enhancer; Antidepressant activity; Anti-anxiety activity; Anti-obssesive activity |                                                                           |                                                        |

**Serotonin Modulators**

| Drug                              | Properties                                                                 | Pharmacogenetics                                      |
|-----------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------|
| **Name:** Nefazodone Hydrochloride; Serzone; Nefazodone Hcl; Dutonin; 82752-99-6; Menfazon |                                                                           | Pathogenic genes: ABCB1, HTR1A, HTR2A |
| **IUPAC Name:** 1-[3-[4-(3-chlorophenyl)piperazin-1-yl][propyl]-3-ethyl-4-(2-phenoxyethyl)-4,5-dihydro-1H-1,2,4-triazol-5-one |                                                                           | Mechanic genes: ADRA1A, HTR1s, HTR2s |
| **Molecular Formula:** C$_{25}$H$_{25}$Cl$_{2}$N$_{2}$O$_{2}$                  |                                                                           |                                                        |
| **Molecular Weight:** 506.46782 g/mol                                           |                                                                           |                                                        |
| **Mechanism:** Blocks potently and selectively postsynaptic 5-HT$_{2A}$ receptors and moderately inhibits serotonin and noradrenaline reuptake. Also blocks 5-HT receptors. Antagonist of adrenoreceptors alpha 1 and 5-hydroxytryptamine receptors 2 |                                                                           |                                                        |
| **Effect:** Serotonin uptake inhibition; Noradrenaline uptake inhibition; Alpha-adrenergic antagonism; Antidepressant activity; Muscle relaxation, Sedation |                                                                           |                                                        |
### Table 4. Cont.

| Drug                              | Properties                                                                 | Pharmacogenetics                  |
|-----------------------------------|---------------------------------------------------------------------------|-----------------------------------|
| **Serotonin Modulators**          |                                                                           |                                   |
| Name: Trazodone Hydrochloride; Desyrel; 25332-39-2; Trazodone HCl; Molipaxin; Trittico |                                                                        | Pathogenic genes: ABCB1, GNB3, HTR1A, HTR2A, SLC6A4  |
| IUPAC Name: 2-(3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-2H,3H-[1,2,4]triazolo [4,3-a]pyridin-3-one |                                                                        | Mechanistic genes: ADRA1s, ADRA2s, HRH1, HTR2A, HTR2C  |
| Molecular Formula: C_{19}H_{23}Cl_{2}N_{5}O |                                                                        | Metabolic genes:                  |
| Molecular Weight: 408.32482 g/mol |                                                                        | Substrate: CYP1A2 (minor), CYP2D6 (minor), CYP3A4 (major), GSTs, SOD2  |
| Mechanism: Inhibits reuptake of serotonin, causes adrenoreceptor subsensitivity, and induces significant changes in 5-HT presynaptic receptor adrenoreceptors. Also significantly blocks histamine (H_{1}) and α_1-adrenergic receptors. |                                                                        | Inhibitor: CYP2D6 (moderate), CYP3A4 (weak), SLC6A4  |
| Effect: Serotonin uptake inhibitor; Anti-anxiety activity; Antidepressant agent; Hypnotic effects |                                                                        | Inducer: ABCB1  |
| **Miscellaneous Antidepressants** |                                                                           |                                   |
| Name: Agomelatine; 138112-76-2; Valdoxan; Thymenanx; Melitor; N-(2-(7-methoxyphenylamino)-1-yl)ethylacetamide |                                                                        | Pathogenic genes: SLC6A3, SLC6A4  |
| IUPAC Name: N-[2-(7-methoxyphenylamino)-1-yl]ethylacetamide |                                                                        | Mechanistic genes: ADRA1A, CHRNB2, DRD2  |
| Molecular Formula: C_{15}H_{17}NO_{2} |                                                                        | Metabolic genes:                  |
| Molecular Weight: 243.30098 g/mol |                                                                        | Substrate: CYP1A1 (major), CYP1A2 (major), CYP2C9 (minor), CYP2C19 (minor)  |
| Category: Melatonergic agonist and 5-HT2C antagonists |                                                                        | Mechanistic genes: HTR2C, MTR1A, MTRN1B  |
| Mechanism: It behaves as an agonist at melatonin receptors and as an antagonist at serotonin (5-HT)(2C) receptors |                                                                        | Metabolic genes:                  |
| Effect: Norepinephrine-dopamine disinhibitor; Antidepressant activity; Anti-anxiety activity; Sleep induction; Circadian rhythms resynchronization; Psychological excitement reduction |                                                                        | Substrate: COMT, CYP1A2 (minor), CYP2A6 (minor), CYP2B6 (major)  |
| **Miscellaneous Antidepressants** |                                                                           |                                   |
| Name: Bupropion Hydrochloride; 31677-93-7; Wellbutrin; Zyban; Bupropion Hcl |                                                                        | Pathogenic genes: SLC6A3, SLC6A4  |
| IUPAC Name: 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one |                                                                        | Mechanistic genes: ADRA1A, CHRNB2, DRD2  |
| Molecular Formula: C_{13}H_{16}Cl_{2}NO |                                                                        | Metabolic genes:                  |
| Molecular Weight: 276.20206 g/mol |                                                                        | Substrate: CYP2A6 (minor), CYP2B6 (major)  |
| Category: Dopamine-Reuptake Inhibitor |                                                                        | Inhibitor: CYP2D6 (strong)  |
| Mechanism: It is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine |                                                                        | Transporter genes: SLC6A2, SLC6A3, SLC6A4  |
| Effect: Dopamine uptake inhibition; Anti-addiction/Substance abuse treatment agent; Smoking cessation enhancer; Antidepressant activity |                                                                        | Pleiotropic genes: DRD2  |
Anxiety is a risk factor for dementia [239, 240], and anxiety-like behaviors are persistent in patients with (T-50C and GSK3-beta*C), BDNF. 5.3. Anxiety Disorders show a better response to lithium), and dose adjustment is highly recommended in patients with the following genotypes: the PGx background of each patient [238]. Lithium PGx is very complex. Caution and personalized treatment agent; Smoking cessation. Anti-addiction/Substance abuse. Mechanism: It has central presynaptic α2-adrenergic antagonist effects, which result in increased release of norepinephrine and serotonin. Also a potent antagonist of 5-HT2 and 5-HT3 serotonin receptors, H1 histamine receptors and a moderate peripheral α1-adrenergic and muscarinic antagonist. Effect: Histamine H1 antagonism; Adrenergic alpha-antagonism; Antidepressant activity; Anxiolytic effects. Pathogenic genes: ABCB1, FKBP5, HTR1A, HTR2A, MAOA, SLC6A3, SLC6A4, TPH2. Mechanistic genes: ADRAl, ADRA2A, CHRMs, FKBP5, HRH1, HTR2, HTR3s. Metabolic genes: Substrate: CYP1A2 (major), CYP2C9 (minor), CYP2D6 (major), CYP3A4 (major), UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B, UGT2B1S. Inhibitor: CYP1A2 (weak), CYP3A4 (weak). CYP2D6 (weak), MAOA, MAOB. Inducer: CYP1A2, CYP2D6, CYP3A4. Transporter genes: ABCB1, SLC6A3, SLC6A4. Pleiotropic genes: TPH2. The influence of PGx factors on the pharmacogenetics and pharmacodynamics of many antidepressants has been reasonably well documented [55, 66, 235–237]; however, important aspects such as body weight gain, suicidality, cyclothymic reactions, cardiovascular risks, and potential neurotoxicity still remain obscure [55]. Lithium is the gold standard for the treatment of bipolar disorder (BPD) and BPD-like symptoms in a reduced number of cases with dementia. The response to lithium is very variable and depends on the PGx background of each patient [238]. Lithium PGx is very complex. Caution and personalized dose adjustment is highly recommended in patients with the following genotypes: BCR (Asn796Ser), BDNF (C/G (rs987478) and G/A (Val66Met)), CACNG2 (rs2284017, rs2284018, and rs3750285), GSK3B (T-50C and GSK3-beta*C), INPP1 (C973A and rs1882891), mtDNA (carriers of the 0398A polymorphism show a better response to lithium), NTRK2 (rs1387923 and rs1565445), and variants in other genes (ABCG2, CCND1, CREB1, DRD1, ESR1, FMR1, GRK2, IMPA1, IMPA2, NR3C1, PTGES, SLC6A4, and VEGFA) [55, 56, 238]. 5.3. Anxiety Disorders Anxiety-like disorders are present in 30–40% of cases with dementia during the disease process. Anxiety is a risk factor for dementia [239, 240], and anxiety-like behaviors are persistent in patients with
dementia. Early-onset AD patients exhibit greater prevalence of all BDs, especially anxiety, irritability, and sleep disorders [241].

The neurobiology of anxiety in dementia is unknown. Subjective cognitive decline (SCD) (self-reported cognitive deficits), without measurable cognitive impairment, has been associated with brain structural alterations and APOE-4. SCD cases show decreased total cortical volumes and cortical surface area, which are especially prominent in APOE-4 carriers. Anxiety symptoms are negatively associated with the right cortical surface area in APOE-4 noncarriers with SCD [242]. Depression, anxiety, and cerebrovascular risk contribute to SCD [243].

Benzodiazepines are currently prescribed for ameliorating this symptomatology; however, benzodiazepines contribute to cognitive and psychomotor dysfunction [244].

5.4. Sleep Disorders

Chronic sleep disorders might represent a risk factor for dementia, and alterations in circadian rhythms and consequent sleep disorders are common in AD and age-related disorders [245–248]. The neurobiology of circadian rhythms in AD is not well documented. Different neurotransmitters influence circadian changes and sleep disorders (insomnia, parasomnias, circadian rhythm sleep-wake disorders, hypersonolence, sleep-related movement disorders, and sleep-related breathing disorders), including melatonin, histamine, GABA, hypocretin, dopamine, noradrenaline, serotonin, and adenosine. Genomic alterations in these systems (e.g., pathogenic genes) may affect the efficacy and safety of anxiolytics and hypnotics used in the treatment of some of these disorders [55].

Over 100 genes have been associated with sleep disorders in AD [249]. In the triple transgenic AD mouse model (3×Tg-AD), there is an abnormal expression of Per genes in the suprachiasmatic nucleus (SCN) [250]. The glymphatic system might be an effective mechanism of brain Aβ-amyloid clearance particularly effective during sleep. Aquaporin-4 may play a role in glymphatic function, since ablation of Aquaporin-4 results in impairment of Aβ clearance mechanism and increased brain Aβ-amyloid deposition. The AQP4 variant rs72878776 is associated with poorer overall sleep quality, and other SNPs might moderate the effect of sleep latency (rs491148, rs9951307, rs7135406, rs3875089, and rs151246) and duration (rs72878776, rs491148, and rs2339214) on brain Aβ-amyloid burden [251]. Homer1a and mGluR1/5 are implicated in sleep function to weaken synapses during sleep and to restore synapse homeostasis [252].

Evening secretion of melatonin is delayed and mildly impaired in patients with AD [253]. Rapid eye movement (REM) sleep influences memory consolidation. Noradrenaline participates in the regulation of REM sleep to maintain neuronal integrity and brain house-keeping functions [254].

Sleep dysfunction and Aβ deposition show synergistic effects to impair brain function. Brain Aβ deposition is associated with subjective measures of sleep quality and cognition. Nocturnal awakenings are associated with Aβ deposition in the precuneus and poor cognitive performance [255]. Extracellular levels of Aβ and tau show a fluctuating pattern during the normal sleep-wake cycle. Increased wakefulness and disturbed sleep lead to increased Aβ production and decreased Aβ clearance; additionally, chronic wakefulness increases Aβ aggregation and deposition, and Aβ accumulation results in disturbed sleep. Sleep deprivation increases brain and CSF tau levels and the spread of tau protein aggregates in neural tissues, correlating with decreased nonrapid eye movement (NREM) sleep slow wave activity [256,257].

Sleep disorders may precede cognitive impairment. Sleep disturbances alter periodic sleep architecture and electroencephalogram (EEG) patterns in prodromal stages [258]. Age-related cognitive impairment is associated with reduced delta, theta, and sigma power as well as spindle maximal amplitude during NREM sleep. Early sleep biomarkers of potential cognitive decline are poor sleep consolidation, lower amplitude, and faster frequency of spindles [259]. Decreased nonrapid eye movement (NREM) sleep slow wave activity associates with Aβ deposition and tauopathy. Aβ decreases nonrapid eye movement sleep and increases wakefulness. Aβ upregulates the expression levels of tau, pTau, orexin A, and adenosine A1 receptor [260]. Orexin receptor antagonists (e.g.,
Suvorexant) have been proposed as potential candidates for the treatment of sleep disorders and BDs in AD [261].

Anxiolytics, hypnotics, and sedatives are associated with the PGx activity of 445 genes. Different categories of anxiolytics (benzodiazepines, diphenylmethane derivatives, carbamates, dibenzo-bicyclo-octadiene derivatives, and azaspirodecanodiones), hypnotics, and sedatives (barbiturates, aldehydes, benzodiazepines, piperidinediones, melatonin receptor agonists, and other chemicals, alone or in combination) are substrates, inhibitors, or inducers of 47, 18, and 30 enzyme/protein gene products, respectively, and are transported by at least 30 protein transporters (Figures 2 and 3 and Table 5). CYP enzymes participate in the metabolism of over 92% of drugs of these pharmacological categories. About 70% of drugs currently used for the treatment of anxiety, panic attacks, sleep disorders, agitation, and behavioral anomalies are major substrates of CYP3A4, followed by CYP2C19 (41%); CYP3A5 (38%); CYP2A6 (36%); CYP2D6 (36%); CYP2C9 (30%); CYP1A2 (27%); CYP2B6 (19%); UGT1A4 (14%); UGT2B15 (11%); and UGT1A1, UGT1A3, UGT1A6, UGT1A10, and UGT2B7 (8%); only 10% are inhibitors of CYP3A4 and CYP2C9; 8% are inducers of CYP3A4, and about 5% are inducers of CYP1A2, CYP2A6, CYP7A1, and ABCC2. Over 50% of these drugs are transported by proteins of the CLCN family, 16% are transported by ABCB1, 9% are transported by NQI12, and 5% are transported by ABCC2, KCNE1, KCNH2, and SLCO1B1. Phenobarbital is associated with 80 pharmagens, Midazolam is associated with 24, Temazepam is associated with 20, Diazepam is associated with 23, and Alprazolam is associated with 14 [55,103].

### Table 5. Pharmacological profile and pharmacogenetics of selected anxiolytics, sedatives, and hypnotics.

| Drug                  | Properties                      | Pharmacogenetics |
|-----------------------|---------------------------------|------------------|
| **Barbiturates**      |                                 |                  |
| Name: **Amobarbital** | Amylobarbitone; Barbamyl; Pentymal; Amytal; Barbamil |
| IUPAC Name: 5-ethyl-5-(3-methylbutyl)-1,3-diazinane-2,4,6-trione |
| Molecular Formula: C₁₃H₁₈N₂O₃ |
| Molecular Weight: 226.27222 g/mol |
| Mechanism: Interferes with transmission of impulses resulting in an imbalance in central inhibitory and facilitatory mechanisms. Binds to alpha or beta subunits of GABA-A receptor. Decreases input resistance, depresses burst and tonic firing, especially in ventrobasal and intralaminar neurons. Increases burst duration and mean conductance at individual chloride channels and the amplitude and decay time of inhibitory postsynaptic currents. Blocks the AMPA receptor and appears to bind neuronal nicotinic acetylcholine receptors. |
| Effect: Hypnotic activity; Sedation; GABA modulator |
| Pathogenic genes: GABRs |
| Mechanistic genes: CHRNAs, CLCNs, GABRA5, GABRB3, GABRG2, GABRD, GABRG3, GABRP, GABRQ, GABRRs |
| Metabolic genes: |
| Substrate: UGT1A6, UGT2B7 |
| Inducer: CYP2A6 |
| Transporter genes: CLCNs |

| Name: **Meprobamate** | Mephorbital; Mebaral; Meprobartone; Enphenal; Prominal; Methylphenobarbital |
| IUPAC Name: 5-ethyl-1-methyl-5-phenyl-1,3-diazinane-2,4,6-trione |
| Molecular Formula: C₁₃H₁₄N₂O₃ |
| Molecular Weight: 246.2686 g/mol |
| Mechanism: Increases seizure threshold in motor cortex. Depresses monosynaptic and polysynaptic transmission in CNS. |
| Effect: Hypnotic activity; Sedation; Anti-anxiety; GABA Modulator, Anticonvulsant |
| Pathogenic genes: GABRA1, GABRB3, GABRG2, GABRD |
| Mechanistic genes: GABRA5, GABRB3, GABRD, GABRE, GABRG2, GABRP, GABRQ, GABRRs |
| Metabolic genes: |
| Substrate: CYP2B6 (minor), CYP2C8 (minor), CYP2C9 (major), CYP2D6 (minor) |
| Inhibitor: CYP2C19 (weak) |
| Inducer: CYP2A6 |
Table 5. Cont.

| Drug | Barbiturates | Pharmacogenetics |
|------|--------------|------------------|
|      | Name: **Pentobarbital**; Pentobarbitone; Nembutal; Mebubarbital; Mebunal; Ethaminda | Pathogenic genes: BDNF, IL6, TNF Mechanistic genes: GABRA6, GABRB3, GRIA1, GRIA2, NPY |
|      | IUPAC Name: 5-ethyl-5-pentan-2-yl-1,3-diazinane-2,4,6-trione | Metabolic genes: Substrate: CYP1A2, CYP2B6, CYP2D6, PTGS1, PTGS2 Inducer: CYP2A6, CYP3A4 |
|      | Molecular Formula: C_{11}H_{18}N_{2}O_{3} | Transporter genes: KCNE1, KCNH2, NR1I2, NR1I3 |
|      | Molecular Weight: 226.2722 g/mol | Pleiotropic genes: APP, BDNF, BLK, CNR1, CRHR1, FOS, ICAM1, IL1B, IL6, KRAS, NPPA, NPY, TNF, TNFRSF1A |
|      | Mechanism: Prolongs the post-synaptic inhibitory effect of GABA in the thalamus. Inhibits the excitatory AMPA-type glutamate receptors, resulting in a profound suppression of glutamatergic neurotransmission | |
|      | Effect: Hypnotic activity; Sedation; GABA Modulator; Anticonvulsant; Anesthesia (Adjuvant) | |
|      | Name: **Phenobarbital**; Luminal; Phenobarbitone; Phenobarbitol; Gardenal; Phenemal | Pathogenic genes: CASR, GABRA6, LEP, PSEN1, PTGS2, TGFBI, TNF |
|      | IUPAC Name: 5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione | Mechanistic genes: CACN6, CLCNs, GABRA6, GRIAs, GSTA1, GSTT1, NR1I3 |
|      | Molecular Formula: C_{12}H_{12}N_{2}O_{3} | Metabolic genes: Substrate: ABCC2, ACSL4, CBR3, CES1, CES2, COMT, CYP1A2 (minor), CYP2C9 (minor), CYP2C19 (major), CYP2E1 (minor), CYP4B1, CYP7A1, EPHX1, GSTM1, GSTP1, GSTT1, NNMT, NQO1, TRXAS1, TPMT |
|      | Molecular Weight: 232.23528 g/mol | Inhibitor: ABCB1, ABCC2, ABCC4, ABCG2, CYP2C19 (strong), CYP2J2 (strong), CYP27A1 (strong), SLC10A1, SULT1A1 |
|      | Mechanism: It is a barbituric acid derivative that acts as a nonselective central nervous system depressant. It potentiates action on GABA-A receptors, and modulates chloride currents through receptor channels. It also inhibits glutamate induced depolarizations | Inducer: ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP4A11, CYP4F3, CYP7A1, CYP8B1, CYP24A1, SCN1A, SLC22A1, SLC01B1, SULT1C2, SULT2A1, TPMT, UGT1A1, UGT1A4, UGT1A7, UGT1A9, UGT2B7 |
|      | Effect: Hypnotic activity; Sedation; GABA Modulator; Anticonvulsant; Carcinogen; Central Nervous System Depressant; Excitatory Amino Acid Antagonist; Respiratory depression (dose-dependent) | Transporter genes: ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCG2, SCN1A, SLC22A1, SLC01B1, SLC01B3, SLC02B1, SLC10A1 |
|      | Pathogenic genes: ABCC4, ABCG2, CYP2C19, CYP27A1 (minor), CYP2D6, PTGS1, PTGS2 | Pleiotropic genes: ACEH, ADIPQ, AHR, APOA1, AP0E, CAT, CBS, CCND1, CDA, CXXCR2, DDC, DPP4, FBG, FKBPS, GH1, GNAS, GRK5, HLA-B, HNF4A, IGF1, IL1B, IL6, LEP, LEPR, LIPC, MET, MTRN1A, NR1I2, NR3C1, PPARC1A, PRKAB1, PSEN2, RB1, RXR, TGFBI, TNF |
|      | Mechanistic genes: ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCG2, CYP2C19, CYP27A1 (minor), CYP2D6, PTGS1, PTGS2 | |
| Drug               | Properties                                                                 | Pharmacogenetics                                                                 |
|--------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Name**: Alprazolam; Xanax; Trankimazin; Tafil; Cassadan; Tranquinal |                                                                                   | Pathogenic genes: GABRs, Mechanistic genes: CLCNs, GABRs                         |
| **IUPAC Name**: 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine |                                                                                   | Metabolic genes: Substrate: CYP1A1 (minor), CYP1A2 (minor), CYP2B6, CYP2C9, CYP2C19 (minor), CYP2D6 (minor), CYP3A4/5 (major) |
| **Molecular Formula**: C_{17}H_{13}ClN_{4} |                                                                                   | Transporter genes: CLCNs                                                          |
| **Molecular Weight**: 308.76492 g/mol |                                                                                   |                                                                                  |
| **Mechanism**: Binds to the GABA benzodiazepine receptor complex, particularly in the limbic system and reticular formation. The inhibitory effect of GABA on neuronal excitability increases the neuronal membrane permeability to chloride ions resulting in hyperpolarization and stabilization |                                                                                  |
| **Effect**: Anti-Anxiety Agent; Hypnotic activity; Sedation; GABA Modulator |                                                                                  |                                                                                  |
| **Name**: Bromazepam; Compedian; Creosedin; Lectopam; Lexaurin; Lexilium |                                                                                   | Pathogenic genes: GABRs, Mechanistic genes: CLCNs, GABRs | Metabolic genes: Substrate: CYP1A2, CYP2C19, CYP3A4 (major), CYP3A5 |
| **IUPAC Name**: 7-bromo-5-pyridin-2-yl-1,3-dihydro-1,4-benzodiazepin-2-one |                                                                                   | Inhibitor: CYP2E1 (weak)                                                          |
| **Molecular Formula**: C_{14}H_{10}BrN_{2}O |                                                                                   | Transporter genes: ABCB1, CLCNs                                                 |
| **Molecular Weight**: 316.1527 g/mol |                                                                                   |                                                                                  |
| **Mechanism**: Binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron in the Central Nervous System (limbic system, reticular formation). Enhances the inhibitory GABA-effect on neuronal excitability by increasing cellular permeability to chloride ions, resulting in hyperpolarization (a less excitable state) and stabilization of cellular membrane |                                                                                  |
| **Effect**: Anti-Anxiety Agent; GABA Modulator; Skeletal muscle relaxant |                                                                                  |                                                                                  |
| **Name**: Chloridiazepoxide; Chlozeapid; Elenium; Chloridiazepoxide; Methaminodiazepoxide; Chloridiazepoxid |                                                                                  | Pathogenic genes: BDNF, CLCNs, GABRs, Mechanistic genes: CLCNs, GABRs |
| **IUPAC Name**: 7-chloro-4-hydroxy-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-imine |                                                                                  | Metabolic genes: Substrate: CYP2D6, CYP3A4 (major)                              |
| **Molecular Formula**: C_{18}H_{14}ClN_{3}O |                                                                                  | Transporter genes: ABCB1, CLCNs                                                  |
| **Molecular Weight**: 299.75486 g/mol |                                                                                  | Pleiotropic genes: BDNF                                                          |
| **Mechanism**: Binds to the GABA receptor type A and increases the inhibitory effect of GABA on neuronal excitability by enhancing neuronal membrane permeability to chloride ions, thus resulting in hyperpolarization and stabilization |                                                                                  |
| **Effect**: Sedation; Anti-Anxiety Agent; GABA Modulator; Skeletal muscle relaxant, Anticonvulsant; Amnesic properties, Anesthesia (Adjuvant) |                                                                                  |                                                                                  |
### Table 5. Cont.

