

TOWARDS PHARMACOGENETICS-GUIDED PRESCRIBING: THE IMPACT OF CYP2C19 AND CYP2D6 ON ANTIDEPRESSANT METABOLISM AND ADVERSE EFFECTS

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Background	Objectives
- Depression remains a leading cause of disability, Current antidepressant prescribing often follows trial-and-error pathways that overlook genetic & nutritional factors.	We integrated pharmacogenetics (PGx) with clinical data to assess the impact of pharmacogenetic markers CYP2D6 and CYP2C19 on antidepressant metabolism and side effects

Methodology
111 blood samples collected from IMH patients who previously were and/or currently are on anti-depressant medication treatment. - Collected data on response, remission, side effects and adverse effects of medications, treatment dose, adherence, clinical outcome, etc. - A subset of 40 samples was sent for microarray-based clinical genotyping at TTSH Personalised Medicine Service to identify CYP2C19 and CYP2D6 metaboliser phenotypes

Results & Discussion
Abbreviations: Normal Metaboliser (NM), Intermediate Metaboliser (IM), Poor Metaboliser (PM), Rapid Metaboliser (RM), Adverse Drug Reactions (ADR) CYP2C19 Findings Metaboliser Type: 18 NM, 16 IM, 5 PM, 1 RM Allele Frequencies: 65% of CYP2C19*1, 23.75% of CYP2C19*2, 8.75% of CYP2C19*3, and 2.5% of CYP2C19*17 4/5 reported side effects to multiple medications (Table 1) vs 2/18 CYP2C19 normal metabolisers. - Sertraline-CYP2C19 and Escitalopram-CYP2C19 supported CPIC/DPWG-guided interpretation of SSRI tolerability in CYP2C19 PMs. - Mirtazapine- and Fluvoxamine-related ADRs were also observed, suggesting broader tolerability patterns not fully captured by current guideline-actionable pairs. - One CYP2C19 rapid metaboliser had fluvoxamine recorded as ineffective, but fluvoxamine-CYP2C19 is not a primary actionable RM pair. CYP2CD6 Findings Metaboliser Type: 26 NM, 12IM, 2 Indeterminate - No CYP2D6 poor/ultrarapid metabolisers were observed in this cohort, but venlafaxine-related ADRs occurred in 1/7 CYP2D6 intermediate vs 0/3 normal metabolisers.

Case	Type of response	Antidepressants / medication issue	CYP2D6 genotype / phenotype	CYP2C19 genotype / phenotype	Drug-Gene Pair	CPIC Actionability	DPWG Actionability
PM-1	ADR	- Fluoxetine: rash; - Mirtazapine: oversedation; - Venlafaxine: sexual side effects; - Bupropion: nausea/headache	*1/*5, IM	*2/*2, PM	Sertraline–CYP2C19PM	Lower starting dose, slower titration, 50% maintenance/dose reduction, or alternative	Don’t exceed 75 mg/day; guide dose by response, side effects, and/or plasma concentration
					Escitalopram–CYP2C19PM	Lower starting dose, slower titration, 50% maintenance/dose reduction, or alternative	Don’t exceed 50% of normal maximum dose
PM-2	ADR	- Fluvoxamine/Faverin: excessive sedation - Sertraline and Fluoxetine exposure	*1/*14, NM	*2/*2, PM	Venlafaxine–CYP2D6 Bupropion–CYP2C19 Fluvoxamine–CYP2C19/CYP2D6 Mirtazapine–CYP2C19/CYP2D6 Fluoxetine–CYP2D6	Non-actionable	Avoid in CYP2D6 IM/PM; if unavoidable and side effects occur, reduce dose and monitor response, side effects or plasma concentrations
PM-3	ADR	- Sertraline stopped due to adverse effects/paradoxical anxiety - Mirtazapine exposure	Indeterminate	*2/*3, PM			Non-actionable / not a primary CYP2C19/CYP2D6 pair
PM-4	No ADR	- Escitalopram 20 mg exposure; - Fluvoxamine 20 mg exposure	*1/*36-*10, NM	*2/*3, PM			Non-actionable; no therapy adjustment recommended
PM-5	ADR	- Escitalopram: increased suicidal thoughts/emotional numbing; - Mirtazapine: considered too drowsy historically - Bupropion exposure	*1/*36-*10, NM	*2/*3, PM			
IE-1	IE	- Fluvoxamine 100 mg recorded as not effective; - Mirtazapine exposure	*2/*2, NM	*1/*17, RM			

Table 1: CYP2C19 poor and rapid metabolisers with response type, prescribed antidepressant, side effects, and genotype/phenotype

Table 2: CPIC/DPWG Guidelines for Dosing of Antidepressants regarding CYP2C19 and CYP2D6 Genotypes

Conclusion
CYP2C19 poor metabolisers may benefit from closer antidepressant medication review. - PGx interpretation needs to be drug-specific and clinically contextualised, not limited only to guideline-actionable pairs. - CPIC/DPWG guidance can support dose adjustment, monitoring, or alternative selection for actionable pairs. PGx-guided review may reduce trial-and-error prescribing when combined with medication history and clinical judgement.

Acknowledgements	References
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