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Supplementary material

Question

Should pharmacogenomic testing be utilised in routine psychiatric practice?

Question Details

Patients: Patients seeking help for psychiatric disorders in Singapore

Intervention: Application of pharmacogenomic tests

Comparison: Standard care - prescription of psychotropic medication without use of pharmacogenomic tests

Main outcomes:

- Recommendations for use of pharmacogenomic tests as an augmenting tool to guide medication selection and dosing (with known gene-drug pairs)
- Recommendations for use of direct-to-consumer pharmacogenomic panels in psychiatric practice

Setting: Psychiatric practice in Singapore

Perspective: Psychiatric healthcare providers

Research Evidence

Outcome: Use of pharmacogenomic tests with known gene-drug pairs with established clinical evidence

Author	Type of Study	Number of studies/participants	Summary of Findings	Certainty of Evidence
Hicks et al, 2015[43]	Systematic review and guideline	50 studies	Review of clinical studies on the association between *CYP2D6* and/or *CYP2C19* genotypes and metabolism of SSRIs or SSRI-related adverse drug events or clinical outcomes was performed. The results supported a recommendation for dose adjustments based on metabolizer	⊕⊕⊕○

			phenotype for *CYP2D6* (paroxetine, fluvoxamine) and *CYP2C19* (citalopram, escitalopram, sertraline).	
Hicks et al, 2016[13]	Systematic review and guideline	79 studies	Systematic review focused on *CYP2D6* and *CYP2C19* genetic variations and their relevance to gene-based dosing of TCAs was conducted. The results supported a recommendation for dose adjustments based on metabolizer phenotype for *CYP2D6* and amitriptyline/nortriptyline and *CYP2C19* and amitriptyline. While other TCAs have comparable pharmacokinetic properties, there was less data supporting dose adjustments for other drugs such as clomipramine, desipramine, doxepin, imipramine and trimipramine.	⊕⊕⊕○
Biernacka et al, 2015[44]	Genome-wide association study and meta-analysis	865 subjects for GWAS, 2394 samples for meta-analysis	865 individuals with baseline and 4-week Hamilton Rating Scale for Depression (HRSD) scores were included for analysis in the GWAS with a focus on identifying pharmacodynamic genes associated with treatment outcomes. Meta-analysis of 3 previous studies was performed. The GWAS data did not detect SNPs significantly associated with %ΔHRSD or response.	⊕⊕⊕○
Zhang et al, 2020[48]	Systematic review and meta-analysis	15 studies	15 studies involving 2125 subjects were included in the meta-analysis conducted following PRISMA guidelines. The dose-adjusted steady-state plasma concentration of risperidone was 2.35-fold higher in *CYP2D6* intermediate metabolizers (IM) and 6.20-fold higher in poor metabolizers (PM). The dose-adjusted plasma concentration of the active moiety of risperidone was 1.18-fold higher in IM and 1.44-fold higher in PM.	⊕⊕⊕○
Jukic et al, 2019[46]	Cohort study	725 risperidone-treated and 890 aripiprazole-treated subjects included for pharmacokinetic analysis	Retrospective cohort study obtaining patient data from a routine therapeutic drug monitoring database in Diakonhjemmet Hospital, Oslo, Norway. Active moiety exposure for risperidone was increased in *CYP2D6* poor metabolizers (1.568 times, odds ratio) and intermediate metabolizers (1.373 times) compared to normal metabolizers. Likewise, active moiety exposure for aripiprazole was increased in *CYP2D6* poor	⊕⊕○○

			metabolizers (1.585 times) and intermediate metabolizers (1.476 times) compared to normal metabolizers.	
Cui et al, 2020[45]	Systematic review and meta-analysis	29 studies	29 studies (a total of 2624 subjects) with determined *CYP2D6* polymorphism were included in the meta-analysis pooling pharmacokinetic parameters of risperidone. Results showed a significant difference in dose-adjusted steady-state concentration (Css/dose) among the *CYP2D6* metabolizer phenotypes for risperidone and total active moiety with a higher median quartile Css/dose for intermediate and poor metabolizers compared to normal metabolizers.	⊕⊕⊕○
Manson et al, 2020[47]	Systematic review	56 studies	Of the included studies, 29 studies evaluated the association of HLA variants and Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN). The studies found a relatively high sensitivity (67-100%) and specificity (73-100%) for *HLA-B*1502* and carbamazepine-induced SJS/TEN. 5 studies reported the association of HLA-B*1502 and lamotrigine-induced SJS/TEN, with a low sensitivity (0-33.3%) but high specificity (81.4-100%) in various populations.	⊕⊕⊕○
Brown et al, 2019[16]	Systematic review and guideline	24 studies	Publications that included analyses for the association between *CYP2D6* genotypes and metabolism of atomoxetine or atomoxetine-related adverse drug events or clinical outcomes or relevant drug-drug interactions were included in the review. The likelihood of favorable treatment response and side effects were both reported to be higher in *CYP2D6* poor metabolizers (PM) compared to non-PMs. Evidence correlating efficacy with other *CYP2D6* metabolizer phenotypes was more limited.	⊕⊕⊕○