| Drug Name | Benzodiazipines Properties | Pharmacogenetics |
|-----------|-----------------------------|------------------|
| **Clorazepate Dipotassium** | Name: Clobazam; Urbanyl; Chlorepin; Clorepin; Frisium; Clobazamum | Pathogenic genes: GABRA1, GABRB3, GABRG2, GABRD |
| | IUPAC Name: 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione | Mechanistic genes: CLCNs, GABRs |
| | Molecular Formula: C_{16}H_{13}ClN_{3}O_{3} | Metabolic genes: Substrate: CYP2B6 (minor), CYP2C18 (minor), CYP2C19 (major), CYP3A4 (major), CYP3A5 (major) |
| | Molecular Weight: 300.73962 g/mol | Transporter genes: CLCNs |
| | Mechanism: Binds to stereospecific receptors on the postsynaptic GABA neuron at several sites within the CNS (limbic system, reticular formation). Enhances the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions, which results in hyperpolarization (a less excitable state) and stabilization | Effect: Anti-Anxiety Agent; GABA Modulator; Anticonvulsant |
| | Effect: | |
| **Clonazepam** | Name: Clonazepam; Rivotril; Antelespin; Iktorivil; Chlonazepam; Clozepam | Pathogenic genes: GABRA1 |
| | IUPAC Name: 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one | Mechanistic genes: GABRA1 | Metabolic genes: |
| | Molecular Formula: C_{15}H_{13}ClN_{2}O_{2} | Substrate: CYP3A4 (major), NAT2 |
| | Molecular Weight: 315.7112 g/mol | Transporter genes: |
| | Mechanism: Enhance the activity of γ-aminobutyric acid (GABA). Suppresses the spike-and-wave discharge in absence seizures by depressing nerve transmission in the motor cortex. Depresses all levels of the CNS, including the limbic and reticular formation, by binding to the benzodiazepine site on the GABA receptor complex and modulating GABA | Effect: Anticonvulsant; GABA Modulator; Antipanic effect |
| | Effect: | |
| **Clobazam** | Name: Clorazepate Dipotassium; Tranxilium; Tranxen; Abbott-55616; 4306 CB; Dipotassium clorazepate | Pathogenic genes: GABRs |
| | IUPAC Name: dipotassium;7-chloro-2-oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepine-3-carboxylate/hydroxide | Mechanistic genes: CLCNs, GABRs |
| | Molecular Formula: C_{16}H_{13}ClK_{2}N_{2}O_{4} | Metabolic genes: Substrate: CYP3A4 (major), CYP3A5 (major) |
| | Molecular Weight: 408.91914 g/mol | Transporter genes: CLCNs |
| | Mechanism: Depresses all levels of the CNS, including the limbic and reticular formation, by binding to the benzodiazepine site on the γ-aminobutyric acid (GABA) receptor complex and modulating GABA, resulting in an increased neuronal membrane permeability to chloride ions which produces a hyperpolarization and stabilization | Effect: Skeletal muscle relaxant. Anti-Anxiety Agent; GABA Modulator; Anticonvulsant |
| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Name**: Diazepam; Valium; Ansiolisa; Diazemuls; Apaurin; Faustan | Pathogenic genes: BDNF, CNR1, GABRD | **Mechanistic genes**: ACHE, BCHE, BDNF, CACNA1C, CHRM6, GABRAs, TSPO |
| **IUPAC Name**: 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one | **Mechanistic genes**: | **Metabolic genes**: |
| **Molecular Formula**: C_{16}H_{11}ClN_{4}O | **Substrate**: CYP1A2 (minor), CYP2A6 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP3A4 (major), UGTs | **Transporter genes**: ABCB1 |
| **Molecular Weight**: 284.74022 g/mol | **Inhibitor**: CYP2C19 (weak), CYP3A4 (weak), UGT2B7 | **Pleiotropic genes**: FOS, IL6, SPG7 |
| **Mechanism**: Binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the CNS, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions, thus resulting in hyperpolarization and stabilization. It antagonizes with translocator protein | | |
| **Effect**: Sedation; Anti-Anxiety Agent; GABA Modulator; Skeletal muscle relaxant; Anticonvulsant; Amnesic properties; Anesthesia; Antiemetics | | |

| Name: Estazolam; Eurodin; Nuctalon; ProSom; Esilgan; Julodin | Pathogenic genes: GABRB3 | **Mechanistic genes**: | **Metabolic genes**: |
| **IUPAC Name**: 8-chloro-6-phenyl-4H-[1,2,4] triazolo[4,3-a][1,4]benzodiazepine | **Substrate**: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 (major), CYP3A5 (major) | **Transporter genes**: CLCNs |
| **Molecular Formula**: C_{16}H_{11}ClN_{4} | **Inhibitor**: CYP2C19 (weak), CYP3A4 (weak), UGT2B7 | | |
| **Molecular Weight**: 294.73834 g/mol | **Transporter genes**: | | |
| **Mechanism**: Binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the CNS, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization | | |
| **Effect**: Anti-Anxiety Agent; GABA Modulator; Hypnotic activity; Sedation; Skeletal muscle relaxant; Anticonvulsant | | | |

| Name: Flurazepam; Dalmane; Dalmadorm; Flurazepamum; Felmane; Noctosom | Pathogenic genes: GABRB3 | **Mechanistic genes**: | **Metabolic genes**: |
| **IUPAC Name**: 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2-one | **Substrate**: CYP3A4 (major), CYP3A5 (major), MAO | **Transporter genes**: ABCB1, CYP2E1 (weak) |
| **Molecular Formula**: C_{21}H_{23}ClF_{3}N_{3}O | **Inhibitor**: ABCB1, CYP2E1 (weak) | **Transporter genes**: ABCB1, CACNA1C, CLCNs |
| **Molecular Weight**: 387.87823 g/mol | | | |
| **Mechanism**: Binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the CNS, including the limbic system, reticular formation. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions | | | |
| **Effect**: Anti-Anxiety Agent; GABA Modulator; Sedation | | | |
Anticonvulsant; Antiemetic; Hypnotic activity; Sedation; Skeletal muscle relaxant; Amnestic properties; Anxiolytic.

**Mechanism:** Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron at several sites within CNS, including limbic system, reticular formation. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization. Binds to GABA receptors enhancing the effects of GABA by increasing GABA affinity for its receptor.

**Effect:** Anti-Anxiety Agent; GABA Modulator; Sedation; Skeletal muscle relaxant; Anticonvulsant. Antiemetic; Hypnotic activity; Preanesthetic agent.

**IUPAC Name:** 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,4-dihydro-1,4-benzodiazepin-2-one

**Molecular Formula:** C_{19}H_{17}ClN_{2}O_{2}

**Molecular Weight:** 321.1581 g/mol

**Mechanism:** Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron at several sites within CNS, including limbic system, reticular formation. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization. Binds to GABA receptors enhancing the effects of GABA by increasing GABA affinity for its receptor.

**Effect:** Sedation; Hypnotic activity; Anti-Anxiety Agent; GABA Modulator; Skeletal muscle relaxant; Amnestic properties; Anesthesia; Preanesthetic agent.

**IUPAC Name:** 7-nitro-5-(2-naphthyl)-3-hydroxy-1,4-dihydro-1,4-benzodiazepin-2-one

**Molecular Formula:** C_{19}H_{17}NO_{3}

**Molecular Weight:** 325.767323 g/mol

**Mechanism:** Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron at several sites within CNS, including limbic system, reticular formation. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization. Binds to GABA receptors enhancing the effects of GABA by increasing GABA affinity for its receptor.

**Effect:** Sedation; Hypnotic activity; Anti-Anxiety Agent; GABA Modulator; Skeletal muscle relaxant; Amnestic properties; Anesthesia; Preanesthetic agent.
**Table 5. Cont.**

| Benzodiazepines | Properties | Pharmacogenetics |
|-----------------|------------|------------------|
| **Name**: Oxazepam; Adumran; Tazezap; Serax; Anxiolit; Praxilen | **IUPAC Name**: 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one | **Pathogenic genes**: GABRs  
**Mechanistic genes**: CLCNs, GABRs  
**Metabolic genes**: Substrate: CYP2D6, UGT2B7, UGT2B15  
Inhibitor: UGT2B7  
**Transporter genes**: CLCNs |
| **Molecular Formula**: C_{16}H_{13}ClN_{2}O_{2} | **Molecular Weight**: 286.71304 g/mol |  
**Mechanism**: Effects appear to be mediated through inhibitory neurotransmitter GABA; site and mechanism of action within the CNS appear to involve macromolecular complex (GABA_A-receptor-chloride ionophore complex) which includes GABA_A receptors, high-affinity benzodiazepine receptors, and chloride channels. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (less excitatable state) and stabilization  
**Effect**: Sedation; GABA Modulator; Anti-Anxiety Agent; Anti-Alcohol withdrawal agent |
| **IUPAC Name**: 7-chloro-5-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)-3H-1,4-benzodiazepine-2-thione | **Molecular Formula**: C_{17}H_{11}ClF_{2}N_{2}S |  
**Pathogenic genes**: GABRB3  
**Mechanistic genes**: CLCNs, GABRs  
**Metabolic genes**: Substrate: CYP2C9 (minor), CYP2C19 (minor), CYP3A4 (major)  
**Transporter genes**: CLCNs |
| **Molecular Weight**: 386.794253 g/mol |  
**Mechanism**: Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron at several sites within CNS (limbic system, reticular formation). Enhances inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions, resulting in hyperpolarization and stabilization  
**Effect**: Hypnotic activity; Sedation; GABA Modulator; Anti-Anxiety Agent |
| **Name**: Temazepam; Euhypnos; Restoril; Hydroxyzidezepam; Methyloxazepam; Crisonar | **IUPAC Name**: 7-chloro-3-hydroxy-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one |  
**Pathogenic genes**: GABRB3  
**Mechanistic genes**: CLCNs, GABRs  
**Metabolic genes**: Substrate: CYP2B6 (major), CYP2C9 (major), CYP2C19 (major), CYP3A4 (major), UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT1A10, UGT2B7, UGT2B15  
**Inhibitor**: UGT1A3, UGT2B7  
**Transporter genes**: CLCNs |
| **Molecular Formula**: C_{16}H_{13}ClN_{2}O_{2} | **Molecular Weight**: 300.73962 g/mol |  
**Mechanism**: A short half-life benzodiazepine. Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron within CNS, including limbic system. Enhances inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitatory state) and stabilization. It antagonizes with translocator protein  
**Effect**: Hypnotic activity; Sedation; GABA Modulator; Anti-Anxiety Agent; Antidepressant activity; Anticonvulsant |
Table S. Cont.

| Drug                          | Properties                        | Pharmacogenetics                   |
|-------------------------------|-----------------------------------|-------------------------------------|
| **Benzodiazepines**           |                                   |                                     |
| Name: Triazolam; Halcion; Songar; Clorazolam; Noviodorm; Trilam | IUPAC Name: 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine | Pathogenic genes: GABRB3 Mechanicin genes: CLCNs, GABRs, TSPO |
| Molecular Weight: 343.20996 g/mol | Mechanism: Binds to stereospecific benzodiazepine receptors on postsynaptic GABA neuron at several sites within CNS, including limbic system, reticular formation. Enhancement of inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (less excitable state) and stabilization. | Metabolic genes: Substrate: CYP3A4 (major), CYP3A5 (major), CYP2C8 (weak), CYP2C9 (weak) Transporter genes: CLCNs |
| Molecular Formula: C$_{21}$H$_{31}$N$_{5}$O$_{2}$ | Effect: Sedation; GABA Modulator; Anesthesia (Adjuvant) | |

| Drug                          | Properties                        | Pharmacogenetics                   |
|-------------------------------|-----------------------------------|                                     |
| **Miscellaneous**             |                                   |                                     |
| Name: Buspirone; Ansial; Buspirona; Buspironum; Bespar; Anxiron | IUPAC Name: 8-[4-(4-pyrimidin-2-yl)piperazin-1-yl][4-azaspiro[4.5]decane-7,9-dione | Mechanicin genes: DRD2, HTR1A, HTR2A, HTR3s |
| Molecular Weight: 385.50314 g/mol | Mechanism: Decreases the spontaneous firing of serotonin-containing neurons in the CNS by selectively binding to and acting as agonist at postsynaptic CNS serotonin 5-HT$_{1A}$ receptors. Possesses partial agonist activity (mixed agonist/antagonist) at postsynaptic 5-HT$_{2A}$ receptors. Does not bind to benzodiazepine-GABA receptors. Binds to dopamine D$_{2}$ receptors | Metabolic genes: Substrate: CYP2D6 (minor), CYP3A4 (major), CYP3A5 (minor) Inducer: CYP3A4 |
| Molecular Formula: C$_{21}$H$_{31}$N$_{5}$O$_{2}$ | Effect: Serotonin receptor agonist; Anti-Anxiety Agent | Pleiotropic genes: DRD2, HTR2A |

| Drug                          | Properties                        | Pharmacogenetics                   |
|-------------------------------|-----------------------------------|                                     |
| Name: Chloral Hydrate; Noctec; Tosyl; 302-17-0; 2,2,2-Trichloroethane-1,1-diol; Trichloracetaldehyde hydrate | IUPAC Name: 2,2,2-trichloroethane-1,1-diol | Pathogenic genes: GABRA5 Mechanicin genes: GABRA5, GLR5, HTR3s |
| Molecular Weight: 165.40302 g/mol | Mechanism: It is converted to the active compound trichloroethanol by hepatic alcohol dehydrogenase. The agent interacts with various neurotransmitter-operated ion channels, thereby enhancing gamma-aminobutyric acid (GABA)-A receptor mediated chloride currents and inhibiting amino acid receptor-activated ion currents. Enhances the agonistic effects of glycine receptors, inhibits AMPA-induced calcium influx in cortical neurons, and facilitates 5-HT 3 receptor-mediated currents in ganglionic neurons. Overall, this results in a depressive effect on the central nervous system | Pleiotropic genes: FOS, IL1B, IL6 |
| Molecular Formula: C$_{2}$H$_{3}$Cl$_{3}$O$_{2}$ | Effect: Hypnotic activity; Sedation; Anticonvulsant; Anesthesia; Analgesic activity; GABA Modulator | |
| Drug Name | Properties | Pharmacogenetics |
|-----------|------------|-----------------|
| **Name:** Dexmedetomidine Hydrochloride; Dexmedetomidina; Dexmedetomidinium; MPV 1440; Precedex; CHEB1:4466 | | |
| IUPAC Name: 5-((S)-1-(2,3-dimethylphenyl)ethyl)-1H-imidazole | | |
| Molecular Formula: C_{17}H_{21}ClN_{2}S | | |
| Molecular Weight: 259.34344 g/mol | | |
| Mechanism: Blocks postsynaptic mesolimbic dopaminergic receptors in brain. Exhibits strong α-adrenergic-blocking effect and depresses release of hypothalamic and hypophysal hormones. Competes with histamine for H1-receptor. Reduces stimuli to brainstem reticular system. The relief of nausea is related to central anticholinergic actions | | |
| Effect: Sédation; Anti-Allergic Agent; Antimetabolic; Anti-emetic; Histamine H1 Antagonist | | |
| **Name:** Promethazine Hydrochloride; Phenergan; Promethazine HCl; 58-33-3; Fenergan; Atosil | | |
| IUPAC Name: N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine;hydrochloride | | |
| Molecular Formula: C_{17}H_{21}ClN_{2}S | | |
| Molecular Weight: 320.88004 g/mol | | |
| Mechanism: Blocks postsynaptic mesolimbic dopaminergic receptors in brain. Exhibits strong α-adrenergic-blocking effect and depresses release of hypothalamic and hypophysal hormones. Competes with histamine for H1-receptor. Reduces stimuli to brainstem reticular system. The relief of nausea is related to central anticholinergic actions | | |
| Effect: Sédation; Anti-Allergic Agent; Antiemetique; Antitippuritique; Histamine H1 Antagonist | | |
| **Name:** Ramelteon; Rozerem; 196597-26-9; TAK-375; Rozerem | | |
| IUPAC Name: N-[2-[(8S)-2,6,7,8-tetrahydro-1H-cyclopenta[e][1]benzofuran-8-yl]ethyl]propanamide | | |
| Molecular Formula: C_{16}H_{21}NO_{2} | | |
| Molecular Weight: 259.34344 g/mol | | |
| Mechanism: Potent, selective agonist of melatonin receptors MT1 and MT2 (with little affinity for MT3) within suprachiasmatic nucleus of hypothalamus | | |
| Effect: Melatonin receptor agonist; Hypnotic activity; circadian rhythm regulation | | |
| **Name:** Zaleplon; Sonata; 151319-34-5; CL-284846; Zerene; CL. 284846 | | |
| IUPAC Name: N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide | | |
| Molecular Formula: C_{17}H_{15}N_{5}O | | |
| Molecular Weight: 305.3339 g/mol | | |
| Mechanism: Interacts with benzodiazepine GABA receptor complex. Nonclinical studies have shown that it binds selectively to brain ω1 receptor situated on α-subunit of GABA-A receptor complex | | |
| Effect: Hypnotic activity; Sedation; Skeletal muscle relaxant; Anti-anxiety agent; Anti-convulsant; GABA Modulator | | |

**Table 5. Cont.**
5.5. Epilepsy

Epilepsy is a prevalent disorder in dementia with prevalence and incidence rates 2–6-fold higher than in age-matched healthy subjects. Subclinical epileptiform activity can lead to accelerated cognitive decline. Aβ deposition may influence the propagation of synchronized abnormal discharges via excitatory pathways [262].

There is a complex epileptogenesis-associated dysregulation of proteins involved in amyloid β processing and regulation in the hippocampus (HC) and parahippocampal cortex during epileptogenesis, in which there is also involvement of tau and proteins of the mitochondrial complexes I, III, IV, and V [263]. Seizures are more prevalent in early-onset AD with rapid progression [264], correlating with high CSF total tau protein levels [265]. A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), which is an α-secretase in APP processing, has been associated with epilepsy as a stage-dependent modulator of epileptogenesis [266].

Potential pathogenic genes for epilepsy include ion channel genes (e.g., SCN1A, KCNQ2, SCN2A, and SCN8A), which account for nearly half of epilepsy genes, together with a number of additional genes, such as CASKL5, STXB1P1, PCDH19, PRRT2, LG1A, Aldh7A1, MecP2, Epm2A, Arx, and Slc2A1 [267]. There is also an association of MTHFR rs1801133 and ABCC2 rs717620 with susceptibility to generalized tonic-clonic epilepsy, while ABCB1 rs717620 is associated with poor response to antiepileptics [268]. The influence of some of these genes in PGx has been investigated under different therapeutic paradigms [55].

### Table 5. Cont.

| Drug          | Properties                                                                 | Pharmacogenetics                                                                 |
|---------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Zolpidem Tartrate; 99294-93-6; schembl40721; Mls001401453; Bio-0153; chembl1723343 | Mechanistic genes: CLCNs, GABA1, TSPO                                            |
|               | IUPAC Name: 2,3-dihydroxybutanedioic acid,N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl) imidazo[1,2-alpyridin-3-yl]acetamide | Metabolic genes: CYP2D6 (weak), CYP3A4 (minor), CYP2C9 (minor)                    |
|               | Molecular Formula: C_{21}H_{27}N_{1}O_{7}                                    | Substrate: CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major)                        |
|               | Molecular Weight: 457.4738 g/mol                                              | Inhibitor: CYP3A4 (strong)                                                        |
|               | Mechanism: Enhances activity of inhibitory neurotransmitter; GABA, via selective agonism at benzodiazepine-1 (BZ1) receptor. Result is increased chloride conductance, neuronal hyperpolarization, inhibition of action potential, and decrease in neuronal excitability | Transporter genes: CLCNs, NR1I2                                                  |
|               | Effect: Central nervous system depression; GABA-A receptor agonist; Hypnotic activity; Sedation |                                                                                  |
| Zopiclone; Imovane; Zimovane; Amoban; (++)-Zopiclone; 43200-80-2 | Mechanistic genes: CLCNs, GABRA1s                                              |
|               | IUPAC Name: [6-(5-chloropyridin-2-yl)-5-oxo-7H-pyrrolo[3,4-b]pyrazin-7-yl]-4-methylpiperazine-1-carboxylate | Metabolic genes: CYP2C8 (major), CYP2C9 (major), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major) |
|               | Molecular Formula: C_{17}H_{15}N_{5}O_{2}                                    | Substrate: CYP3A4 (minor)                                                        |
|               | Molecular Weight: 388.80828 g/mol                                              | Inhibitor: CYP3A4 (strong)                                                        |
|               | Mechanism: Reduces sleep latency, increases duration of sleep, and decreases number of nocturnal awakenings. Binds to the benzodiazepine receptor complex and modulates the GABABZ receptor chloride channel macromolecular complex. Acts on α1, α2, α3 and α5 GABAA containing receptors as a full agonist causing an enhancement of the inhibitory actions of GABA. | Transporter genes: CLCNs                                                        |
|               | Effect: Hypnotic activity; Sedation                                          |                                                                                  |
Treatment of seizures in AD with low-dose antiepileptic drugs (AEDs) is usually well tolerated and efficacious, and selected AEDs might also help in slowing-down disease progression [269,270]. Anticonvulsants may suppress seizures in up to two-thirds of all patients, with no apparent effects on long-term prognosis [271].

Antiepileptics are associated with the PGx activity of approximately 150 genes (Table 6). The GABRG2 gene encodes one of the subunits of the GABA-A receptor, the most abundant receptor of fast synaptic inhibition in the brain. GABRG2 variants (rs211037, rs210987, rs440218, rs2422106, rs211014, and rs401750) and several PRRT2 mutations (c.649delC (p.R217Efs*12), c.649_650insC (p.R217Pfs*8), c.412C>G (p.Pro138Ala), c.439G>C (p.Asp147His), and c.623C>A (p.Ser208Tyr)) are associated with febrile seizures [272]. There is a clear association of rs211037 with epilepsy in Asian patients and of rs211037-rs210987 and rs2422106-rs211014-rs401750 haplotypes with susceptibility to symptomatic epilepsy in Chinese [273].

Different categories of anticonvulsants (barbiturates, hydantoin derivatives, oxazolidines, succinimides, benzodiazepines, carboxamides, fatty acid derivatives, and miscellaneous antiepileptics) are substrates, inhibitors, or inducers of 40, 15, and 24 enzyme/protein gene products, respectively, and are transported by at least 16 protein transporters (Table 6). CYP enzymes participate in the metabolism of over 69% of drugs of these pharmacological categories. Over 65% of drugs currently used for the treatment of epilepsy and related disorders are major substrates of CYP3A4, followed by CYP3A5, CYP2E1, and UGT1A1 (32%); CYP2C8 and CYP2B6 (26%); CYP1A2, CYP2C9, CYP2C19, UGT1A3, UGT1A9, and UGT2B7 (22%); CYP1A1, CYP1A6, CYP2D6, CYP3A7, UGT1A4, and UGT1A6 (16%); and CYP2C18, CYP4B1, UGT1A10, and UGT2B15 (11%). These drugs tend to be strong inhibitors of CYP2C9 (>25%) and, to a lesser extent, of CYP1A6 and SULT1A1 (10%), and they are also potent inducers of CYP3A4 (37%). ABCB1 is the major transporter of 42% of antiepileptics, followed by ABCC2 (16%), SLC6A1 (11%), and SLCO2A1 and SLCO1B1 (10%). Phenobarbital, Valproic acid, and Carbamazepine are the three best-characterized drugs for their pharmacogenomic profile, with over 100 genes involved in their biotransformation and metabolism [55,103,274,275].

