19 - Psychotropic drugs and cytochrome (CYP) funct

Psychotropic drugs and cytochrome (CYP) function

Pharmacokinetics CHAPTER 11 Psychotropic drugs and cytochrome (CYP) function Information on the effect of drugs on CYP function helps predict or confirm suspected interactions that may not have been uncovered in regulatory trials or in clinical use. In addition to the effect of co--administered drugs on CYP function, genetic polymorphism associated with some enzymes may also account for inter-individual variations in the metabolism of certain drugs. Genetic variation influences both likelihood of response and tolerability (see later in this section for more information on genetic variation).1,2 The effects of polymorphism and pharmacokinetic interaction are difficult to predict because some drugs are metabolised by more than one enzyme and an alternative pathway(s) may compensate if other enzyme pathways are inhibited. A further complication is that CYPs are active in sites other than the liver (e.g. gut, brain). The effect of psychotropics on brain CYPs can be markedly different from hepatic CYPs.3 The function of CYPs is not the only consideration. P-glycoprotein (P-gp) is a drug transporter protein found in the gut wall. P-gp can eject (active process) drugs that diffuse (passive process) across the gut wall. P-gp is also found in testes and in the blood– brain barrier. Drugs that inhibit P-gp are anticipated to increase the uptake of other drugs (that are substrates for P-gp), and drugs that induce P-gp are anticipated to reduce the uptake of other drugs (that are substrates for P-gp). Many drugs that are substrates for CYP3A4 have also been found to be substrates for P-gp. Uridine diphosphate (UDP)--glucuronosyltransferase (UGT) has been identified as an enzyme that is responsible for phase II (conjugation) reactions. Valproate is a potent inhibitor of UGT, hence its interaction with lamotrigine, a drug which is primarily metabolised by UGT. UGT enzymes are also involved in the metabolism of lumateperone, olanzapine, topiramate and trifluoperazine. In Table 11.5, drugs highlighted in bold indicate: ■ ■Predominant metabolic enzyme pathway, or ■ ■Predominant enzyme activity (inhibition or induction). Drugs annotated with * are known to be a minor metabolic enzyme pathway or activity (i.e. not demonstrated to be clinically significant). Drugs in normal font

(not bold and without *) indicate metabolic enzyme pathway(s) or activity where significance is unclear or unknown. Table 11.5 does not include details of the effects of non-psychotropics on CYP function.

884 The Maudsley® Prescribing Guidelines in Psychiatry Table 11.5 Effects of psychotropics on CYP function. CYP1A2 Substrates Inhibitors Inducers Asenapine4 Agomelatine Amitriptyline* Bupropion* Caffeine Chlorpromazine Clomipramine* Clozapine Duloxetine Fluphenazine Fluvoxamine Haloperidol Imipramine* Levomepromazine Lumateperone Melatonin Mirtazapine* Olanzapine Perphenazine Pimozide* Ramelteon Zolpidem* CHAPTER 11 Moclobemide Perphenazine CYP2A6 Substrates Inhibitors Inducers Bupropion* Caffeine Nicotine CYP2B6 Substrates Inhibitors Inducers Bupropion Methadone* Nicotine Sertraline* Fluoxetine* Fluvoxamine Memantine Paroxetine* Sertraline* CYP2B7 Substrates Inhibitors Inducers Buprenorphine* Not known Not known ‘Barbiturates’ Carbamazepine Modafinil* Phenobarbital Phenytoin Fluvoxamine Iloperidone Levomepromazine Melatonin5 Tranylcypromine Phenobarbital Carbamazepine* Modafinil* Phenobarbital Phenytoin

Table 11.5 (Continued) CYP2C8 Substrates Inhibitors Inducers Lumateperone Zopiclone* Not known Not known CYP2C9 Substrates Inhibitors Inducers Fluoxetine* Fluvoxamine Modafinil Valproate Agomelatine* Amitriptyline Bupropion* Doxepin Fluoxetine* Lamotrigine Phenobarbital Phenytoin Sertraline* Valproate CYP2C19 Substrates Inhibitors Inducers Escitalopram* Fluoxetine Fluvoxamine Iloperidone Melatonin5 Agomelatine* Amitriptyline Atomoxetine Carbamazepine* Citalopram Clomipramine* Diazepam Escitalopram Fluoxetine* Imipramine* Melatonin Methadone Moclobemide Phenytoin Sertraline* Suvorexant Trimipramine* Valproate Moclobemide Modafinil Topiramate Pharmacokinetics CHAPTER 11 Carbamazepine SJW Carbamazepine SJW (Continued)

886 The Maudsley® Prescribing Guidelines in Psychiatry Table 11.5 (Continued) CYP2D6 Substrates Inhibitors Inducers ‘Amfetamines’ Amitriptyline Aripiprazole Atomoxetine CHAPTER 11 Brexpiprazole Cariprazine Chlorpromazine Citalopram Clomipramine Clozapine* Deutetrabenazine Donepezil* Doxepin Duloxetine Escitalopram Fluoxetine Fluphenazine Fluvoxamine Galantamine Haloperidol Iloperidone Imipramine Methadone* Mianserin Mirtazapine* Moclobemide Nortriptyline Olanzapine Paroxetine Perphenazine Pimavanserin Pimozide* Quetiapine* Risperidone Sertindole Sertraline Trazodone* Trimipramine Valbenazine Venlafaxine Vortioxetine Zuclopenthixol CYP2E1 Substrates Inhibitors Inducers Bupropion Ethanol Disulfiram Paracetamol Ethanol Amitriptyline Asenapine4 Not known Bupropion Chlorpromazine Citalopram* Clomipramine Clozapine Doxepin Duloxetine Escitalopram Fluoxetine Fluphenazine Fluvoxamine* Haloperidol Iloperidone Levomepromazine Methadone* Moclobemide Paroxetine Perphenazine Reboxetine* Risperidone Sertraline* Venlafaxine* Ziprasidone*

Table 11.5 (Continued) CYP3A4 Substrates Inhibitors Inducers Alfentanyl Alprazolam Amitriptyline Aripiprazole Atomoxetine* Fluoxetine Fluvoxamine Iloperidone Blonaserin Brexipiprazole Buprenorphine Bupropion* Buspirone Carbamazepine Cariprazine Chlorpromazine Citalopram Clomipramine* Clonazepam Clozapine* Diazepam Donepezil Dosulepin Escitalopram* Fentanyl Fluoxetine* ?Flurazepam Galantamine Haloperidol Imipramine Lemborexant Levomepromazine Lumateperone Lurasidone Methadone Midazolam Mirtazapine Modafinil Nitrazepam Paliperidone Perphenazine Pimavanserin Pimozide Quetiapine Reboxetine Risperidone* Sertindole Sertraline* Suvorexant Trazodone Trimipramine* Valbenazine Venlafaxine Vilazodone Zaleplon Ziprasidone Zolpidem Zopiclone Zuclopenthixol Levomepromazine Paroxetine Perphenazine Reboxetine*

Ziprasidone* Note: information on CYP function is derived from individual SPCs and US labelling (accessed August 2024), from systematic reviews7,8 and the Flockhart table.9 SJW, St John’s wort; SPC, summary of product characteristics. Asenapine? Carbamazepine Clozapine6 Levomepromazine6 Modafinil Phenobarbital ‘and probably other barbituates’ Phenytoin SJW Topiramate CHAPTER 11

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