ASSESSING THE IMPORTANCE OF SEX/GENDER AND AGE-RELATED INFLUENCES OF CYP ENZYME ACTIVITY; THE NEXT STEP TOWARDS PERSONALISED MEDICINE

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Background

- Between 40% and 70% of patients experience variability in their drug response, encountering either adverse drug reactions (ADRs) or ineffectiveness.
- The human CYP450 system, influencing drug metabolism, plays a crucial role in this variability
- Psychopharmaceuticals, metabolized by CYP450 enzymes, are susceptible to variations in enzyme activity, paving the way for personalized medication selection based on genotype [1].
- Genetic polymorphisms may explain ADRs and inefficiencies in approximately 15-30% of patients. Notably, sex and age differences in CYP450 enzyme activity have been observed, potentially influencing drug metabolism and toxicity risk [2,3].

Primary question: What is the current knowledge on age- and gender-related differences in the rate of CYP450 mediated metabolism and activity in a healthy population?

Methods

- A systematic search across Medline, Embase, PsycINFO, clinicaltrials.gov, and The Cochrane Library via the Ovid app identified peer-reviewed articles focusing on the activities of five major CYP enzymes

Results - Search

- An initial search yielded nearly n=2,200 articles, which were subsequently narrowed down to n=116 potentially useful articles based on set criteria. Two researchers independently and blindly assessed articles for inclusion or exclusion. A final screening involved a thorough review of the full-text articles, leading to the selection of n= 26 articles for further detailed study and data extraction.

