P1173. UNRAVELLING THE PHARMACOGENETIC LANDSCAPE OF ANTIPSYCHOTIC INDUCED HEART-RATE CORRECTED QT INTERVAL PROLONGATION: A SYSTEMATIC REVIEW

Teuntje A. D. Pelgrim[1], Yannika van Oosten[1], Urs Heilbronner[2], European College of Neuropsychopharmacology (ECNP) Working Group Pharmacogenomics & Transcriptomics, The PSY-PGx Consortium, Roos van Westrhenen [1,3,4]

1. Department of Psychiatry, Parnassia Psychiatric Institute, Amsterdam, The Netherlands, 2. Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Germany, 3. Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom, 4. St. John's National Academy of health Sciences, Bangalore, India

Background

- Psychotic disorders are highly burdensome and costly, regularly treated with antipsychotics that often cause side effects.[1]
- Cardiac side effects of antipsychotics, including the risk of prolongation of the heart-rate controlled QT (QTc) interval, can in rare cases lead to Torsade de Pointes arrythmia and sudden cardiac death.[2]
- The variability in antipsychotic response between individuals is influenced by genetic differences in drugs metabolism (pharmacogenetics). [3] The application of pharmacogenetics may be key in reducing the risk of antipsychotic-induced QTc prolongation.

Main aim: to assess the current state of literature on gene variants implicated in antipsychotic-induced QTc prolongation.

Methods

Following PRISMA guidelines, we included prospective studies in English, where participants were treated **longitudinally** with an antipsychotic and **QTc interval was measured at baseline and follow-up**, and associations with genotyping results were reported.

Results

- Our search yielded N=12 included studies, of which n=10 candidate gene studies and n=3 genome-wide association studies (GWAS) (n=1 applied both methods).
- We identified **36 genes** significantly associated with a prolongation of the QTc-interval after antipsychotic use, 8 genes derived from candidate gene studies and 30 from GWAS.

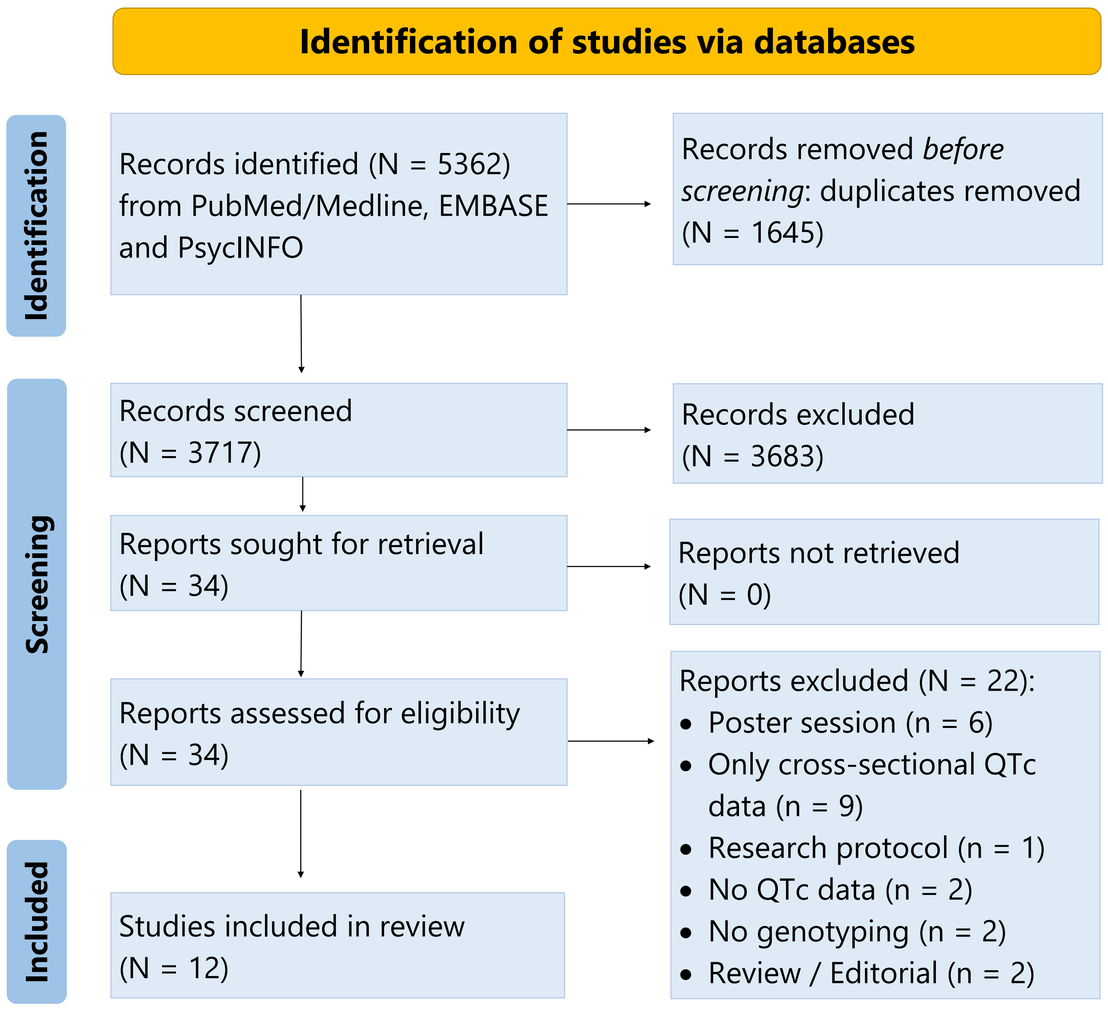

Figure 1. PRISMA flow chart for literature search and selection.

