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The effect of CYP2D6 variation on antipsychotic-induced hyperprolactinaemia: A systematic review and meta-analysis

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Abstract and keywords

Abstract

Hyperprolactinemia is a known adverse drug reaction to antipsychotic treatment. Antipsychotic blood levels are influenced by cytochrome P450 enzymes, primarily CYP2D6. Variation in CYP450 genes may affect the risk of antipsychotic-induced hyperprolactinemia. We undertook a systematic review and meta-analysis to assess whether CYP2D6 functional genetic variants are associated with antipsychotic-induced hyperprolactinemia. The systematic review identified sixteen relevant papers, seven of which were suitable for the meta-analysis (n=303 participants including 134 extreme metabolisers). Participants were classified into four phenotype groups as poor, intermediate, extensive and ultra-rapid metabolisers. A random effects meta-analysis was used and Cohen's d calculated as the effect size for each primary study. We found no significant differences in prolactin levels between CYP2D6 metabolic groups. Current evidence does not support using CYP2D6 genotyping to reduce risk of antipsychotic-induced hyperprolactinemia. However, statistical power is limited. Future studies with larger samples and including a range of prolactin-elevating drugs are needed.

1. Introduction

Antipsychotics are the mainstay treatment for schizophrenia and are also licensed for use in bipolar disorder (1–3). Currently, the prescription of antipsychotics is largely empirical and patients may have several cycles of failed medications due to poor response and/or adverse events (4–6).

Antipsychotic adverse reactions are diverse and potentially serious, including metabolic as well as extrapyramidal side effects (7). The emergence of adverse reactions is a contributing factor to poor adherence to antipsychotics (8). Susceptibility to adverse reactions is likely to be dependent on multiple factors that influence drug metabolism and/or their action (4,9).

Antipsychotic drugs are metabolized by the cytochrome P450 family of enzymes (CYP450), primarily by CYP2D6, CYP2C19, CYP3A4 and CYP1A2 (9,10). CYP2D6 constitutes a major metabolic pathway for many antipsychotics, including haloperidol, risperidone, aripiprazole and zuclophenthixol (10,11). Variation in the CYP2D6 gene is known to influence enzyme activity and individuals can be classified as poor, intermediate, extensive (normal), or ultra-rapid metabolisers (12). Over 70 allelic variants of CYP2D6 have been identified, including fully functional, reduced function and non-functional alleles (11). Individuals considered 'poor metabolisers' (PM) are those who carry two copies of any of the non-functional alleles (either homozygotes or heterozygotes). The intermediate metaboliser phenotype (IM) is typically a result of one non-functional allele and one reduced function allele. The most common phenotype, extensive or normal metabolisers (EM), results from one or two alleles with normal function. The ultra-rapid phenotype (UM) is less well defined, usually relating to copy number variations in CYP2D6 (11).

There is substantial evidence showing a relationship between CYP2D6 genotypes and clinical outcomes to psychotropic medications, with poor metabolisers being more susceptible to toxicity (13,14) and ultra-rapid metabolisers being less likely to improve when treated with standard doses. Thus pharmacogenetic testing has the potential to benefit clinical practice (15–18).

Prolactin is a hormone produced in the anterior lobe of the pituitary gland. A rise in prolactin blood levels (hyperprolactinemia) is a common adverse reaction to antipsychotics. It has been reported in 47-52% of women and 26-28% of men who are treated with antipsychotics(19–21). A diagnosis of hyperprolactinemia is made when serum prolactin levels exceed the upper limit of well-established ranges for particular age/sex groups (22). Mild hyperprolactinemia can be asymptomatic; however, when prolactin levels exceed twice the upper normal limits various symptoms may appear. Women may report galactorrhoea and amenorrhea, and men may experience gynecomastia, decreased libido and erectile dysfunction(22,23). In the long term hyperprolactinemia can cause osteoporosis in both

sexes, with its associated increased risk of fractures (24). Hyperprolactinaemia is therefore an adverse reaction that impacts on quality of life and has potentially serious consequences.

Typical antipsychotics, such as haloperidol, are the most common cause of drug-induced hyperprolactinemia (25). With the exception of Risperidone and Amisulpride, most atypical antipsychotics are less likely to cause hyperprolactinemia. The atypical antipsychotic Aripiprazole can in fact be used to correct antipsychotic-induced hyperprolactinaemia (25).

For prolactin raising antipsychotics, such as Risperidone, prolactin levels have been shown to be correlated positively with antipsychotic serum levels (26,27). Given that antipsychotics serum levels are influenced by the functional status of CYP450 enzymes, such as CYP2D6, the latter might also influence the risk of antipsychotic induced hyperprolactinemia (28).