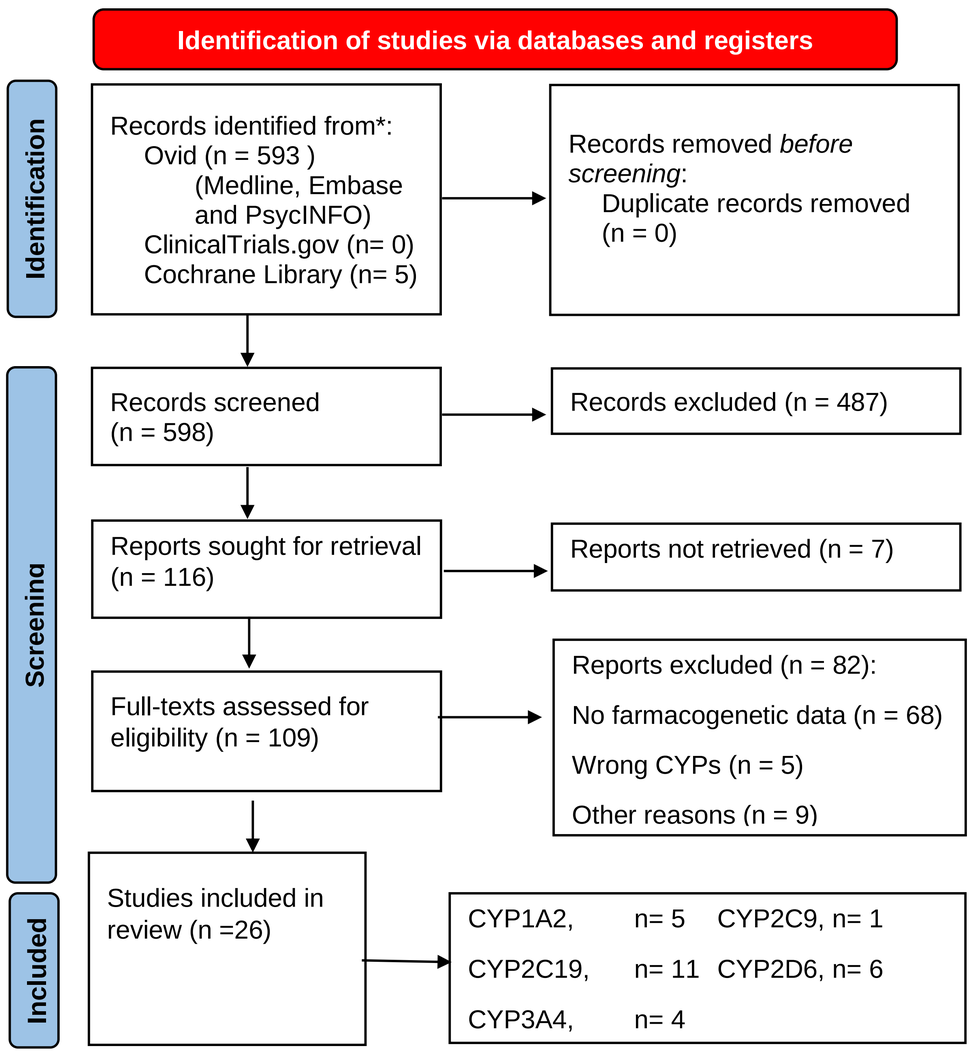

Figure 1. PRISMA flow chart for literature search and study selection.

Results (2) – Excluded articles

- In some studies assessing P450 activity subjects were not genotyped, introducing a potential confounding effect to their results. These studies are excluded in the final article.

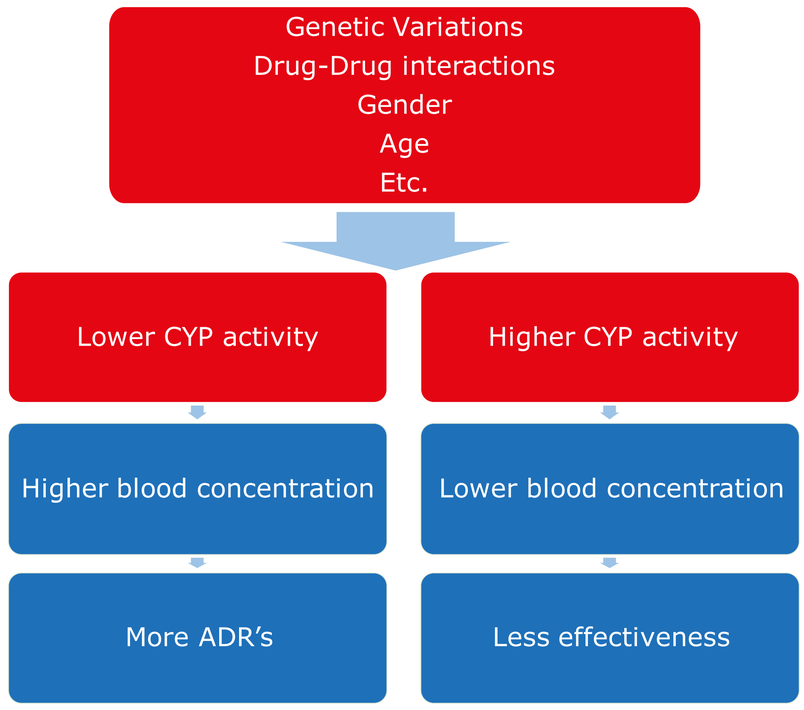

Figure 2. Visualisation of variability in cytochrome P450 enzymes and its effects on drug safety

Preliminary findings

- Preliminary findings indicate a marginal difference in CYP1A2 and CYP2C19 activity between sexes/genders, with other CYPs appearing unaffected.
  - Some articles indicated a higher activity of CYP2C19 enzymes while others indicated the opposite.
  - CYP2D6 seemed to be largely unaffected by sex/gender differences
- Age influences CYP2C19 and CYP3A4 activity, while CYP2D6 seems largely unaffected.
  - One article showed aging had a significant effect on the CYP2C19 EM and IM group in elderly but relatively less on the PM group compared with young adults

Relevance

- Integrating CYP genotyping with data on sex/gender and age promises more efficiently guided pharmacological treatment, empowering clinicians to make informed decisions. This integration represents a significant step towards personalized medicine in psychiatry.

1. van Westrhenen, R. and M. Ingelman-Sundberg, *Editorial: From Trial and Error to Individualised Pharmacogenomics-Based Pharmacotherapy in Psychiatry.* Frontiers in Pharmacology, 2021. **12**.
2. Meibohm, B., I. Beierle, and H. Derendorf, *How Important Are Gender Differences in Pharmacokinetics?* Clinical Pharmacokinetics, 2002. **41**(5): p. 329-342.
3. Sotaniemi, E.A., et al., *Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathologic conditions.* Clinical Pharmacology & Therapeutics, 1997. **61**(3): p. 331-339.

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