UGT2B7 G211T and C161T polymorphisms affect the pharmacokinetics and pharmacodynamics of valproic acid (VPA) [276]. Carriers of the variant UGT1A6 19T>G, 541A>G, and 552A>C allele require higher VPA dosages than noncarriers, and carriers of the variant GRIN2B -200T>G allele are more likely to require lower VPA dosages than noncarriers [277]. VPA-related liver damage has been associated with the formation of a hepatotoxic 4-ene metabolite mediated by CYP2C9 and CYP2A6 enzymes [278]. ABAT rs1731017, SCN2A rs2304016, and ALDH5A1 rs1054899 are associated with VPA response in Chinese patients [279]. Female CYP2C19-PMs are more susceptible to VPA-induced weight gain in the Japanese population [280], and SNPs in the leptin receptor (LEPR) (rs1137101) and ankyrin repeat kinase domain containing 1 (ANKK1) (rs1800497) show associations with VPA-induced weight gain in the Chinese population [281]. Oral clearance (CL/F) of VPA in patients with the LEPR-A668G and G668G (rs1137101) variants is lower than in patients with the LEPR-A668A genotype [282]. Meropenem decreases VPA plasma levels when coadministered together. This interaction is triggered by inhibition of acylpeptide hydrolase (APEH) activity with meropenem. The study of VPA-d6 β-D-glucuronide (VPA-G) concentration in APEH rs3816877 and rs1131095 carriers revealed that patients with the APEH rs3816877 C/C genotype show higher levels than C/T carriers in the Chinese population [283]. Valproate-related neuroprotection in experimentally triggered epileptic seizures has been associated with PKC-dependent GABAAR γ2 phosphorylation at serine 327 residue [284]. SOD2 Val16Ala polymorphism may affect γ-glutamyltransferase (GGT) elevation in epileptic patients treated with VPA [285].

High initial serum concentrations of lamotrigine increase the risk of cutaneous ADRs. Genetic variants of uridine diphosphate glucuronosyltransferase (UGT) 1A4 influence lamotrigine elimination. UGT1A4*2 (P24T) and *3 (L48V) variants are associated with skin reactions but probably not in Caucasians [286]. UGT2B7-161C>T variants influence lamotrigine pharmacokinetics; specifically, the UGT2B7-161TT genotype changes lamotrigine clearance and may be useful in titrating the optimal
Treatment with carbamazepine, oxcarbazepine, or phenytoin is associated with delayed-hypersensitivity reactions (e.g., eosinophilia, Stevens-Johnson syndrome, and toxic epidermal necrolysis) [290]. The FDA-approved label for oxcarbazepine indicates a pharmacogenomic association with hypersensitivity reactions and the HLA antigen allele HLA-B*15:02. Oxcarbazepine has structural similarities with carbamazepine, and HLA-B*15:02 is a risk factor for both carbamazepine- and oxcarbazepine-induced severe cutaneous ADRs, especially in the Asian population [290,291]. HLA-B*15:02 is highly associated with carbamazepine-related Stevens–Johnson syndrome/toxic epidermal necrosis cases as well as phenytoin-related cutaneous ADRs and, to a lesser extent, lamotrigine ADRs; in contrast, HLA-B*40:01 and HLA-B*58:01 carriers show a lower frequency of carbamazepine-related skin complications [292]. HLA-A*31:01 has also been reported to be a genetic marker for carbamazepine-induced ADRs in both Japanese and European populations [293,294].

SCN1A rs3812718 A/G and rs2290732 A/G polymorphisms influence carbamazepine tolerability, and rs2298771 A/G is associated with carbamazepine efficacy [295]. ABCB1 rs1045642 and UGT2B7 rs7439366 affect oxcarbazepine pharmacokinetics and pharmacodynamics in Han Chinese epileptic patients [296]. PXR*1B, HNF4a rs2071197, CYPIA2*1F, ABCC2 1249G>A, and PRRT2 c.649dupC influence the pharmacokinetics and pharmacodynamics of carbamazepine [297]. ABCB1 c.3435C>T, CYP3A4*1G, CYP3A5*3, POR*28, and EPHX1 c.416A>G and c.128G>C variants influence carbamazepine metabolism in Chinese patients [298]. rs776746 and rs15524 in ABCB1 affect carbamazepine metabolism, and rs2032582 and rs10234411 in ABCB1 contribute to interindividual variation in carbamazepine and in carbamazepine-10,11-epoxide transport in epileptic patients treated with carbamazepine in combination with phenytoin or phenobarbital [299]. SCN1A IVS5-91G>A, UGT2B7 c.802T>C, ABCC2 c.1249G>A, and EPHX1 c.337T>C carriers require higher maintenance doses of oxcarbazepine [299,300]. Carriers of the variant SCN1A IVS5-91G>A and EPHX1 c.337T>C allele require higher carbamazepine dosages than noncarriers, and genetic variants in the SCN1A, EPHX1, and UGT2B7 genes interactively affect the concentration–dose ratio of carbamazepine [301].

SCN1A, CYP2C9, CYP2C19, and ABCB1 variants affect phenytoin metabolism. CYP2C9 and CYP2C19 polymorphisms are associated with lower phenytoin maintenance dosage in Asian patients. CYP2C19*2*A2, CYP2C19*3*A3, CYP2C19*2*A3, and heterozygous CYP2C9*A3 variants require lower phenytoin maintenance dosage [301,302]. Phe nytoin may cause cutaneous ADRs with variable severity (maculopapular exanthema, eosinophilia, Stevens–Johnson syndrome, and toxic epidermal necrolysis). At least 16 SNPs in CYP2C genes at 10q23.33 may contribute to this adverse effect. CYP2C9*A3 carriers show a clear propensity to phenytoin-related severe cutaneous ADRs [303]. There is an association between a rare variant in the complement factor H-related 4 (CFHR4) gene and phenytoin-induced maculopapular exanthema in Europeans [304].

CACNA1G, CACNA1H, CACNA1I, and ABCB1 variants are associated with differential short-term seizure outcome in childhood absence epilepsy. In patients treated with ethosuximide, CACNA1H rs61734410/P640L and CACNA1I rs3774178 are more prevalent among not-seizure-free patients, and in patients treated with lamotrigine, ABCB1 rs2032582/S893A is more frequent in not-seizure-free patients, whereas CACNA1H rs2753326 and rs2753325 are more common in seizure-free patients [305].

Resistant epilepsy is an important problem in over 20% of patients treated with antiepileptics [306]. Pharmacoresistance is directly linked to dysfunctions in the pharmacoepigenetic machinery [61]. The C3435T variant of the ABCB1 gene has been proposed as a crucial factor for drug resistance in epilepsy. ABCB1-C3435C carriers show a risk of pharmacoresistance in some studies, but this association has been questioned after further analyses [307]. The ABCB1 G2677T T (rs1128503) and C3435T T (rs1045642) alleles and the TT, CTT, and TTT haplotypes are associated with drug-resistant epilepsy in specific populations [308]. ABCC2 rs717620-24 CT+TT genotypes and ABCC2 rs3740066 (3972C>T) CT+TT genotypes are overrepresented in epileptic patients resistant to antiepileptic drugs in the Chinese.
population, whereas ABCC2 rs2273697 (1249G>A) and ABCB1 rs1045642 (3435C>T) polymorphisms were not found to be associated with drug-resistant epilepsy in this population. The frequency of the haplotype TGT (ABCC2 -24C>T/ABCC2 1249G>A/ABCC2 3972C>T) in resistant patients is double that of responsive patients [309]. The TAGAA haplotype in CACNA1A accumulates in drug-resistant patients in the Chinese population [310]. Glucose type-1 transporter (GLUT1) deficiency syndrome, caused by mutations in the SLC2A1 gene, exhibits pharmacoresistance to antiepileptics. Screening of SLC2A1 pathogenic variants can predict drug response and optimization of antiepileptic drugs for the treatment of this health condition [311]. The SCN1A IVS5-91G>A AA and ABCC2 c.1249G>A GA genotypes have been shown to be associated with carbamazepine/oxcarbazepine-resistant epilepsy in the Chinese Han population. The frequency of SCN1A-AA and ABCC2-AC haplotypes is higher in drug-resistant patients than in responsive patients [312]. Association of ABCC2 rs2273697 and rs3740066 polymorphisms and drug-resistant epilepsy has been reported in Asia Pacific epilepsy cohorts [313]. PCDH19 mutations may cause pharmacoresistant epilepsy and intellectual disability in Dravet-like syndromes. A retrospective study of antiepileptic therapy in females with PCDH19 mutations showed that the most effective drugs in these cases are clobazam and bromide, with responder rates of 68% and 67%, respectively [314]. Clobazam binds to stereospecific receptors on the postsynaptic GABA neuron at several sites within the CNS (limbic system and reticular formation) and enhances the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions, which results in hyperpolarization and stabilization. Clobazam is extensively metabolized by CYP enzymes. Its major metabolite is N-desmethylclobazam (norclobazam), which also display antiepileptic activity. Clobazam is a major substrate of CYP2C19 and CYP3A4 and a minor substrate of CYP2B6 and CYP2C18. CYP2C19-PMs show higher plasma levels of clobazam and increased risk of ADRs. Caution and personalized dose adjustment is recommended in patients with the following genotypes: CYP2C19 (CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7, CYP2C19*8, CYP2C19*17), CYP3A4 (CYP3A4*1, CYP3A4*1B, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*15, CYP3A4*17, CYP3A4*18, CYP3A4*19), and CYP3A5 (CYP3A5*3) [55,56] (Table 6).

In Japanese patients with Dravet syndrome, it seems that CYP2C19 variants may influence a positive response to the antiepileptic effects of stiripentol [315]. Genotype combinations of GABRA1 rs6883877, GABRA2 rs511310, and GABRA3 rs4828696 may affect responses to antiepileptic drugs [316]. γ-aminobutyric-acid (GABA) is the principal inhibitory neurotransmitter in the CNS. Imbalances in GABAergic neurotransmission are involved in the pathophysiology of epilepsy and AD. GABA transporters (GATs) regulate the influx-efflux of GABA with sodium and chloride at the synaptic cleft. GATs belong to the solute carrier 6 (SLC6) transporter family: GAT1-3 (SLC6A1, SLC6A13, and SLC6A11) and betaine/GABA transporter 1 (BGT1 and SLC6A12). BGT1 is a potential target for the treatment of epilepsy. The GAT1/BGT1 selective inhibitor EF1502 and the BGT1 selective inhibitor RPC-425 display anticonvulsant effects [317].
Table 6. Pharmacological properties and pharmacogenetics of selected antiepileptic drugs.

| Name: Carbamazepine | Molecular Formula: C₁₅H₁₂N₂O | Molecular Weight: 236.27 g/mol | Mechanistic genes: EPHX1, HSPA1L, MTHFR, SCN1A | Metabolic genes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2E1, CYP3A4, CYP3A5, CYP3A7, GSTM1, GSTT1, UGT2B7 | Inhibitor: CYP1A2 Inducer: ABCB1, ABCB4, ABCC2, ABCG2, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, GSTA1, SULT1A1, UGT1A4 | Transporter genes: ABCB1, ABCB4, ABCC2 | Pleiotropic genes: HLA-A, HLA-B, IL6 |
|----------------------|--------------------------------|--------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|

**Mechanism:** The anticonvulsant activity of carbamazepine, like phenytoin, principally involves limitation of seizure propagation by reduction of post-tetanic potentiation of synaptic transmission. Carbamazepine has only slight analgesic properties. Carbamazepine appears to provide relief of pain in trigeminal neuralgia by reducing synaptic transmission within the trigeminal nucleus. The drug has also demonstrated sedative, anticholinergic, antidepressant, muscle relaxant, antiarrhythmic, antiadrenergic, and neuromuscular transmission-inhibitory actions. May depress activity in the nucleus ventralis of the thalamus or decrease synaptic transmission or decrease summation of temporal stimulation leading to neural discharge by limiting influx of sodium ions across cell membrane or other unknown mechanism. May decrease the turnover of γ-aminobutyric acid (GABA). Stimulates the release of ADH and potentiates its action in promoting reabsorption of water. Chemically related to tricyclic antidepressants.

**Effect:** Anticonvulsants, Miscellaneous. Antimanic Agents

| Name: Clonazepam | Molecular Formula: C₁₅H₁₀ClN₃O₃ | Molecular Weight: 315.71 g/mol | Mechanistic genes: ALB, GABA-A | Metabolic genes: CYP2E1, CYP3A4, NAT2 | Substrate: CYP2E1, CYP3A4, SULT1A1, UGT1A4, GSTM1, GSTP1, GSTT1, NAT2 | Transporter genes: ABCB1, ABCB4, ABCC2 | Pleiotropic genes: HLA-A, HLA-B, IL6 |
|-------------------|--------------------------------|--------------------------------|---------------------------------|-----------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|

**Mechanism:** Exact mechanism of anticonvulsant, sedative, and antipanic effects is unknown; however, mechanism appears to be related to the drug’s ability to enhance the activity of γ-aminobutyric acid (GABA). Suppresses the spike-and-wave discharge in absence seizures by depressing nerve transmission in the motor cortex. Depresses all levels of the CNS, including the limbic and reticular formation, by binding to the benzodiazepine site on the GABA receptor complex and modulating GABA

**Effect:** Anxiolytics, Sedatives, and Hypnotics; Benzodiazepines. Anticonvulsants; Benzodiazepines
Felbamate, a dicarbamate, is an anticonvulsant agent. Exact mechanism of action unknown, but it is suggested that it increases seizure threshold and reduces seizure spread. In vitro studies indicate that felbamate has weak inhibitory effects on binding at GABA receptors and benzodiazepine receptors. The monocarbamate, p-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug.

**Effect:** Anticonvulsants

### Metabolism

**Mechanistic genes:** CACNA1G

**Substrate:** CYP2E1, CYP3A4, CYP3A5

**Inducer:** CYP2C19

**Inhibitor:** CYP2C19

**Transporter genes:** ABCB1

### Pharmacogenetics

**Inducer:** CYP3A4, UGT1A4, UGT1A9, UGT2B7

**Inhibitor:** UGT1A9, UGT2B7

**Pleiotropic genes:** HLA-B

---

**Table 6. Cont.**

| Drug                  | Properties                                      | Pharmacogenetics                      |
|-----------------------|-------------------------------------------------|----------------------------------------|
| **Eslicarbazepine**   | Name: Eslicarbazepine                           | Metabolic genes:                      |
|                       | IUPAC Name: [S-(-)-10-acetoxy-10,11-dihydro-5H-dibenz [b,f]azepine-5-carboxamide]; BIA 2-093 | Substrate: ABCB1, UGT1A1, UGT1A4, UGT1A9, UGT2B7 |
|                       | Molecular Formula: C17H16N2O3                    | Inhibitor: CYP2C19                     |
|                       | Molecular Weight: 296.32 g/mol                  |                                        |
|                       | Mechanism: The precise mechanisms of action of eslicarbazepine acetate are unknown. However, in vitro electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilize the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing | Mechanistic genes: CACNA1G            |
|                       | Effect: Anticonvulsants, Miscellaneous. Antiepileptics, Carboxamide Derivatives | Substrate: CYP2E1, CYP3A4, CYP3A5      |
|                       |                                                  | Inducer: CYP2C19                      |
|                       |                                                  | Inhibitor: UGT1A9, UGT2B7             |
|                       |                                                  | Pleiotropic genes: HLA-B              |
| **Ethosuximide**      | Name: Ethosuximide                              |                                        |
|                       | IUPAC Name: 2,5-Pyrrolinedione, 3-ethyl-3-methyl-1, (a)-; (a)-2-Ethyl-2-methylsucinimide |                                        |
|                       | Molecular Formula: C8H11NO2                      |                                        |
|                       | Molecular Weight: 141.17 g/mol                   |                                        |
|                       | Mechanism: A succinimide-derivative anticonvulsant. Exact mechanism of anticonvulsant action unknown. Increases seizure threshold in cortex and basal ganglia and reduces synaptic response to low-frequency repetitive stimulation. Suppresses paroxysmal spike and wave activity of the EEG associated with lapses of consciousness common in absence seizures |                                        |
|                       | Effect: Anticonvulsants; Succinimides            |                                        |
| **Felbamate**         | Name: Felbamate                                  |                                        |
|                       | IUPAC Name: 2-Phenyl-1,3-propanediol dicarbamate |                                        |
|                       | Molecular Formula: C11H14N2O4                     |                                        |
|                       | Molecular Weight: 238.24 g/mol                   |                                        |
|                       | Mechanism: Felbamate, a dicarbamate, is an anticonvulsant agent. Exact mechanism of action unknown, but it is suggested that it increases seizure threshold and reduces seizure spread. In vitro studies indicate that felbamate has weak inhibitory effects on binding at GABA receptors and benzodiazepine receptors. The monocarbamate, p-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug |                                        |
|                       | Effect: Anticonvulsants                          |                                        |
|                       |                                                  |                                        |
| **Felbamate**         | Name: Felbamate                                  |                                        |
|                       | IUPAC Name: 2-Phenyl-1,3-propanediol dicarbamate |                                        |
|                       | Molecular Formula: C11H14N2O4                     |                                        |
|                       | Molecular Weight: 238.24 g/mol                   |                                        |
|                       | Mechanism: Felbamate, a dicarbamate, is an anticonvulsant agent. Exact mechanism of action unknown, but it is suggested that it increases seizure threshold and reduces seizure spread. In vitro studies indicate that felbamate has weak inhibitory effects on binding at GABA receptors and benzodiazepine receptors. The monocarbamate, p-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug |                                        |
|                       | Effect: Anticonvulsants                          |                                        |
|                       |                                                  |                                        |
| **Ethosuximide**      | Name: Ethosuximide                              |                                        |
|                       | IUPAC Name: 2,5-Pyrrolinedione, 3-ethyl-3-methyl-1, (a)-; (a)-2-Ethyl-2-methylsucinimide |                                        |
|                       | Molecular Formula: C8H11NO2                      |                                        |
|                       | Molecular Weight: 141.17 g/mol                   |                                        |
|                       | Mechanism: A succinimide-derivative anticonvulsant. Exact mechanism of anticonvulsant action unknown. Increases seizure threshold in cortex and basal ganglia and reduces synaptic response to low-frequency repetitive stimulation. Suppresses paroxysmal spike and wave activity of the EEG associated with lapses of consciousness common in absence seizures |                                        |
|                       | Effect: Anticonvulsants; Succinimides            |                                        |
| **Felbamate**         | Name: Felbamate                                  |                                        |
|                       | IUPAC Name: 2-Phenyl-1,3-propanediol dicarbamate |                                        |
|                       | Molecular Formula: C11H14N2O4                     |                                        |
|                       | Molecular Weight: 238.24 g/mol                   |                                        |
|                       | Mechanism: Felbamate, a dicarbamate, is an anticonvulsant agent. Exact mechanism of action unknown, but it is suggested that it increases seizure threshold and reduces seizure spread. In vitro studies indicate that felbamate has weak inhibitory effects on binding at GABA receptors and benzodiazepine receptors. The monocarbamate, p-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug |                                        |
|                       | Effect: Anticonvulsants                          |                                        |
|                       |                                                  |                                        |
### Table 6. Cont.

| Drug            | Properties | Pharmacogenetics |
|-----------------|------------|------------------|
| **Name: Gabapentin** | IUPAC Name: 2-[1-(aminomethyl)cyclohexyl] acetic acid | Mechanistic genes: GABRR1, GABRR2, KCNH2, SCN2A |
| **Molecular Formula:** C$_8$H$_{14}$N$_2$O$_2$ | **Molecular Weight:** 171.24 g/mol | **Metabolic genes:** |
| **Mechanism:** Gabapentin is an anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter GABA | **Inhibitor:** CYP2A6 | Transporter genes: ABCB1, SLC22A4 |
| **Effect:** Anticonvulsants, Analgesics and Antipyretics | | |
| **Name: Lamotrigine** | IUPAC Name: 1,2,4-Triazine-3,5-diamine, 6-[2,3-dichlorophenyl]-; (2) 3,5-Diamino-6-[2,3-dichlorophenyl]^-as-triazine | Mechanistic genes: ADORA1, ADORA2A, ADRA1A, ADRA2A, ADRB1, CACNA1E, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, GABRA1, GABRA2, GABRA3, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRG1, GABRG2, GABRG3, GABRD, GABRE, GABRP, GABRR1, GABRR2, GABRR3, GABRQ, HRH1, HTR2A, HTR3A, OPRK1, SCN2A |
| **Molecular Formula:** C$_9$H$_7$Cl$_2$N$_4$ | **Molecular Weight:** 256.09 g/mol | **Metabolic genes:** |
| **Mechanism:** Possibly involves inhibition of voltage-sensitive sodium channels, which stabilizes neuronal membranes and consequently modulates release of excitatory amino acid neurotransmitters (e.g. glutamate, aspartate) which play a role in generation and spread of epileptic seizures | | |
| **Effect:** Anticonvulsants, Miscellaneous | | |
| **Name: Levetiracetam** | IUPAC Name: 2-(S)-1-Pyrrolidineacetamide, α-ethyl-2-oxo-α-(α-S)-; (2)(-)-(S)-α-Ethyl-2-oxo-1-pyrrolidineacetamide | Mechanistic genes: CHRM3, CHRM4, ADRA1A, ADRA2A, ADORA1, ADORA2A, ADRA1A, ADRA2A, ADRB1, CACNA1E, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, GABRA1, GABRA2, GABRA3, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRG1, GABRG2, GABRG3, GABRD, GABRE, GABRP, GABRR1, GABRR2, GABRR3, GABRQ, HRH1, HTR2A, HTR3A, OPRK1, SCN2A |
| **Molecular Formula:** C$_8$H$_{14}$N$_2$O$_2$ | **Molecular Weight:** 170.21 g/mol | **Metabolic genes:** |
| **Mechanism:** The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission | | |
| **Effect:** Anticonvulsants | | |

**Table 6 continued...**
Table 6. Cont.

| Drug                  | Antiepileptics                                                                 | Pharmacogenetics               |
|-----------------------|--------------------------------------------------------------------------------|--------------------------------|
| **Name:** Oxcarbazepine| Molecular Weight: 252.27 g/mol                                                    | Mechanistic genes: SCN2A        |
| IUPAC Name: 5H-Dibenzo[b,f]azepine-5-carboxamide, 10,11-dihydro-10-oxo-10,11-Dihydro-10-oxo-5H-dibenzo[b,f]azepine-5-carboxamide | Metabolic genes: CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B7, UGT2B15 |
| Molecular Formula: C_{13}H_{12}N_{2}O_{2} | Mechanism: Pharmacological activity results from both oxcarbazepine and its monohydroxy metabolite (MHD). Oxcarbazepine and MHD block voltage-sensitive sodium channels, stabilizing hyperexcited neuronal membranes, inhibiting repetitive firing, and decreasing propagation of synaptic impulses. These actions are believed to prevent spread of seizures. Oxcarbazepine and MHD also increase potassium conductance and modulate activity of high-voltage activated calcium channels. Protects against electrically induced tonic extension seizures and, to a lesser degree, chemically-induced clonic seizures. May abolish or reduce frequency of chronically recurring focal seizures | Inducer: ABCB1, CYP3A4, CYP3A5 |
| Effect: Anticonvulsants |                                                                                   | Transporter genes: ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, SLC02A1                   |

**Name:** Phenobarbital

| IUPAC Name: 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-ethyl-5-phenyl-; (2) 5-Ethyl-5-phenylbarbituric acid |
| Molecular Weight: 232.24 g/mol |
| Mechanism: Long-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. Barbiturates depress sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. In high doses, barbiturates exhibit anticonvulsant activity. They also produce dose-dependent respiratory depression |
| Effect: Anticonvulsants; Barbiturates. Anxiolytics, Sedatives, and Hypnotics; Barbiturates |

