Supplementary Materials and Methods

**Pharmacogenetic testing in Psychiatry and Neurology: An Overview of Reviews**

Search strategy – Pubmed

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**Table S1.** General characteristics of the included reviews.

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| Author (ref.) | Year |  Type of review | Objectives | Participant details | Setting and context | Number of databases sourced and searched | Date range of database search | Publication date range of studies included in the review that inform each outcome of interest | Number of studies, type of studies and country of origin of studies included in each review  | Instrument used to appraise the primary studies and the rating of their quality | Outcomes reported that are relevant to the umbrella review question |
| Bahar et al. (1) | 2017 | RS | To describe the impact of pharmacogenetics on DDIs and DDGIs involving three major drug­ metabolizing enzymes ­ CYP2C9, CYP2C19, CYP2D6. | NS | CYP2D6, CYP2C9, CYP2C19 mediated drug interaction.  | 2 | From inception to Nov 2015 | May 1993 - June 2015 | 105; not specified; NL | As set out by van Roon et al. 2005 and Swen et al. 2011; NS | Several DDI and DDGI are highly gene-dependent, leading to a different magnitude of interaction. |
| Bahar et al. (2) | 2018 | RS | To systematically evaluate the available evidence and quantify the clinical impact of the DDI. | NS | Metoprolol and paroxetine/fluoxetine combination reporting outcomes of the interaction. | 4 | From inception to 1 Apr 2018 | Mar 2008 - June 2018 | 9; not specified; NL | JBI critical appraisal tools and NHLBI quality assessment tool for a before-after study with no control group; low | CYP2D6-paroxetine and metoprolol: A cohort study indicated that the DDI was associated with the early discontinuation of metoprolol as an indicator of metoprolol-related side effects. In a case-control study, the DDI was not associated with bradycardia. |
| Chang et al. (3) | 2014 | RS with MA | To quantify the effect of functional CYP2C19 allele variants on citalopram/escitalopram exposure. | NS | All subjects received at least one single dose of citalopram/escitalopram orally; genotyping or phenotyping of CYP2C19 was performed on all subjects. | 5 | From inception to 1 May 2014 | Dec 2001 - Jan 2013 | 16; not specified; SE | NS | Compared to subjects with CYP2C19\*1/\*1 genotype, the exposure to (es)citalopram increased by 95% in CYP2C19\*2 or \*3/\*2 or \*3, 30% in CYP2C19\*1/\*2 or \*3, and 25 % in CYP2C19\*17/\*2 or \*3 groups. In contrast, the exposure to (es)citalopram decreased by 36% in CYP2C19\*17/\*17 and by 14 % in CYP2C19\*17/\*1. |
| Chouchi et al. (4) | 2018 | RS with MA | To evaluate the strength of the associations between reported SNPs in potential genes and ADRs associated with CBZ therapy in patients with epilepsy, and to determine the strength of the associations in each of the studied ethnicities. | Epileptic patients | No administration of other non-antiepileptic drugs with CBZ to avoid DDIs; associations between polymorphisms and ADRs to CBZ. | 3 | Jan 1980 - Oct 2016 | Apr 2004 - Nov 2014 | 9; not specified; TN | NS | HLA-B\*15:02 was associated with CBZ SCR risk, while subgroup analyses by ethnicity showed that the association was significant in Han Chinese. It was also associated with the CBZ-SJS subgroup and with the CBZ-SJS/TEN subgroup. |
| Dagenais et al. (5) | 2017 | RS | To evaluate the impact of genetic polymorphisms on phenytoin pharmacokinetics and clinical outcomes in populations originating from the MENA region, and to characterize genotypic and allelic frequencies within the region for genetic polymorphisms assessed. | Originated from the MENA region | Received at least one dose of PHT with a subsequent pharmacokinetic analysis, and were genotyped for a polymorphism that may impact PHT pharmacokinetics. | 4 | 1946 - May 2017; 1974 - May 2017 | Sept 1999 - Mar 2015 | 5; not specified; CA | NHLBI quality assessment tool for observational cohort and cross-sectional studies; low | CYP2C9\*2 and \*3 variants reduced phenytoin metabolism. Appreciable variability in minor allele frequencies existed both between and within countries of the Middle East and North Africa region |
