Influence of CYP2C19 and CYP2D6 on Side Effects of Aripiprazole and Risperidone: A Systematic Review

Emma de Brabander1, Kristian Kleine Schars2, Thérèse van Amelsvoort2, The PSY-PGx Consortium, Roos van Westrhenen3,4

1 Department of Psychiatry & Psychology, Maastricht University, Maastricht, Netherlands
2 Parnassia Psychiatric Institute, Amsterdam, Netherlands
3 Institute of Psychiatry, King’s College London, London, United Kingdom

Background
Adapting medication choice and dose to interindividual differences in genetic variation encoding for hepatic cytochrome P450 (CYP) enzymes responsible for the metabolism of medications may improve treatment outcome [1]. In psychiatry, the CYP enzymes CYP2C19 and CYP2D6 have been of interest for this purpose [2][3]. Patients may be at increased risk of side-effects (in case of decreased metabolism) or inefficacy (in case of increased metabolism). In March 2023, the Dutch Pharmacogenetics Working Group released pharmacogenetic guidelines for antipsychotics based on previous pharmacogenetic studies, advising to reduce the dose of both aripiprazole and risperidone for poor metabolisers [4].

Identification of studies via databases and registers

Records total (n = 2007)
- Identified from: Pubmed (n = 1596)
- Embase (n = 86)
- Cochrane (n = 35)
- Web of Science (n = 193)
- Google Scholar (n = 189)

Records screened (n = 416)
- Reports assessed for eligibility (n = 49)
- Reports excluded after discussion (n = 6)
- Reports excluded: Results do not differentiate per antipsychotic (n = 7)
- Conference abstract (n = 2)
- Drug-drug interaction (n = 1)
- Polypharmacy (n = 1)
- Results did not mention CYP2D6 or CYP2C19 (n = 1)
- Wrong design (n = 1)
- Wrong outcome (n = 1)
- Paper describes same study as previous work (n = 1)

Records removed before screening: Duplicates records (n = 877)
- Records removed due to unrelated topic (n = 642)
- Records due to other reason (n = 72)

Figure 1: PRISMA flowchart

Methods
On October 20th, 2022, a search was performed of the PubMed, PsychINFO, Embase, Central, and Web of Science databases. On October 25th, 2022, Google Scholar was searched. After removal of duplicates, 1143 papers were scanned for inclusion. 34 papers were included.

Side-effects were categorized as “adverse reactions not otherwise specified” (ADR), extrapyramidal symptoms (EPS), prolactin, weight gain, QTc interval changes, and measures not falling in these previous categories.

Results - Aripiprazole
- Four out of eight studies used an adult population, three of which healthy volunteers.
- None examined CYP2C19.
- Two studies in healthy adults reported increased prolactin or higher frequency of reported side-effects.
- One pediatric study found an association with CYP2D6 poor metabolizer status and BMI percentile change.

Results - Risperidone
- 2/3rd of 27 studies examined adults.
- One study examined CYP2C19 on ADR in adults and found a significant association with neurological side-effects.
- Six adult studies found a significant association with CYP2D6 and side-effects, where decreased CYP2D6 activity was associated with increased risk or report of side-effects.

Conclusion
The results remain mixed and available evidence is insufficient. Some contributing factors may be considered:
- Heterogeneity between studies in methodology and sample.
- Lack of randomized clinical trials and control groups.
- Inability to account for confounding factors common in naturalistic designs.

This review demonstrates the need to establish a consensus regarding methodology and highlights the gap of studies examining CYP2C19.

References

This project has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 940151.