**Name:** Phenytoin

| IUPAC Name: 5,5-Diphenylhydantoin |
| Molecular Formula: C_{13}H_{12}N_{2}O_{2} |
| Molecular Weight: 252.27 g/mol |
| Mechanism: Stabilizes neuronal membranes and decreases seizure activity by increasing influx or decreasing influx of sodium ions across cell membranes in motor cortex during generation of nerve impulses. Prolongs effective refractory period and suppresses ventricular pacemaker automaticity, shortens action potential in heart |
| Effect: Class Ib Antiarrhythmics. Anticonvulsants; Hydantoins |

**Mechanistic genes:** SCN2A  
**Metabolic genes:** CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B7, UGT2B15  
**Inducer:** ABCB1, CYP3A4, CYP3A5  
**Transporter genes:** ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, SLC02A1
Table 6. Cont.

| Drug | Properties | Pharmacogenetics |
|------|------------|------------------|
| **Primidone** | Name: Primidone | Mechanistic genes: GABRA1, IGF1, KCNH2, ACSL4, AGXT, CA1-5, GABRAs |
| IUPAC Name: 4,6(1H,5H)-Pyrimidinedione, 5-ethylhydro-5-phenyl-; 5-Ethylhydro-5-phenyl-4,6(1H,5H)-pyrimidinedione | | Metabolic genes: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP3A4 |
| Molecular Formula: C12H14N2O2 | Molecular Weight: 218.25 g/mol | Inducer: CYP3A4 |
| Mechanism: Decreases neuron excitability, raises seizure threshold similar to phenobarbital. Primidone has two active metabolites, phenobarbital and phenylethylmalonamide | | Inhibitor: CYP2E1 |
| Effect: Anticonvulsants; Barbiturates | | Substrate: CES |
| **Rufinamide** | Name: Rufinamide | Mechanistic genes: MAPK10, SCN1A |
| IUPAC Name: 1-[(2,6-difluorophenyl)methyl]-1H-1,2,3-triazole-4 carboxamide | | Metabolic genes: CYP3A4 |
| Molecular Formula: C16H14F2N4O | Molecular Weight: 238.2 g/mol | Inducer: CYP3A4 |
| Mechanism: The precise mechanism(s) by which rufinamide exerts its antiepileptic effect are unknown. The results of in vitro studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide (≥ 1 µM) significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive firing of sodium-dependent action potentials | | Inhibitor: CYP2E1 |
| Effect: Anticonvulsants; Triazole Derivative | | Substrate: CES |
| **Tiagabine** | Name: Tiagabine | Mechanistic genes: ABAT |
| IUPAC Name: 3-Piperidinecarboxylic acid, 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-, hydrochloride, (R)-; (-)-(R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]piperocetic acid, hydrochloride. | | Metabolic genes: CYP3A4 |
| Molecular Formula: C20H19NO5S2 | Molecular Weight: 412.01 g/mol | Transporter genes: SLC6A1 |
| Mechanism: Exact mechanism not definitively known; however, in vitro experiments demonstrate that it enhances activity of gamma-aminobutyric acid (GABA). It is thought that binding to GABA uptake carrier inhibits uptake of GABA into presynaptic neurons, allowing availability of increased amount of GABA to postsynaptic neurons. Based on in vitro studies, tiagabine does not inhibit uptake of dopamine, norepinephrine, serotonin, glutamate, or choline | | Inhibitor: CYP3A4 |
| Effect: Anticonvulsants | | Substrate: CES |
Table 6. Cont.

| Drug                  | Properties                                                                                       | Pharmacogenetics                                                                 |
|-----------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Name: Topimarate      |                                                                                                | Mechanistic genes: ACSL4, AGXT, CAA1-S, GABRA1, IGFL1, KCNH2, NR1D2, SCN1A, SCN2A |
| IUPAC Name:           | β-D-Fructopyranose, 2,3,4,5-bis-O-(1-methylethylidene)-, sulfamate; 2,3,4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate | Metabolic genes: Substrate: CYP3A4, Inhibitor: CYP2C19, Inducer: ABCB1, CYP3A4 |
| Molecular Formula:    | C_{12}H_{21}NO_{5}S                                                                          | Transporter genes: ABCB1                                                        |
| Molecular Weight:     | 339.36 g/mol                                                                                   |                                                                                  |
| Mechanism:            | Blocks neuronal voltage-dependent sodium channels, enhances GABA(A) activity, antagonizes AMPA/kainate glutamate receptors, and weakly inhibits carbonic anhydrase |                                                                                  |
| Effect:               | Anticonvulsants                                                                               |                                                                                  |
| Name: Valproic acid   |                                                                                                | Mechanistic genes: ABAT, ACADSB, ALDH5A1, HDAC2, OGDH, PPARA, PPARD, PPARG          |
| IUPAC Name:           | Pentanoic acid, 2-propyl-; (2) Propylvaleric acid                                             | Metabolic genes: Substrate: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2E1, CYP3A4, CYP3A5, CYP4B1, CYP4F2, PGT51, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B15 |
| Molecular Formula:    | C_{8}H_{16}O_{2}                                                                             | Inhibitor: CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, HDAC9, UGT1A9, UGT2B7, UGT2B15 |
| Molecular Weight:     | 144.21 g/mol                                                                                  | Transporter genes: ALB, SLC16A1, SLC22A5, SLC22A6, SLC22A7, SLC22A8, SLC02B1 |
| Mechanism:            | Causes increased availability of gamma-aminobutyric acid (GABA), to brain neurons or may enhance action of GABA or mimic its action at postsynaptic receptor sites |                                                                                  |
| Effect:               | Anticonvulsants, Miscellaneous, Antimanic Agents, Histone Deacetylase Inhibitor              |                                                                                  |

6. Conclusions

Symptomatic interventions for patients with dementia involve anti-dementia drugs to improve cognition, psychotropic drugs for the treatment of behavioral disorders (BDs), and different categories of drugs for concomitant disorders. Demented patients may take >6–10 drugs/day with the consequent risk for drug–drug interactions (DDIs) and adverse drug reactions (ADRs > 80%) which accelerate cognitive decline. PGx intervention may prevent ADRs and DDIs. The pharmacogenetic machinery is integrated by pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes redundantly and promiscuously regulated by epigenetic mechanisms (DNA methylation, chromatin remodeling/histone changes, and miRNAs). CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 geno-phenotypes are involved in the metabolism of over 90% of drugs currently used in patients with dementia, and only 20% of the population is an extensive metabolizer for this tetragenic cluster. ADRs associated with anti-dementia drugs, antipsychotics, antidepressants, anxiolytics, hypnotics, sedatives, and antiepileptic drugs can be minimized by means of pharmacogenetic screening prior to treatment. These drugs are substrates, inhibitors, or inducers of 58, 37, and 42 enzyme/protein gene products, respectively, and are transported by 40 different protein transporters. APOE is the reference gene in most pharmacogenetic studies. In multifactorial treatments, APOE-3 carriers are the best responders and APOE-4 carriers are the worst responders; likewise, CYP2D6-EMS are the best responders and CYP2D6-PMs are the worst responders. ACHE-BCHE variants also affect the pharmacogenetic outcome as well as some genes encoding components of the epigenetic machinery.

Antipsychotics show limited efficacy in aggressive behaviors and psychotic symptoms and may increase mortality and risk of psychomotor disorders and cerebrovascular events. Major ADRs with
antipsychotics are extrapyramidal symptoms, tardive dyskinesia, weight gain, hyperprolactinemia, and agranulocytosis. Antipsychotics are associated with the activity of ≈100 pharmagenes; antidepressants are associated with 600; and anxiolytics, hypnotics, and sedatives are associated with 445. CYP enzymes are involved in 100% of drugs approved for the treatment of depression, and about 60% of depressive patients are receiving an inappropriate medication according to their pharmacogenetic background. Carbamazepine, oxcarbazepine, or phenytoin may cause delayed-hypersensitivity reactions associated with the HLA antigen allele HLA-B*15:02.

The incorporation of pharmacogenomic strategies for a personalized treatment in dementia is an effective option to optimize limited therapeutic resources and to reduce unwanted side-effects.

### 7. Further Considerations

Drug efficacy and safety are fundamental issues in dementia due to the complexity of the disorder and comorbidities which require polypharmacy [43]. Over 50% of patients over 60 years of age suffering chronic CNS disorders currently take 6–12 drugs/day with a high risk of drug toxicity, ADRs, and DDIs [43,56]. Over 20% of patients with depression develop dementia in a period of approximately 10 years. The chronic use of anticholinergic antidepressants might contribute to this pathogenic transformation [318]. It is also well-known that over 60% of patients chronically treated with antipsychotics develop extrapyramidal symptoms which may induce severe motor disability [319]. Over 80% of nursing home residents are daily consumers of psychotropic drugs [320,321] which are prescribed in excessive doses, for excessive duration, and without adequate monitoring and/or indications for their use [322]. Prescribing errors (≈50%) are common in patients treated with anti-dementia drugs [42], and potentially inappropriate prescribing (PIP) occurs in almost 80% of patients with dementia [323].

With appropriate PGx intervention, the frequency and intensity of PIP and ADRs may be reduced in approximately 50% of the cases. AD patients show diverse age-related comorbidities which require polypharmacy. The implementation of PGx procedures may help to minimize drug–drug interactions. For instance, CYP2C19 variants influence the effects of proton-pump inhibitors and the onset of infections [324]. ACE variants affect the pharmacokinetics and pharmacodynamics of ACE inhibitors which may interact with psychotropic drugs, contributing to cerebrovascular dysfunction [229].

Another important issue is the use of anticoagulants in patients with dementia [103]. Different antithrombotic drugs (Acenocoumarol, Acetylsalicylic acid, Argatroban, Bivalirudin, Cilostazol, Clopidogrel, Dabigatran, Rivaroxaban, Dipyridamole, Lepirudin, Prasugel, Ticagrelor, Ticlopidine, and Warfarin) can be used in patients with atrial fibrillation, thrombophilebitis, and thromboembolic or ischemic stroke. Warfarin is one of the most common anticoagulants due to its low cost; however, its narrow therapeutic window makes it a candidate to a few ADRs in patients with dementia. Warfarin prolongs prothrombin time (PT) and activated partial thromboplastin time (APTT), and phytonadione (vitamin K1) reverses its anticoagulant effect. Warfarin is a substrate of CALU, CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP3A4/5, CYP4F2, EPHX1, and GGCX; an inhibitor of CYP2C9, CYP2C19, and VKORC1; and an inducer of CYP2C9; and is transported by ABCB1. CYP2C9 and VKORC1 variants are determinant in warfarin efficacy and safety [55]. VKORCI variants and CYP2C9*3 are clearly associated with warfarin maintenance dosages. CYP2C9 and VKORC1 genotypes help to identify normal responders (60%), sensitive responders (35%), and highly sensitive responders (3%) to warfarin and characterized patients who can benefit from edoxaban compared with warfarin [325]. VKORC1-AG and GG carriers need higher doses than patients with AA genotypes, and CYP2C9*1/*3 carriers need doses lower than patients with the CYP2C9*1/*1 wild genotype [326]. In the Chinese region of Xinjiang, patients with atrial fibrillation carrying the CT and TT genotypes in the GGCX gene rs259251 loci need higher warfarin doses than GGCX-CC carriers [327].

**ADRB1 Ser49Gly** and **Arg389Gly** variants are associated with cardiovascular and β-blocker response outcomes. In patients with previous history of stroke, the **ADRB1 Gly49** polymorphism is associated with cardiovascular and cerebrovascular ADRs among β-blocker users [328].
In patients with minor ischemic stroke, platelet receptor gene (P2Y12 and P2Y1) and glycoprotein gene (GPIIIa) polymorphisms influence antiplatelet drug responsiveness and clinical outcomes [329], and there are genetic differences (rs12143842) in the response of stroke patients to antihypertensive drugs (chlorothalidone, amlodipine, or lisinopril), especially regarding HNRNP A1P4 and NOS1AP variants in African Americans and PRICKLE1 and NINJ2 variants in non-Hispanic Whites [330].

Rivaroxaban is currently used in thromboprophylaxis. ABCB1 rs1045642, ABCB1 rs4148738, CYP3A4 rs35599367, and CYP3A5 rs776746 variants may influence rivaroxaban pharmacokinetics and prothrombin time dynamics [331].

The platelet-aggregation inhibitor Clopidogrel may also cause frequent complications. This antithrombotic agent is a substrate of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5; and an inhibitor of CYP2B6, CYP2C9, and CYP2C19; and is transported by ABCB1. CYP2C19*2 (G681A and rs4244285), CYP2C19*3 (G363A and rs4986893), CYP2C19*17 (C806T and rs12248560), and ABCB1 (C3435T and rs1045642) carriers with ischemic stroke are particularly sensitive to clopidogrel ADRs [55]. Clopidogrel resistance is frequent in patients with chronic kidney disease. Kidney dysfunction alters the association between CYP2C19 variants and clopidogrel effects in patients with stroke or transient ischemic attack. Carriers of CYP2C19 loss-of-function alleles (CYP2C19*2 and *3) have higher odds of new stroke than noncarriers [332,333] and increased risk of thromboembolic complications following neurointerventional procedures [334]. The AKR1D1*36 (rs1872930) allele is associated with the risk of major adverse cardiovascular and cerebrovascular events in clopidogrel-treated patients [335]. About 16–50% of patients treated with clopidogrel show platelet reactivity and an increased risk of ischemic events. Some methylated CpG sites have been associated with increased stroke recurrence. Lower cg03548645 (TRAF3) DNA methylation correlates with increased platelet aggregation in patients with stroke [336].

Studies on the PGx of anticoagulants for stroke prevention in patients with atrial fibrillation are not conclusive and deserve further investigation to optimize this currently used pharmacological intervention with still unclear results [337].

Orthopedic surgery is relatively frequent in patients with NDDs who experience perioperative neurocognitive disorders (delirium and postoperative cognitive dysfunction) which increase mortality [338]. PGx assessment is highly recommended for selection of appropriate anesthetics and postsurgical treatments in order to reduce postoperative BDs and accelerated cognitive deterioration [55].

Opioid use disorder (OUD) is infrequent in AD; however, in AD cases treated with opioids, it is important to take into account that patients with at least one copy of the CYP3A4*1B allele exhibit an accelerated rate of metabolism compared to the wild-type allele CYP3A4*1 [339] and that CYP2D6-UMs show a better response to opiates than EMs, IMs, and PMs [55].

Several essential elements and metals (zinc, aluminum, copper, and cadmium), environmental toxicants, air pollutants (e.g., nanoparticles, particulate matter, ozone, and traffic-related air pollution), inappropriate medications, and drugs of abuse (amphetamines, cannabis, cocaine, and heroin) may contribute to neurotoxicity and may interfere with conventional treatments in dementia. Over 30% of patients with prodromal dementia are current users of anticholinergic drugs [340]. Chronic exposure to these products alters behavior and deteriorates cognition and psychomotor function in a dose-dependent fashion [341–343]. The pharmacogenetic genotyping of detoxification systems may help to predict risks in susceptible subjects [55].

It is also most important to elucidate the mechanisms underlying the drug-resistance phenomenon, which occurs in over 40% of cases with NPDs and in over 70% of cases with neoplastic processes [61,71]. Globally, over 20% of patients are resistant to conventional drugs [344,345] and it is estimated that pharmacogenetic and pharmacoepigenetic factors are important contributors to drug resistance [61,346–348].

Important issues to take into account in the coming years for the appropriate management of dementia are the identification of symptomatic biomarkers and the discovery of effective drugs.
Predictive markers associated with pathogenic genes for the presymptomatic diagnosis of dementia should incorporate both genomic and epigenetic signatures. Concerning the development of novel anti-pathogenic drugs, actual facts show that most CNS drugs are repressive rather than neuroprotective based on the regulation of a restrictive number of neurotransmitters; however, brain function depends upon the interplay of thousands of neuronal-glial factors pending full characterization. The discovery of novel anti-pathogenic drugs with neuroprotective properties is urgently needed to efficiently treat the different forms of brain dysfunction in dementia. The development of new drugs and clinically validated methods of identifying patients for a specific treatment should rely on PGx strategies.

**Funding:** This paper was funded by IABRA (International Agency for Brain Research and Aging), Corunna, Spain.

**Acknowledgments:** I would like to thank my coworkers at EuroEspes Biomedical Research Center, International Center of Neuroscience and Genomic Medicine, Corunna, for technical support in our studies on pharmacogenomics and epigenetics of dementia.

**Conflicts of Interest:** The author is President of the International Center of Neuroscience and Genomic Medicine, EuroEspes Biotechnology, and IABRA (International Agency for Brain Research and Aging) and is also President of the World Association of Genomic Medicine and Editor-in-Chief of the World Guide for Drug Use and Pharmacogenomics. The author has no other relevant affiliations or financial involvement with any organization or entity with financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**References**

1. Cacabelos, R.; Fernández-Novoa, L.; Lombardi, V.; Kubota, Y.; Takeda, M. Molecular genetics of Alzheimer’s disease and aging. *Methods Find. Exp. Clin. Pharmacol.* **2005**, *27*, 1–573.
2. Cacabelos, R. Pharmacogenomics in Alzheimer’s disease. *Methods Mol. Biol.* **2008**, *448*, 213–357. [CrossRef] [PubMed]
3. Cacabelos, R.; Cacabelos, P.; Torrellas, C.; Tellado, I.; Carril, J.C. Pharmacogenomics of Alzheimer’s disease: Novel therapeutic strategies for drug development. *Methods Mol. Biol.* **2014**, *1175*, 323–556. [CrossRef] [PubMed]
4. Cacabelos, R.; Carril, J.C.; Cacabelos, P.; Teijido, O.; Goldgaber, D. Pharmacogenomics of Alzheimer’s Disease: Genetic determinants of phenotypic variation and therapeutic outcome. *J. Genom. Mol. Pharmacogenom.* **2016**, *1*, 151–209.
5. Cacabelos, R.; Carril, J.C.; Cacabelos, N.; Kazantsev, A.G.; Vostrov, A.V.; Corzo, L.; Cacabelos, P.; Goldgaber, D. Sirtuins in Alzheimer’s Disease: SIRT2-Related GenoPhenotypes and Implications for PharmacoEpiGenetics. *Int. J. Mol. Sci.* **2019**, *20*, 1249. [CrossRef] [PubMed]
6. Arvanitakis, Z.; Shah, R.C.; Bennett, D.A. Diagnosis and Management of Dementia: Review. *JAMA* **2019**, *322*, 1589–1599. [CrossRef] [PubMed]
7. Cacabelos, R. Have there been improvement in Alzheimer’s disease drug discovery over the past 5 years? *Expert Opin. Drug Discov.* **2018**, *13*, 523–538. [CrossRef] [PubMed]
8. Volier, L. Behavioral Problems and Dementia. *Clin. Geriatr. Med.* **2018**, *34*, 637–651. [CrossRef] [PubMed]
9. De Francesco, M.; Marksteiner, J.; Kemmler, G.; Dal-Bianco, P.; Ransmayr, G.; Benke, T.; Mosbacher, J.; Holler, Y.; Schmidt, R. Specific Neuropsychiatric Symptoms Are Associated with Faster Progression in Alzheimer’s Disease: Results of the Prospective Dementia Registry (PRODEM-Austria). *J. Alzheimers Dis.* **2020**, *73*, 125–133. [CrossRef] [PubMed]
10. Sr, P.A.A.; DeFeis, B.; De Wit, L.; O’Shea, D.; Mejia, A.; Chandler, M.; Locke, D.E.C.; Fields, J.; Phatak, V.; Dean, P.M.; et al. Functional ability is associated with higher adherence to behavioral interventions in mild cognitive impairment. *Clin. Neuropsychol.* **2019**, 1–19. [CrossRef] [PubMed]
11. Ilik, F.; Büyükgöl, H.; Kayhan, F.; Ertem, D.H.; Ekiz, T. Effects of Inappropriate Sexual Behaviors and Neuropsychiatric Symptoms of Patients with Alzheimer Disease and Caregivers’ Depression on Caregiver Burden. *J. Geriatr. Psychiatry Neurol.* **2019**, *891988719874123*. [CrossRef] [PubMed]
12. Burhanullah, M.H.; Tschanz, J.T.; Peters, M.E.; Leoutsakos, J.M.; Matyi, J.; Lyketsos, C.G.; Nowrangi, M.A.; Rosenberg, P.B. Neuropsychiatric Symptoms as Risk Factors for Cognitive Decline in Clinically Normal Older Adults: The Cache County Study. *Am. J. Geriatr. Psychiatry* **2020**, *28*, 64–71. [CrossRef] [PubMed]
13. Lai, A.X.; Kaup, A.R.; Yaffe, K.; Byers, A.L. High Occurrence of Psychiatric Disorders and Suicidal Behavior Across Dementia Subtypes. *Am. J. Geriatr. Psychiatry* 2018, 26, 1191–1201. [CrossRef]

14. Cummings, J.; Lai, T.J.; Hemrungroj, S.; Mohandas, E.; Yun Kim, S.; Nair, G.; Dash, A. Role of Donepezil in the Management of Neuropsychiatric Symptoms in Alzheimer’s Disease and Dementia with Lewy Bodies. *CNS Neurosci. Ther.* 2016, 22, 159–166. [CrossRef]

15. Deardorff, W.J.; Grossberg, G.T. Behavioral and psychological symptoms in Alzheimer’s dementia and vascular dementia. *Handb. Clin. Neurol.* 2019, 165, 33–45. [CrossRef] [PubMed]

16. van de Beek, M.; van Steenoven, I.; Ramakers, I.H.G.B.; Aalten, P.; Koek, H.L.; Olde Rikkert, M.G.M.; Mannien, J.; de Jong, F.J.; Lemstra, A.W.; van der Flier, W.M. Trajectories and Determinants of Quality of Life in Dementia with Lewy Bodies and Alzheimer’s Disease. *J. Alzheimers Dis.* 2019, 70, 389–397. [CrossRef] [PubMed]

17. Chen, Y.; Wilson, L.; Kornak, J.; Dudley, R.A.; Merriilees, J.; Byrne, C.M.; Lee, K.; Chiong, W.; Miller, B.L.; et al. The costs of dementia subtypes to California Medicare fee-for-service. *Alzheimers Dement* 2019, 15, 899–906. [CrossRef] [PubMed]

18. Miller, B.; Libre Guerra, J.J. Frontotemporal dementia. *Handb. Clin. Neurol.* 2019, 165, 33–45. [CrossRef]

19. Buss, C.; Pettenuzzo, I.; Pompanin, S.; Roiter, B.; di Bernardo, G.A.; Zorzi, G.; Fragiacomito, F.; Gazzola, G.; Cecchin, D.; Pigato, G.; et al. Psychiatric Phenocopy Syndrome of Behavioral Frontotemporal Dementia: Behavioral and Cognitive Fingerprint. *J. Alzheimers Dis.* 2019, 72, 1159–1164. [CrossRef]

20. Butler, P.M.; Chiong, W. Neurodegenerative disorders of the human frontal lobes. *Handb. Clin. Neurol.* 2019, 163, 391–410. [CrossRef]

21. Bailey, K.C.; Burmaster, S.A.; Schaffert, J.; LoBue, C.; Vela, D.; Rossetti, H.; Cullum, C.M. Associations of Race-Ethnicity and History of Traumatic Brain Injury with Age at Onset of Alzheimer’s Disease. *J. Neuropsychiatry Clin. Neurosci* 2019, appineuropsych19010002. [CrossRef] [PubMed]

22. Schwab, N.; Grenier, K.; Hazrati, L.N. DNA repair deficiency and senescence in concussed professional athletes involved in contact sports. *Acta Neuropathol. Commun.* 2019, 7, 182. [CrossRef] [PubMed]

23. Keszycki, R.M.; Fisher, D.W.; Dong, H. The Hyperactivity-Impulsivity-Irritiability-Disinhibition-Aggression-Agitation Domain in Alzheimer’s Disease: Current Management and Future Directions. *Front. Pharmacol.* 2019, 10, 1109. [CrossRef] [PubMed]

