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Review

Pharmacogenetics and the Blood–Brain Barrier: A Whirlwind Tour of Potential Clinical Utility

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Abstract: Genetic factors influence medication response (pharmacogenetics), affecting the pharmacodynamics and pharmacokinetics of many medicaments used in clinical care. The ability of medications to cross the blood–brain barrier (BBB) represents a critical putative factor in the effectiveness and tolerability of various medications relevant to central nervous system disorders (CNS), cancer, and broader medical conditions at a pharmacokinetic (dosing) level. Pharmacogenetics has the potential to personalise medicine to a greater extent than has been possible, with the potential to help reduce heuristic delays to effective tolerable pharmacotherapy. Here, we critically examine and summarise the evidence, particularly for ABCB1 polymorphisms associated with drug transportation and other clinical relevance. These transporters appear to have a role in BBB pharmacogenetics and may indicate new avenues of research that extend beyond the current paradigm of CYP450 polymorphisms. We identify some of the most promising variants for clinical translation while spotlighting the complexities of the involved systems and limitations of the current empirical literature.

Keywords: pharmacogenetics; blood–brain barrier; drug discovery; personalised medicine; precision medicine; clinical translation

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1. Introduction

The blood–brain barrier (BBB) forms the primary physical defence of the central nervous system against potential toxins and pathogens. It does so by actively and passively moderating the diffusion and effusion of substances into and out of the central nervous system (CNS). A combination of tight endothelial junctions, active transporters, and adjacent pericytes and astrocytes comprise the neurovascular unit of the BBB, a complex system whose basic physiology is still being elucidated [1]. Genetic variants are known to influence medicament permeability across the BBB, though rarely consistently across a population. Specific polymorphisms are purported to interfere with BBB permeability and the drug delivery of specific CNS-acting medications and so can influence optimal medication dose based on BBB pharmacokinetics. Regular medication use is extremely common; 47.9% percent of European Union citizens over the age of 15 reported taking at least one medication in the past two weeks and 64.8% percent of adults in the USA reported using at least one medication in the past 12 months (in both estimates, average use was higher for males than females and trended upward over the lifespan [2,3]. Furthermore, the effectiveness of medication can vary wildly from person to person and across drug

classes; for example, one analysis suggested that the majority of cancer medications with accelerated FDA failed to demonstrate any benefit [4], and recent estimates suggest that as many as around one-third of psychiatric patients are treatment resistant [5]. The clinical and societal significance of ineffective medications is profound.

Medication molecules in the bloodstream encounter the endothelial BBB and, depending on the drug's properties and whether it is a substrate for organic anion transporters (OATs) or organic cation transporters (OCTs), it may be actively transported from the bloodstream. This step is facilitated by active transport mechanisms against a concentration gradient. Numerous medications serve as substrates for organic anion or cation transport, benefiting from facilitated or expedited transport across endothelial cells at the BBB. Expressed in brain capillary endothelial cells forming the BBB, human organic anion transporting polypeptide 1A2 (OATP1A2) facilitates the uptake of various organic anions, including drugs, hormones, and toxins, from the bloodstream into the brain [6,7]. Notably, specific OATP1A2 variants, such as *rs776374083*, *rs864309501*, *rs886050885*, and *rs141502207*, have garnered clinical relevance, as highlighted in research by Wang et al. (2020 [8]). Similarly, organic anion transporter 3 plays a crucial role in converting organic anions from the brain into the bloodstream. Located in the abluminal membrane of brain capillary endothelial cells, OAT3 contributes significantly to maintaining homeostasis in the CNS [9]. Organic cation transporters 1 and 2 (OCT1 and OCT2) are also expressed in the BBB and brain parenchyma. A simplified diagram of the mechanism of action is illustrated in Figure 1.