| Fricke-Galindo et al. (6) | 2017 | RS | To describe HLA alleles that have been associated with different ADRs in populations worldwide, the recommendations of regulatory agencies and pharmacoeconomic information and databases for the study of HLA alleles in pharmacogenetics. | NS | Association of at least one HLA allele was related with the risk of ADR. | 2 | June 2016 | May 2008 | 95; not specified; MX | NS | HLA alleles and haplotypes have been associated with ADRs induced mainly by carbamazepine among other drugs. The strongest associations remain for HLA-B\*15:02 and HLA-A\*31:01 but only in certain populations; therefore, studies on different ethnic groups would be useful. |
| Grover, Kukreti (7) | 2014 | RS with MA | To understand and summarize the heterogeneity and evaluate the contribution of common HLA alleles to susceptibility to cADRs in patients treated with CBZ through a meta-analysis. | NS | Compared CBZ-tolerant patients with those showing CBZ-induced cADRs or normal controls; explored the relationship between HLA alleles and CBZ-induced cADRs. | 4 | From inception to 28 Sept 2013 | Apr 2006 - Sept 2013 | 20; case-control; IN | NS | Stratification by clinical outcome showed HLA-B\*1502 and HLA-B\*1511 as risk and HLA-A\*2402 as protective markers for bullous lesions in Asians. HLA-A\*3101 was observed to be a universal risk marker, irrespective of cADR type. Sensitivity analysis showed HLA-B\*4001 as a protective marker in Chinese population for showing bullous lesions. |
| Jaja et al. (8) | 2008 | RS | To evaluate the evidence on the prevalence of CYP enzyme polymorphisms as potential genetic factors influencing drug efficacy and safety in the indigenous populations of the American hemispheres. | Indigenous american and amerindian | Published studies of CYP450 allelic variations and frequencies. | 1 | 1985 - Apr 2006 | Jan 2005 - Sept 2006 | 10; not specified; USA | NS | Interethnic differences in the frequency of CYP450 genetic variants existed both among the examined indigenous populations and in comparison with African, Asian and European populations. |
| Maruf et al. (9) | 2019 | RS | To systematically identify, review, and critically evaluate the antidepressant pharmacogenetic literature among children and adolescents using standardized tools and consensus criteria. | Children and young adults under 25 years  | Treated with an antidepressant; genotyping was conducted and the results were reported. | 5 | From inception to 31 Mar 2018 | June 2006 | 24; not specified; CA | As set out by Jorgensen, Williamson et al. 2008; moderate | Identified CYP2D6 - paroxetine association. Not replicated independently in children. |
| Plöthner et al. (10) | 2016 | RS | To review the cost-effectiveness of pharmacogenetic test-guided drug therapy and compare the application of drugs with and without prior genetic testing. | NS | Compared the application of targeted agents with prior genetic testing to those without prior genetic testing. | 16 | Jan 2000 - Nov 2015 | Sept 2012 - Feb 2015 | 27; not specified; DE | QHES; high | Pharmacogenetic test-guided therapy represents a cost-effective/cost-saving treatment option. Only seven studies lacked a clear statement of CE or cost-savings, because of uncertainty, restriction to specific patient populations, or assumptions for comparative therapy. |
| Plumpton et al. (11) | 2016 | RS | To systematically review published economic evaluations of pharmacogenetic tests that aim to prevent or reduce the incidence of ADRs. | NS | Full economic evaluations of a pharmacogenetic test that mediated the risk of an ADR or adverse event as a result of prescribed medication. | 3 | From inception to June 2015 | Sept 2012- Feb 2015 | 47; economic evaluation; UK | CHEERS; high | There was evidence supporting the cost effectiveness of testing for HLA-B\*15:02 and HLA-A\*31:01. |