24. Desmarais, P.; Weidman, D.; Wassef, A.; Bruneau, M.A.; Friedland, J.; Bajsaarowicz, P.; Thibodeau, M.P.; Herrmann, N.; Nguyen, Q.D. The Interplay between Post-traumatic Stress Disorder and Dementia: A Systematic Review. *Am. J. Geriatr. Psychiatry* 2020, 28, 46–60. [CrossRef] [PubMed]

25. Cacabelos, R.; Martínez-Bouza, R. Genomics and pharmacogenomics of schizophrenia. *CNS Neurosci. Ther.* 2011, 17, 541–565. [CrossRef] [PubMed]

26. Cacabelos, R.; Torrellas, C. Epigenetics of Aging and Alzheimer’s Disease: Implications for Pharmacogenomics and Drug Response. *Int. J. Mol. Sci.* 2015, 16, 30483–30543. [CrossRef]

27. Cacabelos, R.; Cacabelos, P.; Aliev, G. Genomics and pharmacogenomics of antipsychotic drugs. *Open J. Psychiatry* 2013, 3, 46–139. [CrossRef]

28. Martins, L.B.; Monteze, N.M.; Calarge, C.; Ferreira, A.V.M.; Teixeira, A.L. Pathways linking obesity to neuropsychiatric disorders. *Nutrition* 2019, 66, 16–21. [CrossRef]

29. Morton, R.E.; St John, P.D.; Tyas, S.L. Migraine and the risk of all-cause dementia, Alzheimer’s disease, and vascular dementia: A prospective cohort study in community-dwelling older adults. *Int. J. Geriatr. Psychiatry* 2019, 34, 1667–1676. [CrossRef]

30. Blom, K.; Koek, H.L.; Zwartbol, M.H.T.; van der Graaf, Y.; Kesseler, L.; Biessels, G.J.; Geerlings, M.I.; SMART Study Group. Subjective cognitive decline, brain imaging biomarkers, and cognitive functioning in patients with a history of vascular disease: The SMART-Medea study. *Neurobiol. Aging* 2019, 84, 33–40. [CrossRef]

31. Puzo, C.; Labriola, C.; Sugarman, M.A.; Tripodis, Y.; Martin, B.; Palmissano, J.N.; Steinber, E.G.; Stein, T.D.; Kowall, N.W. Independent effects of white matter hyperintensities on cognitive, neuropsychiatric, and functional decline: A longitudinal investigation using the National Alzheimer’s Coordinating Center Uniform Data Set. *Alzheimers Res. Ther.* 2019, 11, 64. [CrossRef] [PubMed]

32. Rouch, I.; Dorey, J.M.; Padovan, C.; Trombert-Paviot, B.; Benoit, M.; Laurent, B.; PACO group; Boublay, N.; Krolak-Salmon, P. Does Personality Predict Behavioral and Psychological Symptoms of Dementia? Results from PACO Prospective Study. *J. Alzheimers Dis.* 2019, 69, 1099–1108. [CrossRef]
33. Banning, L.C.P.; Ramakers, I.H.G.B.; Deckers, K.; Verhey, F.R.J.; Aalten, P. Affective symptoms and AT(N) biomarkers in mild cognitive impairment and Alzheimer’s disease: A systematic literature review. *Neurosci. Biobehav. Rev.* 2019, 107, 346–359. [CrossRef] [PubMed]

34. Scaricamazza, E.; Colonna, I.; Sancesario, G.M.; Assogna, F.; Orfei, M.D.; Franchini, F.; Sancesario, G.; Mercuri, N.B.; Liguori, C. Neuropsychiatric symptoms differently affect mild cognitive impairment and Alzheimer’s disease patients: A retrospective observational study. *Neurol. Sci.* 2019, 40, 1377–1382. [CrossRef] [PubMed]

35. Showraki, A.; Murari, G.; Ismail, Z.; Barfett, J.J.; Fornazzari, L.; Munoz, D.G. Cerebrospinal Fluid Correlates of TDP-43 and TDP-43 Segmental Amyloidosis in Alzheimer’s Disease. *Neurol. Sci.* 2019, 40, 290–295. [CrossRef]

36. Ramusino, M.C.; Garibotto, V.; Bacchin, R.; Altomare, D.; Dodich, A.; Assal, F.; Mendes, A.; Costa, A.; Tinazzi, M.; Morbelli, S.D.; et al. Incremental value of amyloid-PET versus CSF in the diagnosis of Alzheimer’s disease. *Eur. J. Nucl. Med. Mol. Imaging* 2020, 47, 270–280. [CrossRef]

37. Bayram, E.; Shan, G.; Cummings, J.L. Associations between Comorbid TDP-43, Lewy Body Pathology, and Neuropsychiatric Symptoms in Patients with Alzheimer’s Disease/Mild Cognitive Impairment: A Systematic Review. *J. Alzheimers Dis.* 2019, 71, 477–501. [CrossRef]

38. Sellami, L.; St-Onge, F.; Poulin, S.; Laforce, R., Jr. Schizophrenia Phenotype Preceding Behavioral Variant Frontotemporal Dementia Related to C9orf72 Repeat Expansion. *Cogn. Behav. Neurol.* 2019, 32, 120–123. [CrossRef]

39. Latimer, C.S.; Burke, B.T.; Liachko, N.F.; Currey, H.N.; Kilgore, M.D.; Gibbons, L.E.; Henriksen, J.; Darvas, M.; Domoto-Reilly, K.; Jayadev, S.; et al. Resistance and resilience to Alzheimer’s disease pathology are associated with reduced cortical pTau and absence of limbic-predominant age-related TDP-43 encephalopathy in a community-based cohort. *Acta Neuropathol. Commun.* 2019, 7, 9. [CrossRef]

40. Pirker-Kees, A.; Dal-Bianco, P.; Schmidt, R. Effects of Psychotropic Medication on Cognition, Caregiver Burden, and Neuropsychiatric Symptoms in Alzheimer’s Disease over 12 Months: Results from a Prospective Registry of Dementia in Austria (PRODEM). *J. Alzheimers Dis.* 2019, 71, 623–630. [CrossRef]

41. Bravo-José, P.; Sáez-Lleó, C.I.; Peris-Martí, J.F. Deprescribing antipsychotics in long term care patients with dementia. *Farn. Hosp.* 2019, 43, 140–145. [CrossRef] [PubMed]

42. Mantri, S.; Fullard, M.; Gray, S.L.; Weintraub, D.; Hubbard, R.A.; Hennessy, S.; Willis, A.W. Patterns of Dementia Treatment and Frank Prescribing Errors in Older Adults With Parkinson Disease. *JAMA Neurol.* 2019, 76, 41–49. [CrossRef] [PubMed]

43. Cacabelos, R.; Cacabelos, N.; Carril, J.C. The role of pharmacogenomics in adverse drug reactions. *Expert Rev. Clin. Pharmacol.* 2019, 12, 407–422. [CrossRef]

44. Zheng, W.Y.; Richardson, L.C.; Li, L.; Day, R.O.; Westbrook, J.I.; Baysari, M.T. Drug-drug interactions and their harmful effects in hospitalised patients: A systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* 2018, 74, 15–27. [CrossRef] [PubMed]

45. Patel, R.I.; Beckett, R.D. Evaluation of resources for analyzing drug interactions. *J. Med. Libr. Assoc.* 2016, 104, 290–295. [CrossRef]

46. Shoshi, A.; Müller, U.; Shoshi, A.; Ogultarhan, V.; Hofestadt, R. KALIS—An eHealth System for Biomedical Risk Analysis of Drugs. *Stud. Health Technol. Inform.* 2017, 236, 128–135.

47. Shoshi, A.; Hoppe, T.; Kormeier, B.; Ogultarhan, V.; Hofestadt, R. GraphSAW: A web-based system for graphical analysis of drug interactions and side effects using pharmaceutical and molecular data. *BMC Med. Inform. Decis. Mak.* 2015, 15, 15. [CrossRef]

48. Huang, F.; Fu, Y. A review of clinical pharmacokinetics and pharmacodynamics of galantamine, a reversible acetylcholinesterase inhibitor for the treatment of Alzheimer’s disease, in healthy subjects and patients. *Curr. Clin. Pharmacol.* 2010, 5, 115–124. [CrossRef]

49. Samwald, M.; Miñarro Giménez, J.A.; Boyce, R.D.; Frimuth, R.R.; Adlassnig, K.P.; Dumontier, M. Pharmacogenomic knowledge representation, reasoning and genome-based clinical decision support based on OWL 2 DL ontologies. *BMC Med. Inform. Decis. Mak.* 2015, 15, 12. [CrossRef]

50. Zhang, G.; Zhang, Y.; Ling, Y.; Jia, J. Web resources for pharmacogenomics. *Genom. Proteom. Bioinform.* 2015, 13, 51–54. [CrossRef]

51. PharmGKB. Available online: https://www.pharmgkb.org (accessed on 5 January 2020).

52. Weinshilboum, R.M.; Wang, L. Pharmacogenomics: Precision Medicine and Drug Response. *Mayo Clin. Proc.* 2017, 92, 1711–1722. [CrossRef]
53. Kozyra, M.; Ingelman-Sundberg, M.; Lauschke, V.M. Rare genetic variants in cellular transporters, metabolic enzymes, and nuclear receptors can be important determinants of interindividual differences in drug response. Genet. Med. 2017, 19, 20–29. [CrossRef]

54. Zhou, Z.W.; Chen, X.W.; Sneed, K.B.; Yang, Y.X.; Zhang, X.; He, Z.X.; Chow, K.; Yang, T.; Duan, W.; Zhou, S.F. Clinical association between pharmacogenomics and adverse drug reactions. Drugs 2015, 75, 589–631. [CrossRef]

55. Cacabelos, R. World Guide for Drug Use and Pharmacogenomics; EuroEspes Publishing: Corunna, Spain, 2012.

56. EuroPharmaGenics (EPG). Available online: http://europharmagenics.com (accessed on 2 November 2019).

57. Cacabelos, R. Population-level pharmacogenomics for precision drug development in dementia. Expert Rev. Precis. Med. Drug Disc. 2018, 3, 163–188. [CrossRef]

58. Cacabelos, R. Epigenomic networking in drug development: From pathogenic mechanisms to pharmacogenomics. Drug Dev. Res. 2014, 75, 348–365. [CrossRef]

59. Marcath, L.A.; Pasternak, A.L.; Hertz, D.L. Challenges to assess substrate-dependent allelic effects in CYP450 enzymes and the potential clinical implications. Pharmacogenom. J. 2019. [CrossRef] [PubMed]

60. Lesche, D.; Mostafa, S.; Everall, I.; Pantelis, C.; Bousman, C. Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenocconversion-predicted enzyme activity on clozapine exposure and symptom severity. Pharmacogenom. J. 2019. [CrossRef] [PubMed]

61. Cacabelos, R.; Tellado, I.; Cacabelos, P. The epigenetic machinery in the life cycle and pharmacoepigenetics. In Pharmacoepigenetics; Cacabelos, R., Ed.; Academic Press/Elsevier: Oxford, UK, 2019; pp. 1–100.

62. Cacabelos, R.; Carril, J.C.; Sanmartín, A.; Cacabelos, P. Pharmacoepigenetic processors: Epigenetic drugs, Drug resistance, Toxicoeigenetics, and Nutriepigenetics. In Pharmacoepigenetics; Cacabelos, R., Ed.; Academic Press/Elsevier: Oxford, UK, 2019; pp. 191–424.

63. Apostolova, L.G.; Risacher, S.L.; Duran, T.; Stage, E.C.; Goukasian, N.; West, J.D.; Do, T.M.; Grotts, J.; Wilhalme, H.; Nho, K.; et al. Alzheimer’s Disease Neuroimaging Initiative. Associations of the Top 20 Alzheimer Disease Risk Variants with Brain Amyloidosis. JAMA Neurol. 2018, 75, 328–341. [CrossRef] [PubMed]

64. Cacabelos, R.; Meyyazhagan, A.; Carril, J.C.; Cacabelos, P.; Teijido, O. Pharmacogenetics of Vascular Risk Factors in Alzheimer’s Disease. J. Personalized Med. 2018, 8, 3. [CrossRef]

65. Cacabelos, R. Pleiotropy and promiscuity in pharmacogenomics for the treatment of Alzheimer’s disease and related risk factors. Future Neurol. 2018. [CrossRef]

66. Cacabelos, R.; Torrellas, C. Epigenetic drug discovery for Alzheimer’s disease. Expert Opin. Drug Discov. 2014, 9, 1059–1086. [CrossRef] [PubMed]

67. Cacabelos, R.; Torrellas, C. Pharmacogenomics of antidepressants. HSOA J. Psychiatry Depress. Anxiety 2015, 1, 001. [CrossRef]

68. Foraker, J.; Millard, S.P.; Leong, L.; Thomson, Z.; Chen, S.; Keene, C.D.; Bekris, L.M.; Yu, C.E. The APOE Gene is Differentially Methylated in Alzheimer’s Disease. J. Alzheimers Dis. 2015, 48, 745–755. [CrossRef] [PubMed]

69. Vogelgesang, S.; Cascorbi, I.; Schroeder, E.; Pahnke, J.; Kroemer, H.K.; Siegmund, W.; Kunert-Keil, C.; Walker, L.C.; Warzok, R.W. Deposition of Alzheimer’s beta-amyloid is inversely correlated with P-glycoprotein expression in the brains of elderly non-demented humans. Pharmacogenetics 2002, 12, 535–541. [CrossRef] [PubMed]

70. Szablewski, L. Glucose Transporters in Brain: In Health and in Alzheimer’s Disease. J. Alzheimers Dis. 2017, 55, 1307–1320. [CrossRef] [PubMed]

71. Cacabelos, R.; Lópezmunoz, F. The ABCB1 transporter in Alzheimer’s disease. Clin. Exp. Pharmacol. 2014, 4, e128. [CrossRef]

72. Cacabelos, R.; Cacabelos, P.; Carril, J.C. Epigenetics and pharmacoepigenetics of age-related neurodegenerative disorders. In Pharmacoepigenetics; Cacabelos, R., Ed.; Academic Press/Elsevier: Oxford, UK, 2019; pp. 903–950.

73. Berg, C.N.; Sinha, N.; Gluck, M.A. The Effects of APOE and ABCA7 on Cognitive Function and Alzheimer’s Disease Risk in African Americans: A Focused Mini Review. Front. Hum. Neurosci. 2019, 13, 387. [CrossRef]

74. Pereira, C.D.; Martins, F.; Wiltfang, J.; da Cruz E Silva, O.A.B.; Rebelo, S. ABC Transporters Are Key Players in Alzheimer’s Disease. J. Alzheimers Dis. 2018, 61, 463–485. [CrossRef]
Marquez, B.; Van Bambeke, F. ABC multidrug transporters: Target for modulation of drug pharmacokinetics and drug-drug interactions. *Curr. Drug Targets* 2011, 12, 600–620. [CrossRef]

Haufler, V. Genetic polymorphisms of ATP-binding cassette transporters ABCB1 and ABCC2 and their impact on drug disposition. *Curr. Drug Targets* 2011, 12, 631–646. [CrossRef]

van Assema, D.M.; Lubberink, M.; Rizzu, P.; van Swieten, J.C.; Schuit, R.C.; Eriksson, J.; Scheltens, P.; Koepp, M.; Lammertma, A.A.; van Berckel, B.N. Blood-brain barrier P-glycoprotein function in healthy subjects and Alzheimer’s disease patients: Effect of polymorphisms in the ABCBI gene. *EJNMMI Res.* 2012, 2, 57. [CrossRef] [PubMed]

Chen, K.D.; Chang, P.T.; Ping, Y.H.; Lee, H.C.; Yeh, C.W.; Wang, P.N. Gene expression profiling of peripheral blood leukocytes identifies and validates ABCB1 as a novel biomarker for Alzheimer’s disease. *Neurobiol. Dis.* 2011, 43, 698–705. [CrossRef]

Elali, A.; Rivest, S. The role of ABCB1 and ABCA1 in beta-amyloid clearance at the neurovascular unit in Alzheimer’s disease. *Front. Physiol.* 2013, 4, 45. [CrossRef] [PubMed]

Cascorbi, I.; Flüh, C.; Remmler, C.; Haenisch, S.; Grumbt, M.; Peters, M.; Brenn, A.; Thal, D.R.; Warzok, R.W.; Vogelgesang, S. Association of ATP-binding cassette transporter variants with the risk of Alzheimer’s disease. *Pharmacogenomics* 2013, 14, 485–494. [CrossRef] [PubMed]

Reitz, C.; Jun, G.; Naj, A.; Rajbhandary, R.; Vardarajan, B.N.; Wang, L.S.; Valladares, O.; Lin, C.F.; Larson, E.B.; Graff-Radford, N.R. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ε4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA* 2013, 309, 1483–1492. [CrossRef] [PubMed]

Vasquez, J.B.; Simpson, J.F.; Harpole, R.; Estus, S. Alzheimer’s Disease Genetics and ABCA7 Splicing. *J. Alzheimers Dis.* 2017, 59, 633–641. [CrossRef] [PubMed]

Yamazaki, K.; Yoshino, Y.; Mori, T.; Yoshida, T.; Ozaki, Y.; Sao, T.; Mori, Y.; Ochi, S.; Iga, J.I.; Ueno, S.I. Gene Expression and Methylation Analysis of ABCA7 in Patients with Alzheimer’s Disease. *J. Alzheimers Dis.* 2017, 57, 171–181. [CrossRef]

Stepler, K.E.; Robinson, R.A.S. The Potential of ‘Omics to Link Lipid Metabolism and Genetic and Comorbidty Risk Factors of Alzheimer’s Disease in African Americans. *Adv. Exp. Med. Biol.* 2019, 1118, 1–28. [CrossRef]

Ma, F.C.; Wang, H.F.; Cao, X.P.; Tan, C.C.; Tan, L.; Yu, J.T. Meta-Analysis of the Association between Variants in ABCA7 and Alzheimer’s Disease. *J. Alzheimers Dis.* 2018, 63, 1261–1267. [CrossRef]

Zhou, G.; Mao, X.; Chu, J.; Chen, G.; Zhao, Q.; Wang, L.; Luo, Y. ATP binding cassette subfamily A member 7 rs3764650 polymorphism and the risk of Alzheimer’s disease. *Pharmazie* 2017, 72, 425–427. [CrossRef]

De Roeck, A.; Duchateau, L.; Van Dongen, J.; Cacace, R.; Bjerke, M.; Van den Bossche, T.; Cras, P.; Vandenberghe, R.; De Deyn, P.P.; Engelborghs, S.; et al. An intronic VNTR affects splicing of ABCA7 and increases risk of Alzheimer’s disease. *Acta Neuropathol.* 2018, 135, 827–837. [CrossRef] [PubMed]

Lamartinière, Y.; Boucau, M.C.; Dehouck, L.; Krohn, M.; Pahnke, J.; Candela, P.; Gosselet, F.; Fenart, L. ABCA7 Downregulation Modifies Cellular Cholesterol Homeostasis and Decreases Amyloid-β Peptide Efflux in an in vitro Model of the Blood-Brain Barrier. *J. Alzheimers Dis.* 2018, 64, 1195–1211. [CrossRef] [PubMed]

Güven, G.; Vurgun, E.; Bilgic, B.; Hanagasi, H.; Gurvit, H.; Ozger, E.; Lohmann, E.; Erginel-Unaltna, N. Association between selected cholesterol-related gene polymorphisms and Alzheimer’s disease in a Turkish cohort. *Mol. Biol. Rep.* 2019, 46, 1701–1707. [CrossRef] [PubMed]

Gao, L.; Jiang, Y.; Wei, S.; Shang, S.; Li, P.; Chen, C.; Dang, L.; Wang, J.; Hoo, K.; Deng, M.; et al. The Level of Plasma Amyloid-β40 Is Correlated with Peripheral Transport Proteins in Cognitively Normal Adults: A Population-Based Cross-Sectional Study. *J. Alzheimers Dis.* 2018, 65, 951–961. [CrossRef] [PubMed]

Davis, W.J.; Tew, K.D. ATP-binding cassette transporter-2 (ABCA2) as a therapeutic target. *Biochem. Pharmacol.* 2018, 151, 188–200. [CrossRef]

Xu, X.; Wang, Y.; Wang, L.; Liao, Q.; Chang, L.; Xu, L.; Huang, Y.; Ye, H.; Xu, L.; Chen, C.; et al. Meta-analyses of 8 polymorphisms associated with the risk of the Alzheimer’s disease. *PLOS ONE* 2013, 8, e73129. [CrossRef]

Fehér, Á.; Giricz, Z.; Juhász, A.; Páksi, M.; Janka, Z.; Kálmán, J. ABCA1 rs2230805 and rs2230806 common gene variants are associated with Alzheimer’s disease. *Neurosci Lett.* 2018, 664, 79–83. [CrossRef]

Hu, W.; Lin, X.; Zhang, H.; Zhao, N. ATP Binding Cassette Subfamily A Member 2 (ABCA2) Expression and Methylation are Associated with Alzheimer’s Disease. *Med. Sci. Monit.* 2017, 23, 5851–5861. [CrossRef]