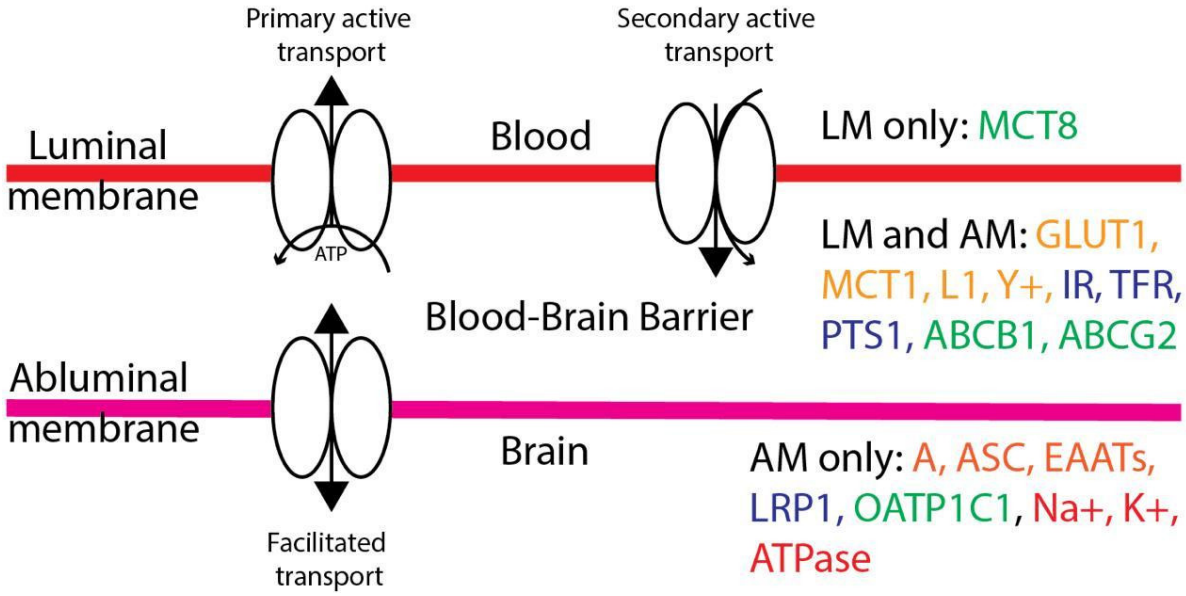

Figure 1. Mechanisms of action of ABCB1 across the luminal membrane (LM) and abluminal membrane (AM) of the blood–brain barrier using nutrient transporters (yellow and orange), peptides transporters, (purple), and ABC transporters (green) ion transporters (red). The direction(s) of transport is indicated by the arrows. Pictured transporters include Monocarboxylate Transporter 8 (MCT8), Glucose transporter 1 (GLUT1), Monocarboxylate Transporter 1 (MCT1), Human L-type amino acid transporter 1 (L1/LAT1), Cationic Amino Acid Transporter (Y+), insulin receptor (IR), transferring receptor (TFR), Peroxisomal Targeting Signal 1 (PTS1), ATP-binding cassette B1 (ABCB1), ATP-binding cassette G2 (ABCG2), sodium-dependent concentrative transporters A (A), Alanine/serine/cysteine transporter (ASC), Excitatory Amino Acid Transporters (EAATs), Low density lipoprotein receptor-related protein 1 (LRP1), Organo Anion Transporter P1C1 (OATP1C1) and Sodium-Potassium ATPase (Na+,K+,ATPase/NKA).

Once the drug enters the endothelial cells, it faces the tight junction barrier. Tight junction proteins (TJP), such as claudin-5 and occludin, restrict the paracellular movement

of the drug between these cells. By sealing the intercellular gaps, TJP prevents the passive diffusion of large and hydrophilic molecules, including medications, from freely traversing between the bloodstream and brain tissue [10]. Claudin-5, the most abundant TJP in the BBB, has undergone extensive clinical investigation due to its critical role in maintaining barrier integrity. As such, polymorphisms in the CLDN5 gene, which encodes Claudin-5, have been scrutinised for their potential to alter BBB permeability and medication response [11]. Notably, four distinct CLDN-5 gene polymorphisms, including *rs1042711*, *rs1042713*, *rs1800888*, and *rs1554115894*, have emerged as subjects of interest in medication response research (ClinVar, [12]). However, further investigation is warranted to elucidate the precise implications of these genetic variations in clinical practice. More thoroughly investigated are the ATP binding cassette (ABC) transporters at the BBB—a family of active transporters highly expressed at the BBB and relevant to medication bioavailability [1].

