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Pharmacodynamic interactions

402 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Pharmacodynamic interactions Pharmacodynamic interactions arise when the effects of one drug are altered by another drug via mechanisms such as direct competition at receptor sites (e.g. dopamine agonists with dopamine antagonists), augmentation of the same neurotransmitter pathway (e.g. fluoxetine with tramadol or a triptan can lead to serotonin syndrome) or an effect on the physiological functioning of an organ/organ system in different ways (e.g. SSRIs impair clotting and non-steroidal anti--inflammatory drugs [NSAIDs] irritate the gastric Table 3.11 (Continued) Antidepressant Substrate for Inhibits TCAs Amitriptyline CYP1A2, CYP2D6, CYP3A4, CYP2C19 Clomipramine Desipramine CYP2D6 Dosulepin CYP2D6 and possibly other pathways Doxepin CYP2D6, CYP1A2 (minor), CYP3A4 (minor) Imipramine CYP1A2, CYP2D6, CYP3A4, CYP2C19 Lofepramine 2D6 (metabolised to desipramine)8 Not known9 Nortriptyline CYP2D6 Trimipramine CYP2D6 Others Agomelatine CYP1A2 Brexanolone10 Metabolised via non-CYP pathways CYP2C9 Bupropion CYP2B6 CYP2D6 (potent) Dextromethorphan/ bupropion11 CYP2B6, CYP2D6 CYP2D6 (potent) Esketamine CYP3A4, CYP2B6 Mianserin CYP2D6 Mirtazapine CYP1A2, CYP2D6, CYP3A4 CYP2D6 (weak) Phenelzine CYP2C19, CYP3A4 Reboxetine CYP3A4 Tranylcypromine12 CYP2A6, CYP2C19 Trazodone CYP3A4 Vortioxetine CYP2D6, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 Vilazodone CYP3A4 CYP2C8 CYP enzymes highlighted in bold indicate predominant metabolic enzyme pathway or potent inhibition of enzyme activity.

Depression and anxiety disorders CHAPTER 3 Table 3.12 Pharmacokinetic interactions: a brief summary of important interactions.13,14 CYP1A2 CYP2B6 CYP2C9 CYP2C19 CYP2D6 CYP3A4/5/7 Genetic polymorphism. Ultra-rapid metabolisers possible. 2–10% of total hepatic CYP content15 5–10% of people of European descent poor metabolisers ~20% of Asian and 3–5% people of European descent poor metabolisers 3–5% of people of European descent poor metabolisers 60% p450 content Induced by: Induced by: Induced by: Induced by: Induced by: Induced by: carbamazepine charcoal cooking tobacco smoke omeprazole phenobarbital phenytoin carbamazepine efavirenz (chronically)16 lopinavir rifampicin ritonavir phenytoin rifampicin apalutamide artemisinin efavirenz enzalutamide rifampicin carbamazepine phenytoin

carbamazepine phenytoin prednisolone rifampicin St John’s wort Inhibited by: Inhibited by: Inhibited by: Inhibited by: Inhibited by: Inhibited by: cimetidine ciprofloxacin erythromycin fluvoxamine clopidogrel efavirenz (acutely)16 ticlopidine voriconazole cimetidine fluoxetine fluvoxamine moclobemide sertraline armodafinil etravirine fluconazole fluoxetine fluvoxamine esomeprazole isoniazid moclobemide modafinil omeprazole voriconazole cimetidine bupropion citalopram chlorpromazine desvenlafaxine duloxetine escitalopram fluoxetine fluphenazine haloperidol paroxetine sertraline tricyclics erythromycin fluoxetine fluvoxamine grapefruit juice ketoconazole norfluoxetine paroxetine sertraline tricyclics Metabolises: Metabolises: Metabolises: Metabolises: Metabolises: Metabolises: agomelatine benzodiazepines caffeine clozapine duloxetine haloperidol mirtazapine olanzapine ramelteon theophylline tizanidine tricyclics warfarin bupropion methadone tramadol agomelatine bupropion citalopram diazepam escitalopram omeprazole phenytoin tricyclics warfarin citalopram diazepam moclobemide aripiprazole atomoxetine brexpiprazole clozapine codeine dextromethorphan donepezil duloxetine haloperidol phenothiazines risperidone tamoxifen tricyclics tramadol trazodone venlafaxine vortioxetine calcium blockers carbamazepine clozapine donepezil erythromycin galantamine levomilnacipran methadone mirtazapine reboxetine risperidone statins tricyclics valproate venlafaxine vilazodone vortioxetine z-hypnotics

404 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 mucosa so, when these drugs are used together, the risk of GI bleeds is increased). Here, we provide a broad summary of these interactions. Up-to-date interaction tables are readily available online and most known interactions are described in an individual product’s literature. Tricyclic antidepressants7,17–19 ■ ■are H1 antagonists (sedative). This effect can be exacerbated by other sedative drugs or alcohol. Beware respiratory depression. ■ ■are anticholinergic (dry mouth, blurred vision, constipation). This effect can be exacerbated by other anticholinergic drugs such as antihistamines or antipsychotics. Also associated with cognitive impairment and GI obstruction. ■ ■are adrenergic α1 blockers (postural hypotension). This effect can be exacerbated by other drugs that block α1 receptors and by antihypertensive drugs in general. As a consequence, falls may be more common. ■ ■are arrhythmogenic. Caution is required with other drugs that can alter cardiac conduction directly or indirectly (see section on antidepressant-induced arrhythmia in this chapter). ■ ■lower the seizure threshold. Caution is required with other proconvulsive drugs (e.g. some antipsychotics) and particularly if the patient is being treated for epilepsy (see section on epilepsy in Chapter 10). ■ ■possess varying degrees of serotonin reuptake inhibition (amitriptyline and clomipramine in particular). There is the potential for these drugs to interact with other serotonergic drugs (e.g. tramadol, SSRIs, MAOIs, triptans) to cause serotonin syndrome. SSRIs/SNRIs7,17,18,20.21 ■ ■increase serotonergic neurotransmission. The main concern when co-prescribed with other serotonergic drugs is serotonin syndrome. ■ ■inhibit platelet aggregation and increase the risk of bleeding, particularly of the upper GI tract. This effect is exacerbated by aspirin and NSAIDs (see section on SSRIs and bleeding in this chapter). ■ ■may be more likely than other antidepressants to cause hyponatraemia (see section on antidepressant-induced hyponatraemia in this chapter). This may exacerbate electrolyte disturbances caused by other drugs such as diuretics. ■ ■are associated with a decrease in bone mineral density. This adds to the negative effects prolactin elevating drugs have on bone mineral density and increases the risks of clinical harm should the patient have a fall. MAOIs12,22,23 ■ ■prevent the metabolism of monoamine neurotransmitters (e.g. serotonin). Co- prescription with serotonergic drugs (in particular, serotonin reuptake inhibitors or releasing agents) risks potentially fatal serotonin syndrome. Examples include SSRI and related antidepressants but also certain over-the-counter medicines (e.g. chlorphenamine,

dextromethorphan), opioids (e.g. tramadol, pethidine), antipsychotics

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Revision #1
Created 2026-01-04 20:15:39 UTC by Omar Ayman
Updated 2026-01-04 20:15:39 UTC by Omar Ayman