Zhang, W.; Sun, S.; Zhang, W.; Shi, Z. Polymorphisms of ABCG2 and its impact on clinical relevance. *Biochem. Biophys. Res. Commun.* 2018, 503, 408–413. [CrossRef]
96. Fehér, Á.; Juhász, A.; László, A.; Pákáski, M.; Kálmán, J.; Janka, Z. Association between the ABCG2 C421A polymorphism and Alzheimer’s disease. *Neurosci. Lett.* **2013**, *550*, 51–54. [CrossRef]  
97. Shubbar, M.H.; Penny, J.I. Effect of amyloid beta on ATP-binding cassette transporter expression and activity in porcine brain microvascular endothelial cells. *Biochim. Biophys. Acta Gen. Subj.* **2018**, *1862*, 2314–2322. [CrossRef] [PubMed]  
98. Schaller, L.; Lauschke, V.M. The genetic landscape of the human solute carrier (SLC) transporter superfamily. *Hum. Genet.* **2019*. [CrossRef] [PubMed]  
99. Yin, R.H.; Yu, J.T.; Tan, L. The Role of SORL1 in Alzheimer’s Disease. *Mol. Neurobiol.* **2015**, *51*, 909–918. [CrossRef] [PubMed]  
100. Britzolaki, A.; Saurine, J.; Klocke, B.; Pitychoutis, P.M. A Role for SERCA Pumps in the Neurobiology of Alzheimer’s Disease. *Front. Neurol.* **2019**, *6*, 23. [CrossRef] [PubMed]  
101. Heinemeyer, T.; Stemmet, M.; Bardien, S.; Neethling, A. Underappreciated Roles of the Translocase of the Outer and Inner Mitochondrial Membrane Protein Complexes in Human Disease. *DNA Cell Biol.* **2019**, *38*, 23–40. [CrossRef] [PubMed]  
102. Belrose, J.C.; Jackson, M.F. TRPM2: A candidate therapeutic target for treating neurological diseases. *Acta Pharmacol. Sin.* **2018**, *39*, 722–732. [CrossRef]  
103. Pan, Y.; Omori, K.; Ali, I.; Tachikawa, M.; Terasaki, T.; Brouwer, K.L.R.; Nicolazzo, J.A. Altered Expression of Small Intestinal Drug Transporters and Hepatic Metabolic Enzymes in a Mouse Model of Familial Alzheimer’s Disease. *Mol. Pharm.* **2018**, *15*, 4073–4083. [CrossRef]  
104. Cacabelos, R. Pharmacogenomics of drugs used to treat brain disorders. *Expert Rev. Precis. Med. Drug Devel.* **2020**, *4*, 479–500. [CrossRef]  
105. Li, D.D.; Zhang, Y.H.; Zhang, W.; Zhao, P. Meta-Analysis of Randomized Controlled Trials on the Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer’s Disease. *Front. Neurosci.* **2019**, *13*, 472. [CrossRef]  
106. Dekker, M.J.H.J.; Bouvy, J.C.; O’Rourke, D.; Thompson, R.; Makady, A.; Jonsson, P.; Gispen-de Wield, C.C. Alignment of European Regulatory and Health Technology Assessments: A Review of Licensed Products for Alzheimer’s Disease. *Front. Med.* **2019**, *6*, 73. [CrossRef]  
107. Cacabelos, R.; Llovo, R.; Fraile, C.; Fernández-Novoa, L. Pharmacogenetic aspects of therapy with cholinesterase inhibitors: The role of CYP2D6 in Alzheimer’s disease pharmacogenetics. *Curr. Alzheimer Res.* **2007**, *4*, 479–500. [CrossRef] [PubMed]  
108. Cacabelos, R. Donepezil in Alzheimer’s disease: From conventional trials to pharmacogenetics. *Neuropsychiatr. Dis. Treat.* **2007**, *3*, 303–333. [PubMed]  
109. Cacabelos, R.; Takeda, M.; Winblad, B. The glutamatergic system and neurodegeneration in dementia: Preventive strategies in Alzheimer’s disease. *Int. J. Geriatr. Psychiatry* **1999**, *14*, 3–47. [CrossRef]  
110. Hays, C.C.; Zlataar, Z.Z.; Meloy, M.J.; Osuna, J.; Liu, T.T.; Galasko, D.R.; Wierenga, C.E. Anterior Cingulate Structure and Perfusion Is Associated with Cerebrospinal Fluid Tau Among Cognitively Normal Older Adult APOEe4 Carriers. *J. Alzheimers Dis.* **2019**, *39*, e607–e612. [CrossRef] [PubMed]  
111. Weintraub, S.; Teylan, M.; Rader, B.; Chan, K.C.G.; Bollenbeck, M.; Kukull, W.A.; Coventry, C.; Rogalski, E.; Bigio, E.; Mesulam, M.M. APOE is a correlate of phenotypic heterogeneity in Alzheimer disease in a national cohort. *Neurology* **2019**, *94*, e607–e612. [CrossRef] [PubMed]  
112. Cacabelos, R. Molecular pathology and pharmacogenomics in Alzheimer’s disease: Polygenic-related effects of multifactorial treatments on cognition, anxiety and depression. *Methods Find. Exp. Clin. Pharmacol.* **2007**, *29*, 1–91.  
113. Cacabelos, R.; Martinez, R.; Fernández-Novoa, L.; Carril, J.C.; Lombardi, V.; Carrera, I.; Corzo, L.; Tellado, I.; Leszek, J.; McKay, A.; et al. Genomics of Dementia: APOE- and CYP2D6-Related Pharmacogenetics. *Int. J. Alzheimers Dis.* **2012**, *2012*, 518901. [CrossRef]  
114. Cacabelos, R.; Torrellas, C.; Carrera, I. Opportunities in Pharmacogenomics for the treatment of Alzheimer’s Disease. *Future Neurol.* **2015**, *10*, 229–252. [CrossRef]  
115. Cacabelos, R.; Torrellas, C.; Teijido, O.; Carril, J.C. Pharmacogenetic considerations in the treatment of Alzheimer’s disease. *Pharmacogenomics* **2016**, *17*, 1041–1074. [CrossRef]  
116. Cacabelos, R.; Fernández-Novoa, L.; Pichel, V.; Lombardi, V.; Kubota, Y.; Takeda, M. Pharmacogenonomic studies with a combination therapy in Alzheimer’s disease. In *Molecular Neurobiology of Alzheimer’s Disease and Related Disorders*; Takeda, M., Tanaka, T., Cacabelos, R., Eds.; Karger: Basel, Switzerland, 2004; pp. 94–107.
117. Cacabelos, R.; Goldgaber, D.; Vostrov, A.; Matsuki, H.; Torrellas, C.; Corzo, D.; Carril, J.C.; Roses, A.D. APOE-TOMM40 in the Pharmacogenomics of demetia. *J. Pharmacogenom. Pharmacoproteom.* 2014, 5, 1. [CrossRef]

118. Cacabelos, R.; Rodriguez, B.; Carrera, C.; Beyer, K.; Lao, J.I.; Sellers, M.A. Behavioral changes associated with different apolipoprotein E genotypes in dementia. *Alzheimer’s Dis. Assoc. Dis.* 1997, 11, S27–S37. [CrossRef]

119. Cacabelos, R. Pharmacogenomics of Alzheimer’s and Parkinson’s diseases. *Neurosci. Lett.* 2018, 133807. [CrossRef]

120. Darreh-Shori, T.; Siawesh, M.; Mousavi, M.; Andreasen, N.; Nordberg, A. Apolipoprotein ε4 modulates phenotype of butyrylcholinesterase in CSF of patients with Alzheimer’s disease. *J. Alzheimers Dis.* 2012, 28, 443–458. [CrossRef] [PubMed]

121. Noetzli, M.; Eap, C.B. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer’s Disease. *Clin. Pharmacokinet.* 2013, 52, 225–241. [CrossRef] [PubMed]

122. Birks, J.S.; Harvey, R.J. Donepezil for dementia due to Alzheimer’s disease. *Cochrane Database Syst. Rev.* 2018, 6, CD001190. [CrossRef] [PubMed]

123. Pilotto, A.; Franceschi, M.; D’Onofrio, G.; Bizzarro, A.; Mangialasche, F.; Cascavilla, L.; Paris, F.; Matera, M.G.; Pilotto, A.; Deniele, A.; et al. Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease. *Neurology* 2009, 73, 761–767. [CrossRef] [PubMed]

124. Noetzli, M.; Guidi, M.; Ebbing, K.; Eyer, S.; Wilhelm, L.; Michon, A.; Thommazic, V.; Stancu, I.; Alnawaqil, A.M.; Bula, C.; et al. Population pharmacokinetic approach to evaluate the effect of CYP2D6, CYP3A, ABCB1, POR and NR1I2 genotypes on donepezil clearance. *Br. J. Clin. Pharmacol.* 2014, 78, 135–144. [CrossRef] [PubMed]

125. Albani, D.; Martinelli, B.F.; Biella, G.; Giaicalone, G.; Lupoli, S.; Clerici, F.; Benussi, L.; Ghidoni, R.; Galimberti, D.; Squitti, R.; et al. Replication study to confirm the role of CYP2D6 polymorphism rs1080985 on donepezil efficacy in Alzheimer’s disease patients. *J. Alzheimers Dis.* 2012, 30, 745–749. [CrossRef]

126. Xiao, T.; Jiao, B.; Zhang, W.; Tang, B.; Shen, L. Effect of the CYP2D6 and APOE Polymorphisms on the Efficacy of Donepezil in Patients with Alzheimer’s Disease: A Systematic Review and Meta-Analysis. *CNS Drugs* 2016, 30, 899–907. [CrossRef]

127. Seripa, D.; Bizzarro, A.; Pilotto, A.; D’Onofrio, G.; Vecchione, G.; Gallo, A.P.; Cascavilla, L.; Paris, F.; Grandone, E.; Meccoci, P.; et al. Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer’s disease. *Pharmacogenet. Genom.* 2011, 21, 225–230.

128. Zhong, Y.; Zheng, X.; Miao, Y.; Wan, L.; Yan, H.; Wang, B. Effect of CYP2D6*10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer’s disease. *Am. J. Med. Sci.* 2013, 345, 222–226. [CrossRef]

129. Yaowaluk, T.; Senanarong, V.; Limwongse, C.; Boonpraseut, R.; Kijsanayotin, P. Influence of CYP2D6, CYP3A5, ABCB1, APOE polymorphisms and nongenetic factors on donepezil treatment in patients with Alzheimer’s disease and vascular dementia. *Pharmacogenom. Personalized Med.* 2019, 12, 209–224. [CrossRef]

130. Ma, S.L.; Tang, N.L.S.; Wat, K.H.Y.; Tang, J.H.Y.; Lau, K.H.; Law, C.B.; Chiue, J.; Tam, C.C.W.; Poon, T.K. Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer’s disease. *Brain Res. Bull.* 2018, 140, 1–4. [CrossRef]

131. Lu, J.; Fu, J.; Zhong, Y.; Yang, Q.; Huang, J.; Li, J.; Huo, Y.; Zhao, Y.; Wan, L.; Guo, C. Association between ABCA1 gene polymorphisms and the therapeutic response to donepezil therapy in Han Chinese patients with Alzheimer’s disease. *Brain Res. Bull.* 2018, 140, 1–4. [CrossRef]

132. Lu, J.; Fu, J.; Zhong, Y.; Yang, Q.; Huang, J.; Li, J.; Huo, Y.; Zhao, Y.; Wan, L.; Guo, C. Association between ABCA1 gene polymorphisms and the therapeutic response to donepezil therapy in Han Chinese patients with Alzheimer’s disease. *Brain Res. Bull.* 2018, 140, 1–4. [CrossRef]

133. Sokolow, S.; Li, X.; Chen, L.; Taylor, K.D.; Ritter, J.I.; Rissman, R.A.; Aisen, P.S.; Apostolova, L.G. Deleterious Effect of Butyrylcholinesterase K-Variant in Donepezil Treatment of Mild Cognitive Impairment. *J. Alzheimers Dis.* 2017, 56, 229–237. [CrossRef]

134. Zhang, C.; Zhang, Y.; Song, Q.; Li, H.; Hu, L.; Zhao, W.; Feng, S.; Gu, F.; Zhao, F.; Zhang, C. The efficacy of a “cocktail therapy” on Parkinson’s disease with dementia. *Neuropsychiatr. Dis. Treat.* 2019, 15, 1639–1647. [CrossRef]
136. Khuanjing, T.; Palee, S.; Chattipakorn, S.C.; Chattipakorn, N. The effects of acetylcholinesterase inhibitors on the heart in acute myocardial infarction and heart failure: From cells to patient reports. *Acta Physiol.* 2019, 228, e13396. [CrossRef]
137. Kawashiri, T.; Shimizu, S.; Shigematsu, N.; Kobayashi, D.; Shimazoe, T. Donepezil ameliorates oxaliplatin-induced peripheral neuropathy via a neuroprotective effect. *J. Pharmacol. Sci.* 2019, 140, 291–294. [CrossRef]
138. Wong, J.C.; Thelin, J.T.; Escayg, A. Donepezil increases resistance to induced seizures in a mouse model of Dravet syndrome. *Ann.Clin. Transl. Neurol.* 2019, 6, 1566–1571. [CrossRef]
139. Jann, M.W.; Shirley, K.L.; Small, G.W. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin. Pharmacokinet.* 2002, 41, 719–739. [CrossRef] [PubMed]
140. Lilienfeld, S. Galantamine—a novel cholinergic drug with a unique dual mode of action for the treatment of Alzheimer’s disease. *Clin. Drug Rev.* 2002, 8, 159–176. [CrossRef] [PubMed]
141. Zhao, Q.; Brett, M.; Van Osselaer, N.; Huang, F.; Raoult, A.; Van Peer, A.; Verhaeghe, T.; Hust, R. Galantamine pharmacokinetics, safety, and tolerability profiles are similar in healthy Caucasian and Japanese subjects. *J. Clin. Pharmacol.* 2002, 42, 1002–1010. [CrossRef] [PubMed]
142. Farlow, M.R. Clinical pharmacokinetics of galantamine. *Clin. Pharmacokinet.* 2003, 42, 1383–1392. [CrossRef]
143. Mannens, G.S.; Snel, C.A.; Hendrickx, J.; Verhaeghe, T.; Le Jeune, L.; Bode, W.; van Beijsterveldt, L.; Lavrijsen, K.; Leempoels, J.; Van Osselaer, N.; et al. The metabolism and excretion of galantamine in rats, dogs, and humans. *Drug Metab. Dispos.* 2002, 30, 553–563. [CrossRef]
144. Noetzli, M.; Guidi, M.; Ebbing, K.; Eyer, S.; Zumbach, S.; Giannakopoulos, P.; von Gunten, A.; Csajka, C.; Eap, C.B. Relationship of CYP2D6, CYP3A, POR, and ABCB1 genotypes with galantamine plasma concentrations. *Ther. Drug Monit.* 2013, 35, 270–275. [CrossRef]
145. Clarke, J.A.; Cutler, M.; Gong, I.; Schwarz, U.I.; Freeman, D.; Dasgupta, M. Cytochrome P450 2D6 phenotyping in an elderly population with dementia and response to galantamine in dementia: A pilot study. *Am. J. Geriatr. Pharmacother.* 2011, 9, 224–233. [CrossRef]
146. Bentué-Ferrer, D.; Tribut, O.; Polard, E.; Allain, H. Clinically significant drug interactions with cholinesterase inhibitors: A guide for neurologists. *CNS Drugs* 2003, 17, 947–963. [CrossRef]
147. Zhai, X.J.; Lu, Y.N. Food-drug interactions: Effect of capsaicin on the pharmacokinetics of galantamine in rats. *Xenobiotica* 2012, 42, 1151–1155. [CrossRef]
148. Carroll, K.M.; DeVito, E.E.; Yip, S.W.; Nich, C.; Sofuoglu, M. Double-Blind Placebo-Controlled Trial of Galantamine for Methadone-Maintained Individuals With Cocaine Use Disorder: Secondary Analysis of Effects on Illicit Opioid Use. *Am. J. Addict.* 2019, 28, 238–245. [CrossRef] [PubMed]
149. Sugarman, D.E.; De Aquino, J.P.; Poling, J.; Sofuoglu, M. Feasibility and effects of galantamine on cognition in humans with cannabis use disorder. *Pharmacol. Biochem. Behav.* 2019, 181, 86–92. [CrossRef] [PubMed]
150. Njoku, I.; Radabaugh, H.L.; Nicholas, M.A.; Kutash, L.A.; O’Neil, D.A.; Marshall, I.P.; Cheng, J.P.; Kline, A.E. Chronic treatment with galantamine rescues reversal learning in an attentional set-shifting test after experimental brain trauma. *Exp. Neurol.* 2019, 315, 32–41. [CrossRef] [PubMed]
151. Choueiry, J.; Blais, C.M.; Shah, D.; Smith, D.; Fisher, D.; Labelle, A.; Knott, V. Combining CDP-choline and galantamine, an optimized α7 nicotinic strategy, to ameliorate sensory gating to speech stimuli in schizophrenia. *Int. J. Psychophysiol.* 2019, 145, 70–82. [CrossRef]
152. Koola, M.M. Potential Role of Antipsychotic-Galantamine-Memantine Combination in the Treatment of Positive, Cognitive, and Negative Symptoms of Schizophrenia. *Mol. Neuropsychiatry* 2018, 4, 134–148. [CrossRef]
153. Birks, J.S.; Grimley Evans, J. Rivastigmine for Alzheimer’s disease. *Cochrane Database Syst. Rev.* 2015, 10, CD001911. [CrossRef]
154. Jia, J.; Ji, Y.; Peng, T.; Ye, Q.; Peng, D.; Kuang, W.; Ning, Y. Sixteen-Week Interventional Study to Evaluate the Clinical Effects and Safety of Rivastigmine Capsules in Chinese Patients with Alzheimer’s Disease. *J. Alzheimers Dis.* 2019. [CrossRef]
155. Polinsky, R.J. Clinical pharmacology of rivastigmine: A new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer’s disease. *Clin. Ther.* 1998, 20, 634–647. [CrossRef]
156. Sonali, N.; Tripathi, M.; Sagar, R.; Velpandian, T.; Subbiah, V. Clinical effectiveness of rivastigmine monotherapy and combination therapy in Alzheimer’s patients. *CNS Neurosci. Ther.* 2013, 19, 91–97. [CrossRef]
173. Tahami Monfared, A.A.; Meier, G.; Perry, R.; Joe, D. Burden of Disease and Current Management of Dementia. *Pharmacopsychiatry* 2015, 48, 111–117. [CrossRef]

172. Inoue, Y.; Ueda, M.; Masuda, T.; Misumi, Y.; Yamashita, T.; Ando, Y. Memantine, a Noncompetitive NMDA Receptor Antagonist, Attenuates Cerebral Amyloid Angiopathy by Increasing Insulin-Degrading Enzyme Expression. *Mol. Neurobiol.* 2019, 56, 8573–8588. [CrossRef]

170. Glinz, D.; Gloy, V.L.; Monsch, A.U.; Kressig, R.W.; Patel, C.; McCord, K.A.; Ademi, Z.; Tomonara, Y.; Schwenkglenks, M.; Bucher, H.C.; et al. Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer’s disease: A meta-analysis. *Swiss Med. Wkly.* 2019, 149, w20093. [CrossRef]

171. Zhou, X.; Wang, L.; Xiao, W.; Su, Z.; Zheng, C.; Zhang, Z.; Wang, Y.; Xu, B.; yang, X.; Hoi, M.P.U. Memantine Improves Cognitive Function and Alters Hippocampal and Cortical Proteome in Triple Transgenic Mouse Model of Alzheimer’s Disease. *Exp. Neurobiol.* 2019, 28, 390–403. [CrossRef]

168. Marwick, K.F.M.; Skehel, P.A.; Hardingham, G.E.; Wylie, D.J.A. The human NMDA receptor GluN2AN615K variant influences channel blocker potency. *Pharmacol. Res. Perspect.* 2019, 7, e00495. [CrossRef] [PubMed]

167. Micuda, S.; Mundlova, L.; Anzenbacherova, E.; Anzenbacher, P.; Chladek, J.; Fuksa, L.; Martinova, J. Inhibitory effects of memantine on human cytochrome P450 activities: Prediction of in vivo drug interactions. *Eur. J. Clin. Pharmacol.* 2004, 60, 583–589. [CrossRef]

166. Noetzli, M.; Guidi, M.; Ebbing, K.; Eyer, S.; Wilhelm, L.; Michon, A.; Thomazic, V.; Alnawaqil, A.M.; Zumbach, S.; Maurer, S.; Zumbach, S.; et al. Population pharmacokinetic study of memantine: Effects of clinical and genetic factors. *Clin. Pharmacokinet.* 2013, 52, 211–223. [CrossRef]

165. Yang, Z.; Zhou, X.; Zhang, Q. Effectiveness and safety of memantine treatment for Alzheimer’s disease. *J. Alzheimers Dis.* 2013, 36, 445–458. [CrossRef]

164. Burgett, R.N.; Farley, T.M.; Beireis, L.A. Acute treatment of psychotic symptoms in a newly diagnosed Lewy body dementia patient with an accelerated titration schedule of rivastigmine and de-escalation of antipsychotics. *BMJ Case Rep.* 2019, 12, e230193. [CrossRef]

162. Henderson, E.J.; Lord, S.R.; Brodie, M.A.; Gaunt, D.M.; Lawrence, A.D.; Close, J.C.; Whone, A.L.; et al. Pharmacogenomics in Alzheimer’s disease: A genome-wide association study of response to cholinesterase inhibitors. *Neurobiol. Aging* 2013, 34, 1711. [CrossRef] [PubMed]

161. Jasiecki, J.; Wasag, B. Butyrylcholinesterase Protein Ends in the Pathogenesis of Alzheimer’s Disease—Could a Genetic Factor Be Involved? *Int. J. Mol. Sci.* 2019, 20, 1587. [CrossRef] [PubMed]

160. Ferris, S.; Nordberg, A.; Soininen, H.; Darreh-Shori, T.; Lane, R. Progression from mild cognitive impairment to Alzheimer’s disease: Effects of sex, butyrylcholinesterase genotype, and rivastigmine treatment. *Pharmacogenet. Genom.* 2009, 19, 635–646. [CrossRef] [PubMed]

159. Martinelli-Boneschi, F.; Giacalone, G.; Magnani, G.; Biella, G.; Coppi, E.; Santangelo, R.; Brambilla, P.; Esposito, F.; Clerici, L.; Benussi, L.; et al. Pharmacogenomics in Alzheimer’s disease: A genome-wide association study of response to cholinesterase inhibitors. *Neurobiol. Aging* 2013, 34, 1711. [CrossRef] [PubMed]

158. Clarelli, F.; Mascia, E.; Santangelo, R.; Mazzeo, S.; Giacalone, G.; Galimberti, D.; Fusco, F.; Zuffi, M.; Fenoglio, C.; Franceschi, M. CHRNA7 Gene and response to cholinesterase Inhibitors in an Italian cohort of Alzheimer’s disease patients. *J. Alzheimers Dis.* 2016, 52, 1203–1208. [CrossRef] [PubMed]

157. Yoon, H.; Myung, W.; Lim, S.W.; Kang, H.S.; Kim, S.; Won, H.H.; Carroll, B.J.; Kim, D.K. Association of the choline acetyltransferase gene with responsiveness to acetylcholinesterase inhibitors in Alzheimer’s disease. *Pharmacopsychiatry* 2015, 48, 111–117. [CrossRef] [PubMed]
175. Lavretsky, H.; Laird, K.T.; Krause-Sorio, B.; Heimberg, B.F.; Yeargin, J.; Grzenda, A.; Wu, P.; Thana-Udom, K.; Ereli, L.M.; Siddarth, P. A Randomized Double-Blind Placebo-Controlled Trial of Combined Escitalopram and Memantine for Older Adults with Major Depression and Subjective Memory Complaints. *Am. J. Geriatr. Psychiatry* 2020, 28, 178–190. [CrossRef] [PubMed]

176. Schaefer, M.; Sarkar, S.; Theophil, I.; Leopold, K.; Heinz, A.; Gallinat, J. Acute and Long-term Memantine Add-on Treatment to Risperidone Improves Cognitive Dysfunction in Patients with Acute and Chronic Schizophrenia. *Pharmacopsychiatry* 2019. [CrossRef]

177. Chen, Y.; Shi, Y.; Wang, G.; Li, Y.; Cheng, L.; Pang, Y. Memantine selectively prevented the induction of dynamic allodynia by blocking Kir2.1 channel and inhibiting the activation of microglia in spinal dorsal horn of mice in spared nerve injury model. *Mol. Pain* 2019, 15, 1744806919838947. [CrossRef] [PubMed]

178. Martin, E.; Sorel, M.; Morel, V.; Marcaillou, F.; Picard, P.; Delage, N.; Tiberghien, F.; Crosmary, M.C.; Najjar, M.; Lavretsky, H.; Laird, K.T.; Krause-Sorio, B.; Heimberg, B.F.; Yeargin, J.; Grzenda, A.; Wu, P.; Thana-Udom, K.; Hassanpour, F.; Zarghami, M.; Mouodi, S.; Moosazadeh, M.; Barzegar, F.; Bagheri, M. Adjunctive Memantine Treatment of Schizophrenia: A Double-Blind, Randomized Placebo-Controlled Study. *J. Clin. Psychopharmacol.* 2019, 39, 634–638. [CrossRef] [PubMed]

179. Schaefer, M.; Sarkar, S.; Theophil, I.; Leopold, K.; Heinz, A.; Gallinat, J. Acute and Long-term Memantine Add-on Treatment to Risperidone Improves Cognitive Dysfunction in Patients with Acute and Chronic Schizophrenia. *Pharmacopsychiatry* 2019. [CrossRef]

180. Krishnan-Sarin, S.; O’Malley, S.S.; Franco, N.; Cavallo, D.A.; Tetrault, J.M.; Shi, J.; Gueorguieva, R.; Pittman, B.; Fuller, J.T.; Choudhury, T.K.; Lowe, D.A.; Balsis, S. Alzheimer’s Disease Neuroimaging Initiative. Hallucinations and delusions signal Alzheimer’s associated cognitive dysfunction more strongly compared to other neuropsychiatric symptoms. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2019, gbz032. [CrossRef]

181. Xu, M.; Xing, Q.; Li, S.; Zheng, Y.; Wu, S.; Hao, R.; Yu, L.; Guo, T.; Yang, Y.; Liu, J.; et al. Detecting Non-cognitive Features of Prodromal Neurodegenerative Diseases. *Curr. Aging Sci.* 2019, 12, 242–249. [CrossRef]