1.1. Active Transporters

Transport proteins, including efflux transporters like the ABCB1 gene encoding P-glycoprotein (P-gp or PGP), are embedded in the membranes of brain capillary endothelial cells. They actively pump specific molecules out of the brain and back into the bloodstream. When a drug molecule enters the endothelial cells from the bloodstream (via passive diffusion or transporters), efflux transporters like P-gp can recognise and transport the medication back into the bloodstream. This efflux mechanism helps protect the brain from potentially harmful substances and sometimes contributes to medication resistance. Genetic variations in the P-gp expression can influence the efflux transport function at the BBB, potentially affecting drug transport and permeability with a broad impact on a host of disorders and conditions. Indeed, some of the earliest investigations into P-gp examined cancer cells with multidrug resistance [13], though research quickly extended to substances as diverse as opioids, dexamethasone, and anti-HIV protease inhibitors. Recent estimates suggest that 30% of the most commonly prescribed medications are substrates of P-gp [14]. Of course, pharmacotherapy extends outside of the CNS and the BBB. For example, many large-molecule drugs are completely unable to cross the BBB and so exert pharmacodynamic influence through other means, including indirect CNS effects [15]. Monoclonal antibodies are a useful case study. The alpha4-integrin cell binding agent natalizumab reduces overall lymphocyte transport into the brain as a means to combat multiple sclerosis progression but does not cross the BBB itself despite exerting a clear impact within the CNS [16]. Treatment response to monoclonal antibodies also has demonstrable genetic variation in multiple sclerosis and advanced cancers [17,18]. In that regard, we see that the pharmacogenetic response for anticancer drugs like bevacizumab is associated with genes outside of the ABCB1, such as within the nitrous-oxide receptor-regulating AGAP1 [19]. Interestingly, despite not being directly associated with drug transport, AGAP1 variants have been associated with treatment resistance to dozens of anticancer drugs in mice [20].

ABCB1-deficient animals experience neurological and foetal drug toxicity attributed to a disruption to the area with prominent P-gp encoding genes, such as blood–brain and blood–placenta barriers [21]. Likewise, Abcb1a−/− knockout mice experiencing brain metastases exhibit successful responses to drug treatments that would typically face challenges penetrating the blood–brain barrier, such as paclitaxel. Notably, Abcb1a−/− knockout mice demonstrate brain-serum ratios for both risperidone and its active metabolite, 9-hydroxy risperidone, which are 10 times higher than those observed in control mice. Furthermore, the double knockout mice, lacking both Abcb1a and Abcb1b, show brain-to-plasma ratios ranging from 1.1 to 2.6 times higher for various CNS medications than their wild-type counterparts [22].

1.2. Personalised and Precision Medicine

Pharmacological treatment of disease is a difficult process even for experienced clinicians following standard guidelines of gold-standard treatments since patient factors alter drug pharmacodynamics and pharmacokinetics leading to unexpected issues with efficacy

and tolerability. The rise of pharmacogenetics in medicine contributed to the emergence of personalised medicine and the more ambitious precision medicine, two innovative healthcare approaches that focus on customising medical treatments to fit each patient's unique genetic and other individual characteristics [23]. Broadly, such approaches aim to create individualised treatment plans tailored to maximise drug responsiveness while minimising side effects without lengthy trial-and-error processes [24]. In psychiatry, treatment resistance is common. For example, 25–33% of those with schizophrenia are treatment-resistant, necessitating third-line clozapine, which carries a significant burden of potentially serious side effects and mandates regular monitoring [25]. Likewise, standard targeted cancer treatments are difficult to maintain if effective, and the response reduces over time (for example, [26]). Many such responses are familial; Angst (1961) [27] first identified strong familial responses to antidepressant medications, later corroborated for lithium in bipolar disorder treatment [28] and antipsychotic response in schizophrenia [29,30]. Genes have long memories, and it is unsurprising that our ancestry also influences our ABCB1 genes; at least two genetic studies failed to detect or observe *rs1211152* in their samples. one from Africa comprising Xhosa, Afrikaans, and English ancestry [31] and another from the United States [32]. Evidence from Dong et al. in 2011 suggests a minor allele frequency (MAF) of <2% among Mexican-American samples, whereas McMahon et al. (2010) [33] observed an MAF of around 9% in a German sample of European ancestry. *Rs2032588* is much more prevalent in African populations (~18%) compared with European populations (~6%) and virtually absent in Asian populations [34]. Guided by the principle of individualised medicine for individual care, researchers have attempted to compare pharmacogenetically-guided treatment to standardised treatment with some success, though few high-quality studies are available (see [35,36]).