In a systematic review and meta-analysis, Fleetman et al (29) showed an association between CYP2D6 genotype and extrapyramidal adverse effects, but they did not explore its influence on hyperprolactinaemia. In another, more recent, systematic review Dodsworth *et al.* (31) looked at the impact of CYP2D6 variation on adverse events caused by risperidone specifically in children and adolescents. They concluded that clinical impact of the relationship between CYP2D6 metabolic phenotypes and risperidone levels on adverse events required further investigation. In the present study, we aimed to undertake a systematic review and meta-analysis to assess whether CYP2D6 functional genetic variants are associated with serum prolactin levels in individuals taking antipsychotics.

2 Material and methods

2.1 Search strategy and selection criteria

We searched the electronic databases PubMed, CINHAL, EMBASE, Medline and PsychINFO for literature published from January 1995 to July 2019 using the following search terms: (Cytochrome* or CYP* or P450*) and (antipsychotic* or neuroleptic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or sertindole or zotepine) and (genot* or allel*) and (PRL or prolactin or hyperprolactinemia or hyperPRL or galactorrhoea or infertility or period* or amenorrhoea or hirsutism or gynecomastia or erectile dysfunction).

We used a wide range of antipsychotics in our search to ensure that all studies investigating a link between hyperprolactinemia and CYP2D6 genotypes were identified. However, only studies involving antipsychotics that are known CYP2D6 substrates were included in the meta-analysis.

We searched for studies published in English. In addition, we searched review articles for any other relevant studies. We selected all suitable papers based on the inclusion/exclusion criteria outlined in Supplementary Table 1. This assessment was conducted independently by two reviewers and any disagreement was resolved by consensus or involvement of a third reviewer if required. Figure 1 describes the search process and results. We reviewed all primary studies to ensure they had no sample overlap and contacted authors for clarification where necessary.

2.2 Data extraction

Data extraction was carried out by one reviewer. A second reviewer checked the accuracy of the extracted data. The outcome of interest was the mean blood or plasma prolactin levels (ng/ml) defined as a quantitative variable. We also included studies with hyperprolactinemia defined as a categorical variable (present/absent). Genotypes for the CYP2D6 gene were also extracted. Depending on their genotype, subjects were divided in four metabolic phenotypes as described in Supplementary Table 2 (33–35). We contacted the authors of 11 primary studies where data required for the meta-analysis was mentioned, but not actually reported in the paper. This enabled the inclusion of three additional primary studies.

2.3 Statistical analysis

We conducted a random effects meta-analysis to investigate the association between CYP2D6 genetic variation and prolactin levels. Study participants were classified into four groups reflecting their metabolic phenotype. The following comparisons were performed: (i) poor versus extensive metabolisers, (ii) intermediate versus extensive metabolisers, (iii) combined poor and intermediate against the combined extensive and ultra-rapid metabolisers.

For each primary study we calculated the effect size as the standardised difference in means between the two groups being compared (Cohen's d; (36)).

A random-effects meta-analysis was chosen due to the variability in methods across the primary studies, including diverse participants and a range of antipsychotic drugs used for their treatment. Heterogeneity between primary studies was assessed using the I^2 statistic (37). Publication bias was assessed using Egger's test (38). We used R version 3.4.3 with the package "meta" to conduct the meta-analysis (https://CRAN.R-project.org/package=meta).

3 Results

From 94 papers identified in the search, only 16 reported CYP2D6 genotypes and either prolactin levels (13 studies: 38–49) or hyperprolactinemia (three studies 50–52) after antipsychotic administration (see summary table 4). A total of 1060 participants were included across the 16 papers. Of these 16 informative papers, seven provided the necessary data to undertake a meta-analysis.

The key characteristics and main conclusions of the 16 studies included in the systematic review and meta-analysis are summarised in Table 1. Further information on these studies can be found in supplementary tables 3 and 4.

3.1 Findings from the meta-analysis

After contacting authors where necessary, a total of seven primary studies provided the data required to undertake a meta-analysis (Supplementary Table 5) (39,40,43,47–49,54). This resulted in a total sample of 303 participants: 47 poor, 72 intermediate, 169 extensive and 15 ultra-rapid metabolisers.

We found no significant differences in prolactin levels between CYP2D6 metabolic groups in any of the three comparisons with the following standardised mean differences: (i) poor versus extensive metabolisers 0.19 (95% CI: -0.54 to 0.92, p = 0.61), (ii) intermediate versus extensive metabolisers -0.1 (95% CI: -0.44 to 0.24, p = 0.58) and combined poor/intermediate versus combined extensive/ultra-rapid metabolisers 0.06 (95% CI: -0.26 to 0.38, p = 0.72). The results of these analyses are described in Figures 2, 3 and 4.