| Polanczyk et al. (12) | 2010 | RS | To identify original studies that have evaluated the effect of genes on the response to medications used to treat psychiatric disorders in children and adolescents. | Children and adolescents up to 18 years with any psychiatric disorder | Assessed the effect of any medication indicated for the treatment of any psychiatric disorder with a candidate-gene or genome-wide association approach. | 1 | NS | Feb 2007 - Apr 2009 | 35; not specified; BR | NS; low | Only two studies investigated atomoxetine as the pharmacological intervention. One study assessed children with depression and anxiety disorders and another assessed children with autism; SSRIs were the pharmacological intervention. |
| Tangamornsuksan et al. (13) | 2013 | RS with MA | To determine the relationship between the HLA-B\*1502 allele and CBZ-induced SJS and TEN. | NS | Investigated the relationship between HLA-B\*1502 and carbamazepine-induced SJS and TEN. | 7 | From inception to 8 Jan 2013 | Feb 2008 - Jul 2012 | 16; not specified; TH | NOS; NS | The summary OR for the relationship between HLA-B\*1502 and carbamazepine-induced SJS and TEN was 79.84. Among individuals of white or Japanese race/ethnicity, no patients with SJS or TEN were carriers of the HLA B\*1502 allele. |
| Tangamornsuksan et al. (14) | 2018 | RS with MA | To systematically review and quantitatively synthesize associations between HLA genotypes and OXC-cADRs, including SJS and maculopapular rash. | NS | All patients received OXC before HLA genotypes screening; HLA genotypes/OXC-cADRs associations were investigated. | 3 | From inception to Jan 2017 | Mar 2011 - Jan 2017 | 6; not specified; TH | NOS; NS | Associations between HLA-B\*1502 and OXC-induced SJS were found in both the general population and in OXC-tolerant individuals. Association between the HLA-B\*1502 and OXC-induced maculopapular rash was found in the general population. |
| Wu et al. (15) | 2018 | RS with MA | To evaluate the association between CYP2C9\*3 and PHT-induced SJS/TEN. | NS | Compared patients with PHT- induced SJS or TEN with PHT- tolerant patients or the general population; explored relationships between CYP2C9\*3 and PHT- induced SJS or TEN.  | 5 | From inception to 5 June 2017 | Aug 2014 - Jul 2017 | 4; case-control; CN | NOS; moderate | SJS and TEN were found to be associated with the CYP2C9\*3 allele, comparing both matched controls with substantial heterogeneity and population controls. |
| Yip et al. (16) | 2012 | RS with MA | To systematically review studies that have assessed the relationship between CBZ hypersensitivity and HLA alleles in order to determine the strength of associations and the ethnicities studied to date, as well as to derive summary estimates for sensitivity and specificity values of genetic testing for patients about to be prescribed CBZ. | NS | All indications and dosages of CBZ; all studies that investigated the association between CBZ hypersensitivity and HLA genotype. | 4 | From 1948; from 1823; from 1898 - up to Nov 2011 | Apr 2006 - Mar 2012 | 23; not specified; UK | As set out by Jorgensen, Williamson et al. 2008; NS | HLA-B\*1502 in Asian patients was associated with a pooled OR of 113.4 for CBZ-induced SJS and TEN. HLA-A\*3101 is associated with all phenotypes of CBZ hypersensitivity in multiple ethnicities with a pooled OR of 9.5.  |

ADRs: adverse drug reactions; CBZ: carbamazepine; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CYP: cytocrome p450; DDGIs: drug-drug-gene interactions; DDIs: drug-drug-interactions; HLA: human leukocyte antigen; JBI: joana briggs institute; MA: meta-analysis; MDR1: multidrug resistance protein 1; MENA: Middle East and North Africa; NHLBI: national heart, lung, and blood institute; NOS: new castle-ottawa scale; NS: no statement; OXC: oxcarbazepine; OXC-cADRs: oxcarbazepine-induced cutaneous adverse drug reactions; PHT: phenytoin; QHES: quality of health economic studies; RS: systematic review; SCR: serious cutaneous reaction; SJS: stevens–johnson syndrome; SNPs: single nucleotide polymorphisms; SR: systematic review; TEN: toxic epidermal necrolysis.

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