1.3. Implicated Single Nucleotide Polymorphisms (SNPs)

To assist pharmacogenetic investigators, we have endeavoured to summarise as much of the existing clinical evidence related to pharmacogenetic factors related to BBB permeability and drug delivery. A search of the PubMed National Centre of Biotechnology Information revealed 29 human ABCB1 polymorphisms with potential drug response properties, which we list in Table 1 and organise according to the current clinical significance assigned by the Single Nucleotide Polymorphism Database (dbSNP). For example, extensive investigations have been carried out on the *rs2032582* allele. Studies on a humanised mouse model with the 2677 G > T mutation revealed no change in P-glycoprotein expression levels in brain capillary fractions, yet this SNP resulted in increased brain penetration of verapamil, a representative substrate of P-glycoprotein [37]. Moreover, placentas from mothers with the TT/TT genotype exhibited significantly reduced P-glycoprotein expression [38]. A correlation was also observed between the binding potential of verapamil and the dosage of T alleles [39], and Margier et al. (2019) [40] observed an association between *rs868755* and increased plasma concentration of 25-hydroxycholecalciferol.

Table 1. Clinical investigations of pharmacogenetically informed drug response of SNPs in the ABCB1 gene. Alternative names are listed in parentheses.

	Drug Response and Pharmacokinetics	Limited Information
Rs ID	*rs3842*, *rs1045642* (*C3435T*), *rs1922240*, *rs2032582* (*G2677T/A*), *rs2235013*, *rs2235033*, *rs2235046*, *rs2888599*, *rs4148727*, *rs9282564*, *rs13237132*, *rs17064*, *rs868755*, *rs1128503*, *rs1202168*, *rs1211152*, *rs1922242*, *rs2032588*, *rs2214102*, *rs2214103*, *rs2235018*, *rs2235020*, *rs2235035*, *rs2235074*, *rs3213619*, *rs10276036*	*rs2235015* (*DRD2 Taq1A*), *rs55852620*, *rs58898486*

These polymorphisms in the ABCB1 gene are of interest in pharmacogenetics due to their potential function of P-gp, the interaction for drug transport, response, and pharmacokinetics. Furthermore, the presence of likely relevant but under-investigated SNPs suggests potential areas for future research. Given that the specific effects of each polymor-

phism can vary depending on the drug and the individual's genetic background, research continues exploring their clinical implications and relevance in optimising drug therapy for individual patients.

2. Results

Given the breadth of research into these SNPs and the heterogeneity of the samples, we have grouped our findings according to the conditions investigated.

2.1. Alzheimer's

Rs2032582 has been investigated in two studies examining Swiss and Italians with Alzheimer's disease, though the authors observed no association between the SNP and donepezil efficacy [41,42].

2.2. Cancer and Non-Cancerous Tumours

Investigations into pharmacogenetic factors and cancer are relatively common. For example, in multiple myeloma patients, *rs2235013* carriers present with increased drug response and decreased mortality [43] and with improved chemotherapy response and recurrence-free survival in late-stage lung cancer patients with the same [44]. A similar treatment response in chemotherapy-treated stage III lung cancer has been seen for *rs2235046*. Furthermore, Caronia et al. (2011) [45] found a strong association between the genotype *rs10276036* and increased five-year survival rates in osteosarcoma patients treated with a combination of cisplatin, adriamycin, methotrexate, vincristine, and cyclophosphamide. Similarly, Weissfeld et al. (2014) [44] reported an association between the genotype and increased survival and disease-free status at four years post-diagnosis in stage III-IV lung cancer patients treated with chemotherapy, suggesting that the genetic marker might have some prognostic value in cancer treatment. While *rs3213619* has been associated with grade two neurotoxicity in oesophageal squamous cell carcinoma [46], it was not associated with survival or prognosis in adriamycin cancer patients treated with taxane-containing regimens [47]. The variant is also potentially protective against paclitaxel-induced peripheral neuropathy [48], particularly in breast cancer [49]. Carriers of *rs1045642* report less fatigue and fewer sleep disorders in prolactin adenoma patients treated with cabergoline [50], but higher rates of seizures but a lower incidence of posterior reversible encephalopathy syndrome (PRES) in children with lymphatic leukaemia undergoing treatment [51]. *Rs3842* has been associated with improved survival rates in chronic myeloid leukaemia patients treated with dasatinib [52].