Although six of the seven studies included both male and female patients, there was a higher number of male patients than female patients overall. There is an established difference in prolactin levels in men and women, as well as in children compared to adults. Thus, we ran the meta-analysis twice, once combining male and female subjects and once including only male subjects. We found the conclusions to be the same. The forest plots showing the results of the analysis in only male subjects can be seen in the supplementary material figures 1, 2 and 3. There were not enough studies to conduct a female-only analysis.

Three of the seven studies included in this meta-analysis were conducted in healthy volunteers following a single dose oral administration of antipsychotic medication (39,40,43). The remaining four studies were conducted in patients following long term treatment with antipsychotics. Given the limited literature available, we included all seven studies together in the primary meta-analysis. As hyperprolactinaemia is typically observed during ongoing treatment, we ran secondary me ta-

analyses excluding all the single-dose healthy volunteer primary studies. The conclusions from our results were found to be the same in both instances.

Three of the seven studies included paediatric samples. To investigate the potential impact of age on prolactin levels we ran the analysis using data from the adult only studies. As with the previous analyses, we found no association between CYP2D6 metabolic status and prolactin levels. The forest plots showing the results of the analysis excluding paediatric data can be seen in the supplementary material figures 4, 5 and 6.

3.2 Systematic review of a further nine informative studies that could not be included in the meta-analyses

Of the 16 informative studies reviewed, nine could not be included in the meta-analysis. The reasons for their exclusion, as well as an overview of the studies and their conclusions, are summarised in Table 1. Seven of these nine studies support the conclusions of the meta-analysis and do not show a significant relationship between CYP2D6 genotype hyperprolactinemia. One study (44) showed higher prolactin levels in patients with the poor metaboliser phenotype compared to extensive metaboliser phenotype, but this result was only significant in female patients. A second study (42) found that the number of active CYP2D6 alleles was associated with a significant decrease in plasma prolactin levels, but this result was seen only in men.

4 Discussion

This systematic review and meta-analysis summarised and quantified the available evidence on the effect of CYP2D6 variation on blood prolactin levels after antipsychotic treatment. This potential gene-environment interaction has a major impact in clinical practice due to the unpleasant and potentially severe consequences of raised prolactin. It is also a surprisingly under-researched question, given its importance.

We did not find evidence of an association between CYP2D6 genetic variation and prolactin blood levels during antipsychotic exposure. The pooled effect sizes from our meta-analyses were small (with Cohen's of 0.2 or less) and none of them reached statistical significance. Though the effect sizes calculated for many of the primary studies were of a medium or large magnitude, they showed opposite directions, which resulted in the small overall effect size when combined into the meta-analysis. Furthermore, very few of the primary studies reported statistically significant results.

However, this finding cannot be considered conclusive since there are several limitations in the literature. Only seven of the 16 studies identified provided the data necessary to enable their

inclusion in the meta-analysis. We also reviewed the findings of the remaining nine studies, which covered an overall sample of 867 participants and mainly agreed in a lack of association.

Only two of the 16 studies included in this review concluded that there was a relationship between CYP2D6 genotype and prolactin levels (42,44). Vandenberghe *et al.* observed that prolactin levels were more elevated in poor and intermediate metabolisers, or if the subjects were taking CYP2D6 inhibitors. This result was significant only in women. Schoretsanitis *et al.* observed a significant decrease in plasma prolactin levels among subjects with more active CYP2D6 alleles. This result was observed only in men, and was seen even after controlling for the serum concentration of risperidone and its metabolite. Notably, these studies are some of the largest included in this review, involving 150 (41 poor, 10 intermeidate) and 110 (3 poor, 9 intermediate) patients respectively, treated with risperidone.

The 16 studies reviewed had similar caveats: Each had only between 22 and 150 participants and were individually underpowered to test this genetic association. There is extensive research showing that in the general population only 7% of Caucasians, 3% of Africans and 1% of Asians are CYP2D6 poor metabolisers, and that ultra-rapid metabolisers are even rarer (55–57). After pooling all the published data, the total participants were 303 with only 44 poor and 72 intermediate metabolisers. Thus, even a meta-analysis would have limited power to detect a difference between metabolic groups. Therefore, further studies involving large samples and mega-analyses are necessary to guarantee inclusion of sufficient participants with these rarer phenotypes. This was a key recommendation from a Health Technology Assessment examining the potential benefits of CYP2D6 testing for mental health drugs (17), but such studies have not yet been conducted.