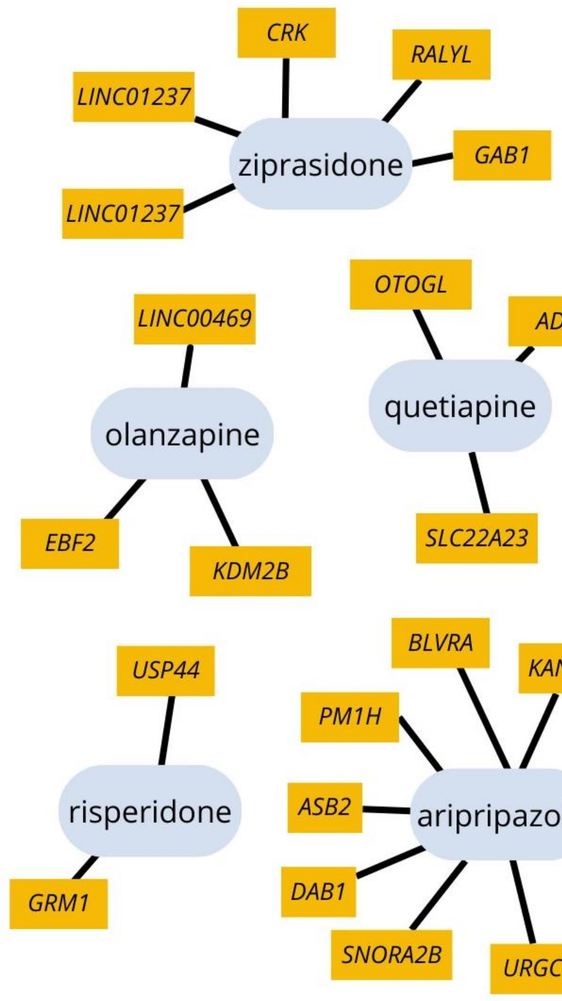

Figure 2. Genes associated with antipsychotic (AP)-induced QTc prolongation in literature. Boxes represent significant genes. Black lines are associations derived from GWAS; blue lines from candidate gene studies. Combined*: derived from study samples treated with multiple or combinations of APs.

No significant PGx findings for AP-induced QTc prolongation for: haloperidol, perphenazine, levosulpiride, clozapine, amisulpride, palpiperone.

- (Only) two significant gene associations, *CACNA1C* (*calcium channel subunit*) and *NUBPL* (*associated with mitochondria*) were reported twice by different studies.
- Most significant GWAS findings ($P<5*10^{-8}$) were genes *ATAD3B* (*associated with mitochondrial function*) and *SKIL* (*associated with cell growth and differentiation)* in N=2040 participants.[4]
- Several candidate gene studies (n=5) did not find significant results or were unable to replicate previous findings.
- Most studies (n=7) focused on psychotic disorders, while other studies, that did not find significant results, investigated healthy participants or non-psychotic patients.
- Differences between studies in sample size, diagnoses and assessed genes/alleles may explain the heterogeneity in results.

Conclusions

- Antipsychotic-induced QTc prolongation is a complex phenotype in which likely multiple genes are involved.
- Further research, especially through well-powered GWAS, is warranted to identify specific gene variants involved in the cardiac risks linked to antipsychotic use.
- Identifying these variants could help tailor treatment, reducing harmful side effects and improving adherence and efficacy.

References: [1] Kotzeva, A. et al. Socioeconomic Burden of Schizophrenia: A Targeted Literature Review of Types of Costs and Associated Drivers across 10 Countries. J Med Econ 2023, 26, 70–83. [2] Salvo, F. et al. Sudden Cardiac and Sudden Unexpected Death Related to Antipsychotics: A Meta-Analysis of Observational Studies. Clin Pharmacol Ther 2016, 99, 306–314. [3] van Westrhenen, R.; Ingelman-Sundberg, M. Editorial: From Trial and Error to Individualised Pharmacogenomics-Based Pharmacotherapy in Psychiatry. Front Pharmacol 2021, 12. [4] Lu, Zhe, et al. "ATAD3B and SKIL polymorphisms associated with antipsychotic-induced QTc interval change in patients with schizophrenia: a genome-wide association study." Translational Psychiatry 12.1 (2022): 56.

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 945151.