The presence of other SNPs might signal a more difficult treatment and recovery for patients. Carriers of *rs1202168* appear to have an increased risk of colorectal cancers in two predominantly Caucasian samples (German and Czech; [53]) but might be protective against colorectal cancers in German menopausal hormone replacement therapy patients [54]. Just as concerning is that women homozygous for the *rs2214102* allele were found to be at a significantly increased breast cancer risk when taking combined oestrogen–progestogen contraceptive pills [55]. Likewise, patients with breast cancer carrying the ancestral homozygous genotype (GG) had significantly worse progression-free survival than carriers of the non-ancestral allele [56]. Similarly, Sági et al. (2021) [51] found an association between *rs1128503* and higher rates of seizures and CNS relapse in children with lymphatic leukaemia, particularly with the CC allele, which trends toward worse outcomes at six months compared to other variants, as reported by Cousar et al. (2013) [57]. Still, more research suggests that *rs2235074* could potentially be related by haploblock to xenobiotic efflux in myeloma [58]. Furthermore, Burgueño-Rodríguez et al. (2023) [59] identified an association between *rs9282564* and increased risk of neurotoxicity in paediatric acute lymphoblastic leukaemia patients treated with prednisone, vincristine, L-asparaginase, daunorubicin, and methotrexate, indicating potential limitations or risks associated with this treatment regimen. The *rs2235035* allele has been observed as associated with increased daunorubicinol clearance in a paediatric oncology sample [60].

Other findings have been less straightforward. *Rs2235033* was not found to be associated with methotrexate response in halo-hematopoietic stem cell transplantation in paediatric patients with malignant haematological diseases [61]. *Rs13237132* has no available evidence directly addressing drug response in this SNP, though, despite some earlier findings, it does not appear to be associated with ovarian cancer outcomes [62], particularly when treated with taxane [63]. Even less is known about the associated function of *rs2235015*, which has been found to be unrelated to the side effects of treatment with cabergoline in patients with prolactinomas [50].

2.3. Depression

Depression, particularly major depressive disorder (MDD), is another popular target for pharmacogenetic investigation. *Rs1045642* appears to act as *a* protective factor for depression in a Chinese sample (Xie et al., 2015) [64], though this contrasts observation with a Japanese sample, which demonstrated increased depression rates in carriers [65]. The ABCB1 genotypes of *rs1922242* exhibited a significant association with the severity of depressive symptoms in MDD patients who underwent continuous escitalopram treatment for 8 weeks [66]. Elsewhere, Chang et al. (2015) [67] observed that MDD patients with the *rs2032582* polymorphism exhibited worse responses to antidepressant treatment, though peri-treatment cortisol levels were unchanged regardless. Conversely, Shan et al. (2019) [68] found no correlation between ABCB1 polymorphisms *rs1045642*, *rs2032582*, *rs2235040*, *rs1128503*, or *rs2235015* and response to SSRIs and SNRIs in the Chinese population, though carriers of *rs2032583* reported improved SSRI treatment response, particularly if carrying the TT genotype. Likewise, carriers of *rs1128503* (particularly TT genotypes) displayed significantly improved treatment response and escitalopram, venlafaxine [69], or paroxetine [70] efficacy. Ray et al. (2015) [71] also observed an association between *rs9282564* and a greater likelihood and faster remission of MDD with sertraline treatment.