Another limitation comes from the heterogeneity of the samples in the primary studies. Out of the seven studies selected for meta-analysis, three were conducted with healthy volunteers, whereas the remaining four included patients receiving long-term antipsychotic treatment. Similarly, prolactin levels vary by sex but the literature did not provide enough data to examine a potential sex difference in CYP2D6 influence on antipsychotic-induced hyperprolactinaemia risk.

Although CYP2D6 is a key metabolic pathway for antipsychotics, other factors, such as other enzyme systems involved in the metabolism of some antipsychotics and genes coding for receptor targets, could mediate the effect of antipsychotics on prolactin levels. As with other complex traits, prolactin levels might be influenced by several genetic and environmental factors as well as interactions between them. A genome-wide association study of prolactin identified 12 single nucleotide polymorphisms (SNPs) associated with increased prolactin levels in both plasma and cerebrospinal fluid (58). A recent meta-analysis conducted in patients with schizophrenia found that prolactin

levels were significantly higher in dopamine D2 receptor Taq1A (rs1800497) A1 carriers than in non-carriers (59). In the future, investigating the influence of these genetic variants in combination with CYP2D6 variants could improve the identification of patients at risk of developing hyperprolactinemia when taking antipsychotic medication.

The majority of studies included in this meta-analysis administered risperidone (4 studies: 42,46–48) or haloperidol (1 study: 53). Both risperidone and haloperidol are known substrates of CYP2D6 and are primarily metabolised by this enzyme. However, two of the studies administered olanzapine (43) or quetiapine (40). Although there is evidence that CYP2D6 is involved in their metabolism, it is not their only pathway. Olanzapine is primarily metabolised by CYP1A2 and quetiapine by CYP3A4 (60,61). This could explain why these two studies did not demonstrate any difference between CYP2D6 metabolic groups. In order to be confident that this was not skewing our results we ran the meta-analysis with only risperidone and haloperidol treated samples and found our results to be the same.

The only randomised controlled clinical trial available looking at CYP2D6 testing concluded that poor and ultra-rapid metaboliser patients incur higher treatment expenses and that CYP2D6 testing can curtail these excess costs (62); however prolactin was not reported as one of their outcomes. This trial included over 200 participants and used methods to enrich the sample with sufficient numbers of extreme metabolisers (20% poor or ultra-rapid metabolisers in each treatment arm). There are very few trials investigating the effect of CYP2D6 testing on specific adverse reactions to antipsychotics. Future research should also examine other pathways involved in the metabolism of antipsychotics and polygenic risk scores, capturing the effects of genome wide variants on the pharmacokinetics and pharmacodynamics of antipsychotics.

Cytochrome P450 is a crucial metabolic pathway for most antipsychotics (33,63), thus the genetic profiling of CYP2D6 and other CYP functional polymorphisms offers a potential tool to identify patients at particular risk of developing hyperprolactinaemia who would benefit from choosing alternative antipsychotics.

Although our systematic review and meta-analysis indicate that genetic variation in CYP2D6 activity does not influence antipsychotic-induced hyperprolactinemia, the statistical power of the current literature, with 303 participants and only 134 of them with impaired drug metabolism, is limited. Indeed, based on our meta-analysis the effect size for the association between CYP2D6 and antipsychotic-induced hyperprolactinemia is estimated to be 0.2, which is a small yet clinically meaningful difference. Samples with at least 260 poor metabolisers would be required to reach 80%

power to detect such a small group difference in this important gene-environment interaction. The current literature does not have such large samples yet.

There is growing evidence from drug labels and clinical guidelines supporting the use of CYP2D6 testing to guide personalised treatment with antidepressants and antipsychotics (18,34,64,65). Nevertheless, the prescription of mental health medication remains primarily empirical and pharmacogenetics testing is not part of routine practice in the UK and most countries. Larger studies and clinical trials designed to include sufficient extreme metabolisers are needed to investigate the potential cost-effectiveness of pharmacogenetics testing for antipsychotics (10,66–68).

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Conflict of interest

The authors declare they have no conflict of interests.

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Figure Legends

Figure 1. PRISMA 2009 flow diagram outlining search process and results (32).

Table 1. Summary of the key characteristics and main conclusions of the 16 papers included in the systematic review and the meta-analysis

Figure 2. Forest plots comparing prolactin levels between 44 poor (PMs) and 115 extensive metabolisers (EMs).

Figure 3. Forest plots comparing prolactin levels between 72 intermediate (IMs) and 124 extensive metabolisers (EMs).

Figure 4. Forest plots comparing prolactin levels between 133 poor and intermediate metabolisers combined (PMs + IMs) versus 170 extensive and ultra-rapid metabolisers combined (EMs + UMs).