Outcome: Use of direct-to-consumer pharmacogenomic panels

Author	Type of Study	Number of studies/participants	Summary of Findings	Certainty of Evidence
Tiwari et al, 2022[24]	RCT	371 subjects	52-week, multi-centre, patient- and rater-blinded, randomised controlled study evaluating clinical outcomes among patients whose treatment was guided by combinatorial pharmacogenomic (PGx) testing. The study aimed to recruit 570 patients with Major Depressive Disorder (MDD) for three arms, two of which were intervention arms (standard combinatorial PGx test report [GEN], and an extended test report [EGEN]) with a treatment-as-usual arm [TAU]. Enrolment was terminated early due to subsequent determination of lack of power, with a total of 371 subjects included for the intention-to-treat (ITT) cohort. No significant difference was found in the primary outcome of percent decrease in Hamilton Depression Rating Scale (HAM-D17) between the GEN and TAU arms for both ITT and per-protocol analyses.	⊕⊕○○
Greden et al, 2019[25]	RCT	1541 subjects	24-week, multi-centre, patient- and rater-blinded, randomised controlled study evaluating outcomes when a combinatorial PGx test was used to guide medication selection compared to TAU in patients with MDD. 1541 subjects were included in the ITT cohort with an exclusion of a further 143 patients for the per-protocol cohort. At week 8, there was no significant difference in the primary outcome of percent decrease in HAM-D17 in the guided-care arm compared to the TAU arm. However, response and remission rates were noted to be significantly higher in the guided-care arm (26.0% and 15.3% respectively) compared to TAU arm (19.9% and 10.1% respectively).	⊕⊕⊕○
Perlis et al, 2020[27]	RCT	304 subjects	8-week, multi-centre, patient- and rater-blinded, randomised controlled trial evaluating change in HAM-D17 for patients with MDD in a PGx assay-guided treatment arm vs TAU. The Genecept Assay comprising 45 variants of 7 pharmacokinetic cytochrome P450 genes and 12 variants of 11 pharmacodynamic or other genes was used in the study.	⊕⊕⊕○

			No significant differences were detected between the assay-guided arm compared to TAU for change in HAM-D17, response and remission.	
Oslin et al, 2022[26]	RCT	1944 subjects	24-week, multi-centre, open-label randomised trial comparing treatment guided by a PGx assay with TAU for subjects with MDD. The intervention resulted in statistically significantly greater prescription of medications with no drug-gene interactions (45% vs 18% in TAU group). While there was a statistically significant difference in remission of symptoms at week 12 in the intervention group (16.5% vs 11.2%), there were no significant differences in remission and response rates at week 24.	⊕⊕⊕○
Shan et al, 2019[28]	RCT	71 subjects	8-week, single centre, rater-blinded randomised trial comparing treatment guided by a proprietary PGx assay with TAU for subjects with MDD. There were no significant differences found in HAM-D17 scores, response and remission rates at the end of the treatment between the guided and unguided groups. There was also no statistical difference found between the groups in the incidence rate of adverse reactions.	⊕⊕⊕○

The review of combinatorial panels was focused on MDD as available evidence supporting pharmacogenetic testing of multiple genes with established gene-drug pairs exists mainly for antidepressants and not the other classes of psychotropics.

Papastergiou et al, 2021[49], was excluded due to difference in practice setting (subjects were recruited from community pharmacies and included if they were prescribed one or more antidepressants for MDD and/or generalised anxiety disorder (GAD) and dissatisfied with their current treatment). Additionally, subjects with MDD and GAD were analysed together.

McCarthy et al, 2021[50], was excluded as subjects were recruited trans-diagnostically so long as significant depression was a prominent clinical feature. There was no consideration of diagnosis upon group assignment and no further breakdown of proportion of diagnoses was provided.

Certainty of Evidence

What is the overall certainty of the evidence of effects?

Outcome	Author	Type of Study	Number of studies/participants	Overall Certainty of Evidence
Known gene-drug pairs	Hicks et al, 2015[43]	Systematic review and guideline	50 studies	⨁⨁⨁◯
	Hicks et al, 2016[13]	Systematic review and guideline	79 studies	
	Biernacka et al, 2015[44]	Genome-wide association study and meta-analysis	865 subjects for GWAS, 2394 samples for meta-analysis	
	Zhang et al, 2020[48]	Systematic review and meta-analysis	15 studies	
	Jukic et al, 2019[46]	Cohort study	725 risperidone-treated and 890 aripiprazole-treated subjects included for pharmacokinetic analysis	
	Cui et al, 2020[45]	Systematic review and meta-analysis	29 studies	
	Manson et al, 2020[47]	Systematic review	56 studies	
	Brown et al, 2019[16]	Systematic review and guideline	24 studies	
Direct-to-consumer	Tiwari et al, 2022[24]	RCT	371 subjects	⨁⨁◯◯

pharmaco-genomic panels	Greden et al, 2019[25]	RCT	1541 subjects	
	Perlis et al, 2020[27]	RCT	304 subjects	
	Oslin et al, 2022[26]	RCT	1944 subjects	
	Shan et al, 2019[28]	RCT	71 subjects	

Recommendations

1. Strong recommendation for individual pharmacogenomic tests to only be utilised as an augmenting tool to guide medication selection and dosing and be limited to the known gene-drug pairs with established clinical evidence.
2. Qualified recommendation against use of direct-to-consumer pharmacogenomic panels in psychiatric practice. At present, the direct-to-consumer combinatorial panels that assay multiple genes and analyse them via proprietary algorithms have not demonstrated clear evidence of benefit in clinical outcomes. Further development of panels (targeting gene-drug pairs with good clinical evidence) and research of large sample size, with inclusion of subjects of Asian ancestry and a focus on clinical outcomes may help in future evaluation of the role of combinatorial panels.