Though Menu et al. (2010) [72] found no impact on antidepressant therapy efficacy or tolerance, others found that a specific polymorphism of *rs1045642-TT* predicted lower effective doses of escitalopram and increased response from venlafaxine [66,69]. However, Kato et al. (2008) [70] suggested that carriers might have poorer responses to paroxetine, suggesting differential treatment responses based on genetic factors. The *rs2032582* polymorphism significantly affects both citalopram plasma and cerebrospinal fluid concentrations [73]. The results are more conflicting for paroxetine, where it was associated with paroxetine response in a Japanese cohort [70] but not Swiss [74] or Slovakian cohorts [75]. By comparison, *rs2235020* has been associated with improved rates of remission of MDD in a sample of Mexican Americans treated with fluoxetine [76].

Inpatients with MDD who were homozygous *rs2235015* GG/TT carriers had an inverse association between medication dosage and hospital stay [77]. However, no association with the polymorphism was observed for symptom severity, and this finding was corroborated in a larger naturalised cohort study of Dutch participants with depressive or anxious disorders [78]. Recent examinations suggest a negative association with depressive symptoms after at least two weeks of antidepressant treatment [79]. The mixed evidence is summarised best by the systematic review and meta-analysis by Magarbeh et al. (2023) [80], who found little robust evidence of an association in antidepressant treatment efficacy for outpatients. Otherwise, Silberbauer et al. (2022) [81] observed that the presence of the minor allele A (or AC) is associated with lower serotonin transporter occupancy than those with the major allele. Though investigated, it further appears to be unrelated to sexual dysfunction in women taking SSRIs for depression [82]. Elsewhere, and despite extensive research, most studies have not demonstrated an association between *rs2032588* and psychotropic response or side effect profile. A large (n = 789) naturalistic Dutch cohort study demonstrated a reduction in PGP-dependent antidepressant (citalopram, venlafaxine, paroxetine, and fluvoxamine) side effects [83]. Though *rs58898486* has been associated with an increased risk of MDD in Mexican Americans, the researchers do not appear to have included the SNP in their investigation of antidepressant response [76].

2.4. Diabetes Mellitus

Some evidence suggests that the SNP *rs4148727* is associated with the lipid profile in type II diabetes mellitus, most strongly for apolipoprotein-A and triglycerides, with likely implications for statin management in the condition [84].

2.5. Epilepsy and Other Convulsant Disorders

Zimprich et al. (2004) [85] reported a significant link between drug resistance and the *rs2032582* allele in epilepsy patients, later confirmed by Hung et al. (2005) [86]. Though Vahab et al. (2009) [87] and Sun et al. (2016) [88] found no significant association between these genetic polymorphisms and antiepileptic drug resistance, Lovric et al. (2012) [89] observed higher lamotrigine concentrations in Croatian epilepsy patients with this polymorphism and Smolarz et al. (2017) [90] identified a significant association with drug-resistant epilepsy in the Polish population. Others separately reported associations between genetic variations and drug-resistant epilepsy in Mexican, Tunisian, Han Chinese, and Uygur populations [91–94]. Additionally, a Jordanian cross-sectional study found an association between *rs2032588* and anticonvulsant drug resistance in a cohort of 86 Jordanian men, but not women, with epilepsy [95].

No association with *rs868755* was found with drug resistance or sensitivity among children with refractory epilepsy [96]. Meanwhile, the *rs1202168* variant is potentially related to the development of abnormal haline dispositions in mesial temporal lobe epilepsy [97], and Louis et al. (2022) [98] have reported an associated decreased seizure occurrence after surgical resections for drug-resistant temporal epilepsy in people with *rs10276036*.

2.6. HIV

Rs3842 was not associated with plasma concentrations of dolutegravir in HIV-positive patients [99]. Though there is some evidence that the gene is associated with efavirenz plasma concentration in Tanzanian and Ethiopian patients [100], there was no association observed in a Brazilian study of predominantly African ancestry [101]. However, the *rs10276036* genotype TT is strongly associated with an increased risk of nevirapine drug hypersensitivity in people with HIV infections [102,103].