182. Sundararajan, T.; Manzarzo, A.M.; Butler, M.G. Functional analysis of schizophrenia genes using GeneAnalytics program and integrated databases. *Gene* 2018, 641, 25–34. [CrossRef]

183. Garcia-Segura, M.E.; Fischer, C.E.; Schweizer, T.A.; Munoz, D.G. APOE ε4/ε4 Is Associated with Aberrant Motor Behavior Through Both Lewy Body and Cerebral Amyloid Angiopathy Pathology in High Alzheimer’s Disease Pathological Load. *J. Alzheimers Dis.* 2019. [CrossRef]

184. Seifan, A.; Ganzer, C.A.; Ryon, K.; Lin, M.; Mahmudur, R.; Adolfo, H.; Shih, C.; Jacobs, A.R.; Greenwald, M.; Isaacson, R.S. Detecting Non-cognitive Features of Prodromal Neurodegenerative Diseases. *Curr. Aging Sci.* 2019, 11, 242–249. [CrossRef]

185. Schaefer, M.; Sarkar, S.; Theophil, I.; Leopold, K.; Heinz, A.; Gallinat, J. Acute and Long-term Memantine Add-on Treatment to Risperidone Improves Cognitive Dysfunction in Patients with Acute and Chronic Schizophrenia. *Pharmacopsychiatry* 2019. [CrossRef]

186. Schaefer, M.; Sarkar, S.; Theophil, I.; Leopold, K.; Heinz, A.; Gallinat, J. Acute and Long-term Memantine Add-on Treatment to Risperidone Improves Cognitive Dysfunction in Patients with Acute and Chronic Schizophrenia. *Pharmacopsychiatry* 2019. [CrossRef]

187. Ohno, Y.; Kunisawa, N.; Shimizu, S. Antipsychotic Treatment of Behavioral and Psychological Symptoms of Dementia (BPSD): Management of Extrapyramidal Side Effects. *Front. Pharmacol.* 2019, 10, 1045. [CrossRef] [PubMed]

188. Xu, M.; Xing, Q.; Li, S.; Zheng, Y.; Wu, S.; Gao, R.; Yu, L.; Guo, T.; Yang, Y.; Liu, J.; et al. Pharmacogenetic effects of dopamine transporter gene polymorphisms on response to chlorpromazine and clozapine and on extrapyramidal syndrome in schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2010, 34, 1026–1032. [CrossRef] [PubMed]

189. Zivković, M.; Mihaljević-Peles, A.; Bozina, N.; Sagud, M.; Mikolac-Perkovic, M.; Vuksan-Cusa, B.; Muck-Seler, D. The association study of polymorphisms in DAT, DRD2, and COMT genes and acute extrapyramidal adverse effects in male schizophrenic patients treated with haloperidol. *J. Clin. Psychopharmacol.* 2013, 33, 593–599. [CrossRef] [PubMed]

190. Mas, S.; Gassó, P.; Lafuente, A.; Bioque, M.; Lobo, A.; González-Pinto, A.; Olmeda, M.S.; Corropio, I.; Llerena, A.; Cabrera, B.; et al. Pharmacogenetic study of antipsychotic induced acute extrapyramidal symptoms in a first episode psychosis cohort: Role of dopamine, serotonin and glutamate candidate genes. *Pharmacogenom.* 2016, 16, 439–445. [CrossRef]
192. Turčin, A.; Dolžan, V.; Porcelli, S.; Serretti, A.; Plesničar, B.K. Adenosine Hypothesis of Antipsychotic Drugs Revisited: Pharmacogenomics Variation in Nonacute Schizophrenia. OMICS 2016, 20, 283–289. [CrossRef] [PubMed]

193. Gareeva, A.E.; Zakirov, D.F.; Valinurov, R.G. Polymorphism of RGS2 gene: Genetic markers of risk for schizophrenia and pharmacogenetic markers of typical neuroleptics efficiency. Mol. Biol. 2013, 47, 934–941. [CrossRef]

194. Greenbaum, L.; Alkelai, A.; Zozulinsky, P.; Kohn, Y.; Lerer, B. Support for association of HSPG2 with tardive dyskinesia. J. Psychiatr. Res. 2012, 46, 260–266. [CrossRef] [PubMed]

195. Lee, H.J.; Kang, S.G. Genetics of tardive dyskinesia. Int. Rev. Neurobiol. 2011, 98, 231–264. [CrossRef]

196. Mas, S.; Gassó, P.; Ritter, M.A.; Malagelada, C.; Bernardo, M.; Lafuente, A. Pharmacogenetic predictor of extrapyramidal symptoms induced by antipsychotics: Multilocus interaction in the mTOR pathway. Eur. Neuropsychopharmacol. 2015, 25, 51–59. [CrossRef]

197. Lanning, R.K.; Zai, C.C.; Müller, D.J. Pharmacogenetics of tardive dyskinesia: An updated review of the literature. Pharmacogenomics 2016, 17, 1339–1351. [CrossRef]

198. Tanaka, S.; Syu, A.; Ishiguro, H.; Inada, T.; Horiiuch, Y.; Ishikawa, M.; Koga, M.; Noguchi, E.; Ozaki, N.; Someya, T.; et al. DPPI as a candidate gene for neuroleptic-induced tardive dyskinesia. Pharmacogenom. J. 2013, 13, 27–34. [CrossRef]

199. Lelo, H.J.; Kang, S.G. Genetics of tardive dyskinesia. Int. Rev. Neurobiol. 2011, 98, 231–264. [CrossRef]

200. Koola, M.M.; Tsapakis, E.M.; Wright, P.; Smith, S.; Kerwin Rip, R.W.; Nugent, K.L.; Aitchison, K.J. Association of tardive dyskinesia with variation in CYP2D6: Is there a role for active metabolites? J. Psychopharmacol. 2014, 28, 665–670. [CrossRef]

201. Yoshikawa, A.; Li, J.; Meltzer, H.Y. A functional HTR1A polymorphism, rs6295, predicts short-term response to lurasidone: Confirmation with meta-analysis of other antipsychotic drugs. Pharmacogenom. J. 2020, 20, 260–270. [CrossRef] [PubMed]

202. Zai, C.C.; Tiwari, A.K.; Zai, G.C.; Maes, M.S.; Kennedy, J.L.; Remington, G.; Kennedy, J.L. Association study of the vesicular monoamine transporter gene SLC18A2 polymorphisms in lipoprotein lipase gene in a Han Chinese population. Psychiatr. Genet. 2013, 3059, 74 of 82 [CrossRef], 665–670. [CrossRef] [PubMed]
211. Kohlrausch, F.B.; Severino-Gama, C.; Lobato, M.I.; Belmonte-de-Abreu, P.; Carracedo, A.; Hutz, M.H. The CYP1A2-163C>A polymorphism is associated with clozapine-induced generalized tonic-clonic seizures in Brazilian schizophrenia patients. Psychiatry Res. 2013, 209, 242–245. [CrossRef] [PubMed]

212. Schuhmacher, A.; Becker, T.; Rujescu, D.; Quednow, B.B.; Lennertz, L.; Wagner, M.; Benninghoff, J.; Rietschel, M.; Hafner, H.; Franke, P.; et al. Investigation of tryptophan hydroxylase 2 (TPH2) in schizophrenia and in the response to antipsychotics. J. Psychiatr. Res. 2012, 46, 1073–1080. [CrossRef]

213. Chi, S.; Wang, C.; Jiang, T.; Zhu, X.C.; Yu, J.T.; Tan, L. The prevalence of depression in Alzheimer’s disease: A systematic review and meta-analysis. Curr. Alzheimer Res. 2015, 12, 189–198. [CrossRef]

214. Kuring, J.K.; Mathias, J.L.; Ward, L. Prevalence of Depression, Anxiety and PTSD in People with Dementia: A Systematic Review and Meta-Analysis. Neuropsychol. Rev. 2018, 28, 393–416. [CrossRef]

215. Sol, K.; Zaheed, A.B.; Kraal, A.Z.; Sharifian, N.; Arce Renter, K.; Fleischhacker, W.W. et al. Does apolipoprotein E4 increase the risk of depression in Alzheimer’s disease? A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2020, 21, 73 of 82.

216. Bennett, S.; Thomas, A.J. Depression and dementia: Cause, consequence or coincidence? Maturitas 2014, 79, 184–190. [CrossRef]

217. Norton, J.; Carrière, I.; Pérès, K.; Gabelle, A.; Bell, A.; Ritchie, K.; Ancelin, M.L. Sex-specific depressive symptoms as markers of pre-Alzheimer dementia: Findings from the Three-City cohort study. Transl. Psychiatry 2019, 9, 291. [CrossRef]

218. Youn, H.; Lee, S.; Han, C.; Kim, S.H.; Jeong, H.G. Association between brain amyloid accumulation and neuropsychological characteristics in elders with depression and mild cognitive impairment. Int. J. Geriatr. Psychiatry 2019. [CrossRef]

219. Capogna, E.; Manca, R.; De Marco, M.; Hall, A.; Soininen, H.; Verretti, A. Understanding the effect of cognitive/brain reserve and depression on regional atrophy in early Alzheimer’s disease. Postgrad. Med. 2019, 131, 533–538. [CrossRef] [PubMed]

220. Amieva, H.; Meillon, C.; Proust-Lima, C.; Dartigues, J.F. Is Low Psychomotor Speed a Marker of Brain Vulnerability in Late Life? Digit Symbol Substitution Test in the Prediction of Alzheimer, Parkinson, Stroke, Disability, and Depression. Dement. Geriatr. Cogn. Disord. 2019, 47, 297–305. [CrossRef]

221. Fischer, C.E.; Kortebi, I.; Karameh, W.K.; Kumar, S.; Gallagher, D.; Golas, A.; Munoz, D.; Barfett, J.; Butter, M.A.; Marshe, V.S.; Islam, F.; Maciukiewicz, M.; Bousman, C.; Eyre, H.A.; Lavretsky, H.; Mulhant, B.H.; Reynolds, C.F.; Lenze, E.J.; Moller, D.J. Pharmacogenetic Implications for Antidepressant Pharmacotherapy in Late-Life Depression: A Systematic Review of the Literature for Response, Pharmacokinetics and Adverse Drug Reactions. Am. J. Geriatr. Psychiatry. 2020. [CrossRef]

222. Marshe, V.S.; Islam, F.; Maciukiewicz, M.; Bousman, C.; Eyre, H.A.; Lavretsky, H.; Mulhant, B.H.; Reynolds, C.F.; Lenze, E.J.; Moller, D.J. Pharmacogenetic Implications for Antidepressant Pharmacotherapy in Late-Life Depression: A Systematic Review of the Literature for Response, Pharmacokinetics and Adverse Drug Reactions. Am. J. Geriatr. Psychiatry. 2020. [CrossRef]

223. Banning, L.C.; Ramakers, I.H.G.B.; Deckers, K.; Verhey, F.R.J.; Aalten, P. Apolipoprotein E and affective symptoms in mild cognitive impairment and Alzheimer’s disease dementia: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2019, 96, 302–315. [CrossRef] [PubMed]

224. Burke, A.D.; Goldfarb, D.; Bollam, P.; Khokher, S. Diagnosing and Treating Depression in Patients with Alzheimer’s Disease. Neurol. Ther. 2019, 8, 325–350. [CrossRef]

225. Orgeta, V.; Tabet, N.; Niforoorshen, R.; Howard, R. Efficacy of Antidepressants for Depression in Alzheimer’s Disease: Systematic Review and Meta-Analysis. J. Alzheimers Dis. 2017, 58, 725–733. [CrossRef]

226. Cassano, T.; Calcagnini, S.; Carbona, A.; Bukke, V.N.; Orkisz, S.; Villani, R.; Romano, A.; Avolio, C.; Gaetani, S. Pharmacological Treatment of Depression in Alzheimer’s Disease: A Challenging Task. Front. Pharmacol. 2019, 10, 1067. [CrossRef]

227. Cacabelos, R. Trial-and-Error versus Personalized Treatment in Depression: The Power of Pharmacogenomics. J. Psychiatry Depress Anxiety 2016, 2. [CrossRef]

228. Ni, H.; Xu, M.; Zhan, G.L.; Fan, Y.; Zhou, H.; Jiang, H.Y.; Lu, W.H.; Tan, L.; Zhang, D.F.; Yao, Y.G.; et al. The GWAS Risk Genes for Depression May Be Actively Involved in Alzheimer’s Disease. Curr. Genom. 2017, 18, 442–449. [CrossRef] [PubMed]
246. Thomas, J.; Overeem, S.; Claassen, J.A.H.R. Long-Term Occupational Sleep Loss and Post-Retirement
241. 
230. Thase, M.E.; Parikh, S.V.; Rothschild, A.J.; Dunlop, B.W.; DeBattista, C.; Conway, C.R.; Mondimore, F.M.;
Shelton, R.C.; Macaluso, M.; Li, J.; et al. Impact of Pharmacogenomics on Clinical Outcomes for Patients
Taking Medications With Gene-Drug Interactions in a Randomized Controlled Trial. J. Clin. Psychiatry 2019,
80, 19m12910. [CrossRef] [PubMed]
231. Maggo, S.D.S.; Sycamore, K.L.V.; Miller, A.L.; Kennedy, M.A. The Three Ps: Psychiatry, Pharmacy, and
Pharmacogenomics, a Brief Report from New Zealand. Front. Psychiatry 2019, 10, 690. [CrossRef] [PubMed]
232. Eugene, A.R. Optimizing drug selection in psychopharmacology based on 40 significant CYP2C19- and
CYP2D6-biased adverse drug reactions of selective serotonin reuptake inhibitors. PeerJ 2019, 7, e7860.
[CrossRef] [PubMed]
233. Danese, A.; Federico, A.; Martini, A.; Mantovani, E.; Zucchella, C.; Tagliapietra, M.; Tamburin, S.; Cavallaro, T.;
Marafioti, V.; Monaco, S.; et al. QTc Prolongation in Patients with Dementia and Mild Cognitive Impairment:
Neuropsychological and Brain Imaging Correlations. J. Alzheimers Dis. 2019, 72, 1241–1249. [CrossRef]
[PubMed]
234. Kanders, S.H.; Pisanu, C.; Bandstein, M.; Jonsson, J.; Castelao, E.; Pistis, G.; Gholam-Rezaee, M.; Eap, C.B.;
Preisig, M.; Schioto, H.B.; et al. A pharmacogenetic risk score for the evaluation of major depression severity
under treatment with antidepressants. Drug Dev. Res. 2020, 81, 102–113. [CrossRef]
235. de Oliveira, F.F.; Berretta, J.M.; de Almeida Junior, G.V.; de Almeida, S.S.; Chen, E.S.; Smith, M.C.;
Bertolucci, P.H.F. Pharmacogenetic analyses of variations of measures of cardiovascular risk in Alzheimer’s
dementia. Indian J. Med. Res. 2019, 150, 261–271. [CrossRef]
236. Hicks, J.K.; Bishop, J.R.; Gammal, R.S.; Sangkuh, K.; Bousman, C.A.; Leeder, J.S. A Call for Clear and
Consistent Communications Regarding the Role of Pharmacogenomics in Antidepressant Pharmacotherapy.
Clin. Pharmacol. Ther. 2019. [CrossRef]
237. Caudle, K.E.; Sangkuhl, K.; Whirl-Carrillo, M.; Swen, J.J.; Haider, C.E.; Klein, T.E.; Gammal, R.S.;
Relling, M.V.; Scott, S.A.; Hertz, D.L.; et al. Standardizing CYP2D6 Genotype to Phenotype Translation:
Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch
Pharmacogenetics Working Group. Clin. Transl. Sci. 2020, 13, 116–124. [CrossRef]
238. Nofziger, C.; Turner, A.J.; Sangkuhl, K.; Whirl-Carrillo, M.; Agüindez, J.A.G.; Black, J.L.; Dunnenberger, H.M.;
Ruano, G.; Kennedy, M.A.; Phillips, M.S.; et al. PharmVar GeneReview: CYP2D. Clin. Pharmacol. Ther. 2020,
107, 154–170. [CrossRef] [PubMed]
239. Pagani, R.; Gasparini, A.; Ielmini, M.; Caselli, I.; Poloni, N.; Ferrari, M.; Marino, F.; Callegari, C. Twenty years
of Lithium pharmacogenetics: A systematic review. Psychiatry Res. 2019, 278, 42–50. [CrossRef] [PubMed]
240. Becker, E.; Orellana Rios, C.L.; Lahmann, C.; Rücker, G.; Bauer, J.; Boeker, M. Anxiety as a risk factor of
Alzheimer’s disease and vascular dementia. Br. J. Psychiatry 2018, 213, 654–660. [CrossRef]
241. Santabárbara, J.; Lipnicki, D.M.; Bueno-Notivol, J.; Olaya-Guzmán, B.; Villagrása, B.; López-Antón, R.
Updating the evidence for an association between anxiety and risk of Alzheimer’s disease: A meta-analysis
of prospective cohort studies. J. Affect. Disord. 2019, 262, 397–404. [CrossRef]
242. Baillon, S.; Gasper, A.; Wilson-Morkeh, F.; Pritchard, M.; Jesu, A.; Velayudhan, L. Prevalence and Severity
of Neuropsychiatric Symptoms in Early- Versus Late-Onset Alzheimer’s Disease. Am. J. Alzheimers Dis. Other
Demen. 2019, 34, 433–438. [CrossRef]
243. Sun, Y.; Wang, X.; Wang, Y.; Dong, H.; Lu, J.; Scheininger, T.; Ewers, M.; Jesse, F.; Zuo, X.; Han, Y. Anxiety
correlates with cortical surface area in subjective cognitive decline: APOE ε4 carriers versus APOE ε4
non-carriers. Alzheimers Res. Ther. 2019, 11, 50. [CrossRef]
244. Vlachos, G.S.; Cosentino, S.; Kosmidis, M.H.; Anastasiou, C.A.; Yannakoulia, M.; Dardiotis, E.;
Hadjigeorgiou, G.; Sakka, P.; Ntanasi, E.; Scarneos, N. Prevalence and determinants of subjective cognitive
decline in a representative Greek elderly population. Int. J. Geriatr. Psychiatry. 2019, 34, 846–854. [CrossRef]
[PubMed]
245. Nafti, M.; Sirois, C.; Kröger, E.; Carmichael, P.H.; Laurin, D. Is Benzodiazepine Use Associated With the Risk
of Dementia and Cognitive Impairment-Not Dementia in Older Persons? The Canadian Study of Health and
Aging. Ann. Pharmacother. 2020, 54, 219–225. [CrossRef]
246. Thomas, J.; Overeem, S.; Claassen, J.A.H.R. Long-Term Occupational Sleep Loss and Post-Retirement
Cognitive Decline or Dementia. Dement. Geriatr. Cogn. Disord. 2019, 48, 105–112. [CrossRef]
247. Leng, Y.; Musiek, E.S.; Hu, K.; Cappuccio, F.P.; Yaffe, K. Association between circadian rhythms and
neurodegenerative diseases. Lancet Neurol. 2019, 18, 307–318. [CrossRef]
248. Minakawa, E.N.; Wada, K.; Nagai, Y. Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer’s Disease. *Int. J. Mol. Sci.* 2019, 20, 803. [CrossRef] [PubMed]

249. Duncan, M.J. Interacting influences of aging and Alzheimer’s disease on circadian rhythms. *Eur. J. Neurosci.* 2020, 51, 310–325. [CrossRef] [PubMed]

250. Yesavage, J.A.; Noda, A.; Heath, A.; McNerney, M.W.; Domingue, B.W.; Hernandez, Y.; Benson, G.; Hallmayer, J.; O’Hara, R.; Williams, L.M.; et al. Sleep-wake disorders in Alzheimer’s disease: Further genetic analyses in relation to objective sleep measures. *Int. Psychogeriatr.* 2019, 1–7. [CrossRef]

251. Wu, M.; Zhou, F.; Yang, J.; Bai, Y.; Yan, X.; Cao, J.; Qi, J. Abnormal circadian locomotor rhythms and Per gene expression in six-month-old triple transgenic mice model of Alzheimer’s disease. *Neurosci. Lett.* 2018, 676, 13–18. [CrossRef]

252. Rainey-Smith, S.R.; Mazzucchelli, G.N.; Villemagne, V.L.; Brown, B.M.; Porter, T.; Weinborn, M.; Bucks, R.S.; Milicic, L.; Sohrabi, H.R.; Taddei, K.; et al. Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden. *Transl. Psychiatry* 2018, 8, 47. [CrossRef]

253. Martin, S.C.; Monroe, S.K.; Diering, G.H. Homer1a and mGluR1 Signaling in Homeostatic Sleep Drive and Output. *Yale J. Biol. Med.* 2019, 92, 93–101.