2.7. Influenza

Research suggests increased neuropsychiatric adverse reactions in *rs1045642* or *rs2032582* carrier children with oseltamivir-treated influenza H1N1/09 [104]. Children with heterozygous diplotype SNPs had neuropsychiatric adverse reactions at three times the rate of wild-type homozygous children, though small sample sizes prevented statistical significance.

2.8. Ischaemic Events and Stroke

The presence of *rs4148727* was not associated with an increased risk of ischaemic stroke in a South Korean sample but was associated with reduced severity [105]. No significant association was observed for an improvement in clopidogrel efficacy compared to aspirin for stroke prevention in a large Chinese sample of high-risk patients [106].

2.9. Nephrotic Syndrome

Zaorska et al. (2021) [107] established a link between *rs1922240* and nephrotic syndrome, where the rare G allele is associated with the occurrence of childhood nephrotic syndrome, steroid dependence (for the AAC haplotype), and mesangial proliferative glomerulonephritis (wild A and AA alleles).

2.10. Opioid Response and Dependence

Rs2032582 has been associated with a higher likelihood of requiring increased methadone doses [108] and improved methadone plasma concentrations and treatment outcomes [109] in Taiwanese patients, thus influencing both the kinetics of methadone-P-

glycoprotein interaction and methadone's potency [110,111]. The need for higher doses of methadone was also reported in Han Chinese [112]. These data suggest the *rs2032582* allele increases methadone potency via increasing BBB permeability, which is of considerable clinical significance given the high inter-individual variability in methadone response coupled with the significant toxicity of methadone in terms of cardiac and CNS effects, as well as potential drug–drug interactions via being a substrate for various CYP450 enzymes relevant to psychotropics (i.e., 2B6, 3A4, and 2D6) [113]. Similar impacts on plasma concentration and toxicity have been seen with *rs1045642* although there are conflicting results. Higher methadone levels were highlighted as a potential risk factor during opioid replacement therapy by Iwersen-Bergmann et al. (2021) [114], linked to higher pain sensitivity by Zahari et al. (2017) [115] in a Malay sample. Though investigated in several other settings, *rs1128503* has not been linked to methadone concentration [114].

A series of alleles, *rs1211152*, *rs2214103*, *rs2235018*, *rs2235020*, *rs2235074*, *rs2888599,* and *rs55852620* have been investigated for tramadol response by the Bruce Budowle Laboratory (University of North Texas Health Science Center; [116]), though the results do not appear to have been published yet. This is not dissimilar to *rs9282564,* which has had several investigations, though few corroborating findings from the clinical literature. Indirect evidence suggests that the SNP might be protective against opioid overdose ([117]). However, children undergoing tonsillectomy using intravenous morphine with GG and GA genotypes of ABCB1 polymorphism *rs9282564* had higher risks of opioid-related respiratory depression, [118].

2.11. Psychotic Disorders

In studies of antipsychotic medications and *rs2032582*, Geers et al. (2020) [119] found a protective effect against antipsychotic-induced hyperprolactinemia in a subgroup of schizophrenia patients treated with risperidone or paliperidone. Cho et al. (2010) [120] reported significantly higher pharmacokinetic parameters following levosulpiride administration, increased sleep duration was observed in Russian adolescents during episodes of psychosis [121], and Kuzman et al. (2008) [122] reported that women with schizophrenia were less prone to significant weight gain during risperidone treatment. Interestingly, male *rs1045642* carriers are associated with higher clozapine serum concentrations and with an associated body mass index increase [123].

Though Skogh et al. (2011) [124] demonstrated elevated serum and CSF olanzapine concentrations, Consoli et al. (2009) [125] noted lower clozapine concentrations and Rafaniello et al. (2018) [126] found a lower aripiprazole concentration-to-dose ratio. These findings were corroborated by Belmonte et al. (2018) [127], Hattori et al. (2018) [128], and Koller et al. (2018) who identified that the variants *rs1045642*, *rs2235048*, *rs1128503*, and *rs2032582* as especially relevant [129] for aripiprazole and by Xing et al. (2006) [130] and Yasui-Furukori et al. (2007) [131] for risperidone. In contrast, additional research carried out by Suzuki et al. (2014) [132] observed that within a Japanese sample, *CYP2D6-variant* carriers but not *ABCB1-variant* carriers had an increased aripiprazole concentration and dose ratios compared to non-carriers.

2.12. Post-Surgical Recovery

Sánchez-Lázaro et al. (2015) [133] reported an association between *rs9282564* and significantly lower renal function after heart transplantation when treated with calcineurin inhibitors (tacrolimus or cyclosporine), which could be a potential risk factor for adverse outcomes in transplant patients. Other work suggests that the SNP *rs2235013* is associated with increased cyclosporine levels in the months following heart transplant [134], and should be similarly monitored.

2.13. Rheumatoid Arthritis

Numerous associations for methotrexate treatment in rheumatoid arthritis and ACBB1-variants have been observed; rs868755, rs10280623, and rs1858923 were associated with

methotrexate toxicity, with the latter also associated with toxicity. Carriers of homogeneous TT and G genotypes appear particularly susceptible [135].

2.14. Traumatic Brain Injury

Patients with severe traumatic brain injuries possessing homogeneous T-allele *rs1045642* had more favorable six-month recovery compared to G allele carriers [57].

3. Discussion

Our review has attempted to summarise a considerable body of work into the pharmacogenetics of the BBB and drug delivery in hopes of assisting future research into personalised medicine. Tailoring medicine to the individual by accounting for genetic variation in the permeability of the BBB holds a great deal of promise, particularly within oncology and psychiatry. A slim majority of the identified SNPs (15/29) have been investigated for treatment response or survival in various cancer populations, with more than a handful of clinically relevant findings. Certainly, the severity and impact of cancer have contributed to such research impetus and such work has yielded good fruit for medicine; the observation that *rs2235046* was associated with improved treatment response and disease-free survival in stage III lung cancer patients and *rs10276036* for stage IV could provide hope for those affected [44]. The promise of pharmacogenetics in psychiatry appears comparably strong. We observed substantial evidence of clinical utility for improved treatment response for MDD, schizophrenia, and epilepsy. Similarly to our findings with oncology, our observation that *rs2032583-TT* and *rs1128503-TT* are strongly associated with superior SSRI and venlafaxine efficacy in treating MDD compared to other genotypes could lead to more precise psychiatric treatment.

Implications and Next Steps

ABCB1 is not the only target for pharmacogenetically-guided medicine. A recent meta-analysis into the benefits of pharmacogenetically-guided medicine over traditional approaches for MDD examined twelve randomised controlled trials that instead used the hepatic CYP450 *CYP2D6* and *CYP2C19* SNPs. The authors observed strong benefits in pharmacogenetically guided conditions for improvement over time, remission of symptoms, and recovery, though they noted that the effects appeared to diminish in more recent studies [136]. Slightly earlier meta-analytic work in MDD but without a specific focus on any particular gene suggested slightly less substantial but still favourable benefits over traditional treatment approaches. Overall, the findings suggest that pharmacogenetics has the potential to significantly improve patient quality of life through targeted approaches and that this benefit might be improved further as additional research identifies more and better targets. Crucially, most existing work that compares pharmacogenetic treatment to traditional approaches focuses on psychiatric medicine, and almost exclusively MDD. However, there are some indications for optimism. At least one early meta-analysis suggests that patients who were administered warfarin at a pharmacogenetically guided dosage experienced substantially fewer major bleeding and thromboembolic events compared to patients treated under standard conditions, and that this benefit increased for longer treatment durations [137]. However, updated analyses have dampened enthusiasm somewhat as earlier significant effects have not been replicated (as is the case for thromboembolic events) and costs remain prohibitive [138,139]. As with MDD, *CYP-variants* appear to have been the main focus.

As the field of hepatic pharmacogenetics, which explores the genetic variations influencing drug metabolism and response in the liver, gains wider clinical adoption in psychiatry, we are of the considered view that the addition of ABC transporter variants has the scope to enhance dose optimisation. As many psychotropic medications are substrates for active efflux by ABC transporters such as ABCB1, the addition of such variants to phase I hepatic metabolism variants stands to enhance the accuracy of psychotropic pharmacogenetics for dose finding.

Further basic and clinical studies will help pave the way to the future enhancement of psychotropic pharmacogenetics.

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