254. Manni, R.; Cremascoli, R.; Perretti, C.; De Icco, R.; Picascia, M.; Ghezzi, C.; Cerri, S.; Sinforiani, E.; Terzaghi, M. Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity. *Sleep Med.* 2019, 63, 122–126. [CrossRef] [PubMed]

255. Chauhan, A.K.; Mallick, B.N. Association between autophagy and rapid eye movement sleep loss-associated neurodegenerative and patho-physio-behavioral changes. *Sleep Med.* 2019, 63, 29–37. [CrossRef]

256. You, J.C.; Jones, E.; Cross, D.E.; Lyon, A.C.; Kang, H.; Newberg, A.B.; Lippa, C.F. Association of β-Amyloid Burden With Sleep Dysfunction and Cognitive Impairment in Elderly Individuals With Cognitive Disorders. *JAMA Netw. Open* 2019, 2, e1913383. [CrossRef]

257. Wang, C.; Holtzman, D.M. Bidirectional relationship between sleep and Alzheimer’s disease: Role of amyloid, tau, and other factors. *Neuropsychopharmacology* 2020, 45, 104–120. [CrossRef] [PubMed]

258. Zhao, B.; Liu, P.; Wei, M.; Li, Y.; Liu, J.; Ma, L.; Shang, S.; Jiang, Y.; Huo, K.; Wang, J.; et al. Chronic Sleep Restriction Induces Aβ Accumulation by Disrupting the Balance of Aβ Production and Clearance in Rats. *Neurochem. Res.* 2019, 44, 859–873. [CrossRef]

259. Zhang, F.; Zhong, R.; Li, S.; Fu, Z.; Wang, R.; Wang, T. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer’s disease preceding the disease pathology and cognitive decline. *Alzheimers Dement.* 2019, 15, 590–597. [CrossRef]

260. Taillard, J.; Sagaspe, P.; Berthomier, C.; Brandewinder, M.; Amieva, H.; Dartigues, J.F.; Rainfranq, M.; Harston, S.; Micoulaud-Franchi, J.A.; Philip, P. Non-REM Sleep Characteristics Predict Early Cognitive Impairment in an Aging Population. *Front. Neurol.* 2019, 10, 197. [CrossRef]

261. Liu, Z.; Wang, F.; Tang, M.; Zhao, Y.; Wang, X. Amyloid β and tau are involved in sleep disorder in Alzheimer’s disease by orexin A and adenosine A1 receptor. *Int. J. Mol. Med.* 2019, 43, 435–442. [CrossRef] [PubMed]

262. Herring, W.J.; Roth, T.; Krystal, A.D.; Michelson, D. Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. *J. Sleep Res.* 2019, 28, e12782. [CrossRef] [PubMed]

263. Nicastro, N.; Assal, F.; Seeck, M. From here to epilepsy: The risk of seizure in patients with Alzheimer’s disease. *Epileptic Disord.* 2016, 18, 1–12. [CrossRef] [PubMed]

264. von Rüden, E.L.; Zellinger, C.; Gedon, J.; Walker, A.; Bierling, V.; Deeg, C.A. Regulation of Alzheimer’s Disease-Associated Proteins During the Course of Epileptogenesis: Differential Proteomic Analysis in a Rat Model. *Neuroscience* 2020, 424, 102–120. [CrossRef]

265. Zelano, J.; Brigo, F.; Garcia-Patek, S. Increased risk of epilepsy in patients registered in the Swedish Dementia Registry. *Eur. J. Neurol.* 2020, 27, 129–135. [CrossRef]

266. Tábuas-Pereira, M.; Durães, J.; Lopes, J.; Sales, F.; Bento, C.; Duro, D.; Santiago, B.; Almeida, M.R.; Leitao, M.J.; Balderias, I.; et al. Increased CSF tau is associated with a higher risk of seizures in patients with Alzheimer’s disease. *Epilepsy Behav.* 2019, 98, 207–209. [CrossRef]

267. Zhou, X.; Tao, H.; Cai, Y.; Cui, L.; Zhao, B.; Li, K. Stage-dependent involvement of ADAM10 and its significance in epileptic seizures. *J. Cell Mol. Med.* 2019, 23, 4494–4504. [CrossRef]
284. Wen, Z.P.; Fan, S.S.; Du, C.; Yin, T.; Zhou, B.T.; Peng, Z.F.; Xie, X.Y.; Zhang, W.; Chen, Y.; Tang, J.; et al. Mapping the knowledge structure and trends of epilepsy genetics over the past decade: A co-word analysis based on medical subject headings terms. Medicine 2019, 98, e16782. [CrossRef] [PubMed]
269. Al-Eitan, L.N.; Al-Dalalah, I.M.; Mustafa, M.M.; Alghamdi, M.A.; Elshammar, A.K.; Khreisat, W.H.; Aljamil, H.A. Effects of MTHFR and ABCB2 gene polymorphisms on antiepileptic drug responsiveness in Jordanian epileptic patients. Pharmgenom. Personalized Med. 2019, 12, 87–95. [CrossRef] [PubMed]
270. Vossel, K.A.; Tartaglia, M.C.; Nygaard, H.B.; Zeman, A.Z.; Miller, B.L. Epileptic activity in Alzheimer’s disease: Causes and clinical relevance. Lancet Neurol. 2017, 16, 311–322. [CrossRef]
271. Giorgi, F.S.; Guida, M.; Vergallo, A.; Bonuccelli, U.; Zaccara, G. Treatment of epilepsy in patients with Alzheimer’s disease. Expert Rev. Neurother. 2017, 17, 309–318. [CrossRef] [PubMed]
272. Thijs, R.D.; Surges, R.; O’Brien, T.J.; Sander, J.W. Epilepsy in adults. Lancet 2019, 393, 689–701. [CrossRef]
273. He, Z.W.; Qu, J.; Zhang, Y.; Mao, C.X.; Wang, Z.B.; Mao, X.Y.; Deng, Z.; Zhou, B.; Yin, J.; Long, H.; et al. PRRT2 mutations are related to febrile seizures in epileptic patients. Int. J. Mol. Sci. 2014, 15, 23408–23417. [CrossRef]
274. Haerian, B.S.; Baum, L.; Kwan, P.; Cherry, S.S.; Shin, J.G.; Kim, S.E. Contribution of GABRG2 polymorphisms to risk of epilepsy and febrile seizures: A multicenter cohort study and meta-analysis. Mol. Neurobiol. 2016, 53, 5457–5467. [CrossRef]
275. Zhu, M.M.; Li, H.L.; Shi, L.H.; Chen, X.P.; Luo, J.; Zhang, Z.L. The pharmacogenomics of valproic acid. J. Hum. Genet. 2017, 62, 1009–1014. [CrossRef] [PubMed]
276. Zhu, X.; Yun, W.; Sun, X.; Qiu, F.; Zhao, L.; Guo, Y. Effects of major transporter and metabolizing enzyme gene polymorphisms on carbamazepine metabolism in Chinese patients with epilepsy. Pharmacogenomics 2014, 15, 1867–1879. [CrossRef]
277. Haerian, B.S.; Baum, L.; Kwan, P.; Cherry, S.S.; Shin, J.G.; Kim, S.E. Contribution of GABRG2 polymorphisms to risk of epilepsy and febrile seizures: A multicenter cohort study and meta-analysis. Mol. Neurobiol. 2016, 53, 5457–5467. [CrossRef]
278. Zhu, M.M.; Li, H.L.; Shi, L.H.; Chen, X.P.; Luo, J.; Zhang, Z.L. The pharmacogenomics of valproic acid. J. Hum. Genet. 2017, 62, 1009–1014. [CrossRef] [PubMed]
279. Balestrini, S.; Sisodiya, S.M. Pharmacogenomics in epilepsy. Neurosci. Lett. 2018, 667, 27–39. [CrossRef] [PubMed]
280. Li, X.; Zhang, J.; Wu, X.; Yan, H.; Zhang, Y.; He, R.H.; Tang, Y.J.; He, Y.J.; Tan, D.; Mao, X.Y.; et al. Polymorphisms of ABAT, SCN2A and ALDH5A1 may affect valproic acid responses in the treatment of epilepsy in Chinese. Pharmacogenomics 2016, 17, 2007–2014. [CrossRef] [PubMed]
281. Noai, M.; Soraoka, H.; Kajiwara, A.; Tanamachi, Y.; Oniki, K.; Nakagawa, K.; Ishitsu, T.; Saruwatari, J. Cytochrome P450 2C19 polymorphisms and valproic acid-induced weight gain. Acta Neurol. Scand. 2016, 133, 216–223. [CrossRef]
282. Li, H.; Wang, X.; Zhou, Y.; Zhou, Y.; Ni, G.; Su, Q.; Chen, Z.; Chen, Z.; Li, J.; Chen, X.; et al. Association of LEPR and ANKK1 Gene Polymorphisms with Weight Gain in Epilepsy Patients Receiving Valproic Acid. Int. J. Neuropsychopharmacol. 2015, 18, pyv021. [CrossRef] [PubMed]
283. Xu, S.; Chen, Y.; Zhao, M.; Guo, Y.; Wang, Z.; Zhao, L. Population pharmacokinetics of valproic acid in epileptic children: Effects of clinical and genetic factors. Eur. J. Pharm. Sci. 2018, 122, 170–178. [CrossRef]
284. Wen, Z.P.; Fan, S.S.; Du, C.; Yin, T.; Zhou, B.T.; Peng, Z.F.; Xie, X.Y.; Zhang, W.; Chen, Y.; Tang, J.; et al. Influence of acylpeptide hydrolase polymorphisms on valproic acid level in Chinese epilepsy patients. Pharmacogenomics 2016, 17, 1219–1225. [CrossRef]
285. Li, Q.; Li, Q.Q.; Jia, J.N.; Cao, S.; Wang, Z.B.; Wang, X. Sodium valproate ameliorates neuronal apoptosis in a kainic acid model of epilepsy via enhancing PKC-dependent GABAAR γ2 serine 327 phosphorylation. Neurochem. Res. 2018, 43, 2343–2352. [CrossRef] [PubMed]
286. Ogusu, N.; Saruwatari, J.; Nakashima, H.; Noai, M.; Nishimura, M.; Deguchi, M.; Oniki, K.; Yasui-Furokori, N.; Kaneko, S.; Ishitsu, T.; et al. Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between valproic acid exposure and elevation of γ-glutamyltransferase in patients with epilepsy: A population pharmacokinetic-pharmacodynamic analysis. PLoS ONE 2014, 9, e11066. [CrossRef] [PubMed]
287. Shirzadi, M.; Reimers, A.; Helde, G.; Sjursen, W.; Brodtkorb, E. No association between non-bullous skin reactions from lamotrigine and heterozygosity of UGT1A4 genetic variants *2(P24T) or *3(L48V) in Norwegian patients. Seizure 2017, 45, 169–171. [CrossRef] [PubMed]
288. Aoki, M.; Hosono, N.; Takata, S.; Nsksmura, Y.; Kamatani, N.; Kubo, M. New pharmacogenetic test for lamotrigine in Chinese children with epilepsy. *Ther. Drug Monit.* **2018**, *40*, 730–737. [CrossRef] [PubMed]

289. Chen, Y.; Xu, S.; Wang, Z.; Zhao, M.; Wang, H.; Lu, T.; Zhao, L. A population Pharmacokinetic-Pharmacogenetic model of lamotrigine in Chinese children with epilepsy. *Epilepsy Res.* **2016**, *127*, 186–190. [CrossRef]

290. Zhou, Y.; Wang, X.; Li, H.; Zhang, J.; Chen, Z.; Xie, W.; Zhang, J.; Li, J.; Zhou, L.; Huang, M. Polymorphisms in ABCG2, ABCB1 and HNF4a are associated with Lamotrigine concentrations in epilepsy patients. *Drug Metab. Pharmacokinet.* **2015**, *30*, 282–287. [CrossRef] [PubMed]

291. Phillips, E.J.; Sukasem, C.; Whirl-Carrillo, M.; Müller, D.J.; Dunnenberger, H.M.; Chantratita, W.; Goldspiel, B.; Chen, Y.T.; Carleton, B.C. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin. Pharmacol. Ther.* **2018**, *103*, 574–581. [CrossRef] [PubMed]

292. Liu, Y.; Yu, Y.; Nie, X.; Zhao, L.; Wang, X. Association between HLA-B*15:02 and oxcarbazepine-induced cutaneous adverse reaction: A meta-analysis. *Pharmacogenomics* **2018**, *19*, 547–552. [CrossRef]

293. Cheung, Y.K.; Cheng, S.H.; Chan, E.J.; Lo, S.V.; Ng, M.H.; Kwan, P. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. *Epilepsia* **2013**, *54*, 1307–1314. [CrossRef]

294. Simper, G.S.; Gräser, L.S.; Celik, A.A.; Kuhn, J.; Kunze-Schumacher, H.; Wolkings, S.; et al. Genetic variation in CFH predicts phenytoin-induced maculopapular exanthema in European-descent patients. *Neurology* **2018**, *90*, e332–e341. [CrossRef]
306. Glauser, T.A.; Holland, K.; O’Brien, V.P.; Keddache, M.; Martin, L.J.; Clark, P.O.; Cnaan, A.; Dlugos, D.; Hirtz, D.G.; Shinnar, S.; et al. Pharmacogenetics of antiepileptic drug efficacy in childhood absence epilepsy. *Ann. Neurol.* 2017, 81, 444–453. [CrossRef]

307. Rogawski, M.A. The intrinsic severity hypothesis of pharmacoresistance to antiepileptic drugs. *Epilepsia* 2013, 54, 33–40. [CrossRef]

308. Haerian, B.S.; Roslan, H.; Raymond, A.A.; Tan, C.T.; Lim, K.S.; Zulkiﬁli, S.Z.; Mohamed, E.H.; Tan, H.J.; Mohamed, Z. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: A systematic review and meta-analysis. *Seizure* 2010, 19, 339–346. [CrossRef] [PubMed]

309. Ajmi, M.; Boujaafar, S.; Zouari, N.; Amor, D.; Nasr, A.; Rejeb, N.B.; Amor, S.B.; Omezzine, A.; Benammou, S.; Bouslama, A. Association between ABCB1 polymorphisms and response to first-generation antiepileptic drugs in a Tunisian epileptic population. *Int. J. Neurosci.* 2018, 128, 705–714. [CrossRef] [PubMed]

310. Qu, J.; Zhou, B.T.; Yin, J.Y.; Xu, X.J.; Zhao, Y.C.; Lei, G.H.; Tang, Q.; Zhou, H.H.; Liu, Z.Q. ABCC2 polymorphisms and haplotype are associated with drug resistance in Chinese epileptic patients. *CNNS Neurosci. Ther.* 2012, 18, 647–651. [CrossRef] [PubMed]

311. Lv, N.; Qu, J.; Long, H.; Zhou, L.; Cao, Y.; Long, L.; Liu, Z.; Xiao, B. Association study between polymorphisms in the CACNA1A, CACNA1C, and CACNA1H genes and drug-resistant epilepsy in the Chinese Han population. *Seizure* 2015, 30, 64–69. [CrossRef] [PubMed]

312. Daci, A.; Bozialia, A.; Jashari, F.; Krasniqi, S. Individualizing treatment approaches for epileptic patients with glucose transporter type1 (GLUT-1) deficiency. *Int. J. Mol. Sci.* 2018, 19, 122. [CrossRef]

313. Ma, C.L.; Wu, X.Y.; Zheng, J.; Wu, Z.Y.; Hong, Z.; Zhong, M.K. Association of SCN1A, SCN2A and ABCC2 gene polymorphisms with the response to antiepileptic drugs in Chinese Han patients with epilepsy. *Pharmacogenomics* 2014, 15, 1323–1336. [CrossRef] [PubMed]

314. Sha’ari, H.M.; Haerian, B.S.; Baum, L.; Saruwatari, J.; Tan, H.J.; Rafia, M.H.; Ali, R.A.; Kwan, P.; Ishitu, T.; Nakagawa, K.; et al. ABCB2 rs2273697 and rs3740066 polymorphisms and resistance to antiepileptic drugs in Asia Pacific epilepsy cohorts. *Pharmacogenomics* 2014, 15, 459–466. [CrossRef]

315. Lotte, J.; Bast, T.; Borusiak, P.; Coppola, A.; Cross, J.H.; Dimova, P. Effectiveness of antiepileptic therapy in patients with PCDH19 mutations. *Seizure* 2016, 35, 106–110. [CrossRef]

316. Koug, T.; Shimbo, H.; Iai, M.; Yamashita, S.; Ishii, A.; Ihara, Y.; Hirose, S.; Yamakawa, K.; Osaka, H. Effect of CYP2C19 polymorphisms on stiripentol administration in Japanese cases of Dravet syndrome. *Brain Dev.* 2015, 37, 243–249. [CrossRef]

317. Hung, C.C.; Chen, P.L.; Huang, W.M.; Tai, J.J.; Hsieh, T.J.; Ding, S.T.; Hsieh, Y.W.; Liou, H.H. Gene-wide tagging study of the effects of common genetic polymorphisms in the α subunits of the GABA(A) receptor on epilepsy treatment response. *Pharmacogenomics* 2013, 14, 1849–1856. [CrossRef]

318. Kickinger, S.; Hellsberg, E.; Froilund, B.; Schousboe, A.; Ecker, G.F.; Wellendorph, P. Structural and molecular aspects of betaine-GABA transporter 1 (BGT1) and its relation to brain function. *Neuropsychopharmacology* 2019, 161, 107644. [CrossRef] [PubMed]

319. Heath, L.; Gray, S.L.; Boudreau, D.M.; Thummel, K.; Edwards, K.L.; Fullerton, S.M.; Crane, P.K.; Larson, E.B. Cumulative antidepressant use and risk of dementia in a prospective cohort study. *J. Am. Geriatr. Soc.* 2018, 66, 1948–1955. [CrossRef]

320. Kirgaval, R.S.; Revanakar, S.; Sri rangapattana, C. Prevalence of extrapyramidal side effects in patients on antipsychotics drugs at a Tertiary Care Center. *J. Psychiatry* 2017, 20, 419. [CrossRef]

321. Patterson, S.M.; Hughes, C.M.; Crealey, G.; Cardwell, C.; Lapan, K.L. An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in Northern Ireland (Fleetwood Northern Ireland study). *J. Am. Geriatr. Soc.* 2010, 58, 44–53. [CrossRef] [PubMed]

322. Barber, N.D.; Allired, D.P.; Raynor, D.K.; Dickinson, R.; Garﬁeld, S.; Jesson, B.; Lim, R.; Savagem, I.; Standage, C.; Buckle, P.; et al. Care homes’ use of medicines study: Prevalence, causes and potential harm of medication errors in care homes for older people. *Qual. Saf. Health Care* 2009, 18, 341–346. [CrossRef] [PubMed]

323. Hughes, C.M.; Lapan, K.L. Pharmacy interventions on prescribing in nursing homes: From evidence to practice. *Ther. Adv. Drug Saf.* 2011, 2, 103–112. [CrossRef]

324. Eshetie, T.C.; Nguyen, T.A.; Gillam, M.H.; Kalisch Ellett, L.M. Potentially inappropriate prescribing in people with dementia: An Australian population-based study. *Int. J. Geriatr. Psychiatry* 2019, 34, 1498–1505. [CrossRef]
325. Bernal, C.J.; Aka, I.; Carroll, R.J.; Coco, J.R.; Lima, J.J.; Acra, S.A.; Roden, D.M.; Van Driest, S.L. CYP2C19 Phenotype and Risk of Proton Pump Inhibitor-Associated Infections. *Pediatrics* 2019, 144, e20190857. [CrossRef]

326. Mega, J.L.; Walker, J.R.; Ruff, C.T.; Vandell, A.G.; Nordio, F.; Deenadayalu, N.; Murphy, S.A.; Lee, J.; Mercuri, M.F.; Giugliano, R.P.; et al. Genetics and the clinical response to warfarin and edoxaban: Findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015, 385, 2280–2287. [CrossRef]

327. Chen, W.; Wu, L.; Liu, X.; Shen, Y.; Liang, Y.; Zhu, J.; Tan, H.; Yang, Y.; Liu, Q.; Wang, M.; et al. Warfarin dose requirements with different genotypes of CYP2C9 and VKORC1 for patients with atrial fibrillation and valve replacement. *Int. J. Clin. Pharmacol. Ther.* 2017, 55, 126–132. [CrossRef]

328. Kamali, X.; Wulasihan, M.; Yang, Y.C.; Lu, W.H.; Liu, Z.Q.; He, P.Y. Association of GGCX gene polymorphism with warfarin dose in atrial fibrillation population in Xinjiang. *Lipids Health Dis.* 2013, 12, 149. [CrossRef] [PubMed]

329. Magvanjav, O.; McDonough, C.W.; Gong, Y.; McClure, L.A.; Talbert, R.L.; Horenstein, R.B.; Shuldiner, A.R.; Benavente, O.R.; Mitchell, B.D.; Johnson, J.A.; et al. Pharmacogenetic associations of β1-adrenergic receptor polymorphisms with cardiovascular outcomes in the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes). *Stroke* 2017, 48, 1337–1343. [CrossRef] [PubMed]

330. Yi, X.; Zhou, Q.; Wang, C.; Lin, J.; Liu, P.; Fu, C. Platelet receptor Gene (P2Y12, P2Y1) and platelet glycoprotein (GPIIIa) polymorphisms are associated with antiplatelet drug responsiveness and clinical outcomes after acute minor ischemic stroke. *Eur. J. Clin. Pharmacol.* 2017, 73, 437–443. [CrossRef] [PubMed]

331. Sørensen, I.F.; Vazquez, A.I.; Irvin, M.R.; Sørensen, P.; Davis, B.R.; Ford, C.E.; Boerwinkle, E.; Eckfeldt, J.H.; Arnett, D.K. Pharmacogenetic effects of ‘candidate gene complexes’ on stroke in the GenHAT study. *Pharmacogenet. Genom.* 2014, 24, 556–563. [CrossRef]

332. Sychev, D.; Minningulov, R.; Bochkov, P.; Ryzhikova, K.; Yudina, I.; Lychagin, A.; Morozova, T. Effect of CYP3A4, CYP3A5, ABCB1 Gene Polymorphisms on Rivaroxaban Pharmacokinetics in Patients Undergoing Total Hip and Knee Replacement Surgery. *High Blood Press. Cardiovasc. Prev.* 2019, 26, 413–420. [CrossRef]

333. McDonough, C.W.; McClure, L.A.; Mitchell, B.D.; Gong, Y.; Horenstein, R.B.; Lewis, J.P.; Lewis, J.P.; Field, T.S.; Talbert, R.L.; Benavente, O.R.; et al. CYP2C19 metabolizer status and clopidogrel efficacy in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. *J. Am. Heart Assoc.* 2015, 4, e001652. [CrossRef]

334. Wu, Y.; Zhou, Y.; Pan, Y.; Zhao, X.; Liu, L.; Wang, D.; Li, H.; Johnston, S.C.; Meng, X.; Wang, Y.; et al. Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. *Pharmacogenom. J.* 2018, 18, 713–720. [CrossRef] [PubMed]

335. Duconge, J.; Hernandez-Suarez, D.F. Potential usefulness of clopidogrel Pharmacogenetics in cerebral endovascular procedures and carotid artery stenting. *Curr. Clin. Pharmacol.* 2017, 12, 11–17. [CrossRef] [PubMed]

336. Kapedanovska-Nestorovska, A.; Dimovski, A.J.; Sterjev, Z.; Matevska-Geskovska, N.; Suturkova, L.; Ugurov, P.; Mitrev, Z.; Rosalia, R. The AKR1D1*36 (rs1872930) allelic variant is independently associated with clopidogrel treatment outcome. *Pharmacogenom. Personalized Med.* 2014, 7, 193–199. [CrossRef]

337. Gallego-Fabrega, C.; Carrera, C.; Reny, J.L.; Fontana, P.; Sowik, A.; Pera, J.; Pizzini, A.; Serrano-Heras, G.; Segura, T.; Marti-Fabregas, J.; et al. TRAF3 epigenetic regulation is associated with vascular recurrence in patients with ischemic stroke. *Stroke* 2016, 47, 1180–1186. [CrossRef]

338. Kampouraki, E.; Kamali, F. Pharmacogenetics of anticoagulants used for stroke prevention in patients with atrial fibrillation. *Expert Opin. Drug Metab. Toxicol.* 2019, 15, 449–458. [CrossRef] [PubMed]

339. Miller-Rhodes, P.; Kong, C.; Baht, G.S.; Saminathan, P.; Rodriguez, R.M.; Wetsel, W.; Gelbard, H.A.; Terrando, N. The broad spectrum mixed-lineage kinase 3 inhibitor URMC-099 prevents acute microgliosis and cognitive decline in a mouse model of perioperative neurocognitive disorders. *J. Neuroinflamm.* 2019, 16, 193. [CrossRef]

340. Ettienne, E.B.; Ofoegbu, A.; Maneno, M.K.; Briggs, J.; Ezeude, G.; Williams, S.; Walker, C.; Chapman, E. Pharmacogenomics and OUD: Clinical Decision Support in an African American Cohort. *J. Natl. Med. Assoc.* 2019, 11, 674–681. [CrossRef] [PubMed]

341. Narayan, S.W.; Pearson, S.A.; Litchfield, M.; Le Couteur, D.G.; Buckley, N.; McLachlan, A.J.; Zoege, H. Anticholinergic medicines use among older adults before and after initiating dementia medicines. *Br. J. Clin. Pharmacol.* 2019, 85, 1957–1963. [CrossRef] [PubMed]
342. Yoshida, K.; Gi, M.; Fujioka, M.; Teramoto, I.; Wanibuchi, H. Long-term administration of excess zinc impairs learning and memory in aged mice. *J. Toxicol. Sci.* 2019, 44, 681–691. [CrossRef] [PubMed]

343. Thomson, E.M. Air Pollution, Stress, and Allostatic Load: Linking Systemic and Central Nervous System Impacts. *J. Alzheimers Dis.* 2019, 69, 597–614. [CrossRef]

344. Exley, C.; Mold, M.J. Aluminium in human brain tissue: How much is too much? *J. Biol. Inorg. Chem.* 2019, 54, 1279–1282. [CrossRef]

345. Kalilani, L.; Sun, X.; Pelgrims, B.; Noack-Rink, M.; Villanueva, V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. *Epilepsia* 2018, 59, 2179–2193. [CrossRef]

346. Kong, S.T.; Hom, C.S.; Ho, P.C.; Lium, S.H. Prevalence of drug resistant epilepsy in adults with epilepsy attending a neurology clinic of a tertiary referral hospital in Singapore. *Epilepsy Res.* 2014, 108, 1253–1262. [CrossRef] [PubMed]

347. Kalozoumi, G.; Kel-Margoulis, O.; Vafiadaki, E.; Greenberg, D.; Bernard, H.; Soreq, H.; Depaulis, A.; Sanoudou, D. Glial responses during epileptogenesis in Mus musculus point to potential therapeutic targets. *PLoS ONE* 2018, 13, e0201742. [CrossRef]

348. Orlandi, A.; Paolino, M.C.; Striano, P.; Parisi, P. Clinical reappraisal of the influence of drug-transporter polymorphisms in epilepsy. *Expert Opin. Drug Metab. Toxicol.* 2018, 14, 505–512. [CrossRef] [PubMed]

© 2020 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).