Antidepressant drug interactions: evidence and clinical significance

Stephen Bleakley MRPharmS, MSc, FCMHP

Antidepressants are widely used in the general population, primarily to treat depression but also commonly in conditions such as anxiety disorders and neuropathic pain. This article considers the significant pharmacodynamic and pharmacokinetic drug interactions of different antidepressants, whilst remembering that individual patient characteristics are of utmost importance in the prescribing decision.

Antidepressants are one of the most widely taken medicines nationwide with 11% of women and 6% of men reporting regular use. While they are primarily used to treat depression they are also commonly used in other conditions such as anxiety disorders and neuropathic pain. This makes antidepressants one of the most likely medicines both mental health specialists and general practitioners will encounter. Having an appreciation of the potential and clinical significance of drug interactions with the antidepressants should therefore be considered an important skill for many prescribers and pharmacists.

Drug interactions are broadly classified as either pharmacodynamic or pharmacokinetic. Pharmacodynamic drug interactions, often expressed as the effect a drug has on the body, suggests that as two drugs are used concomitantly their mechanisms of actions or adverse-effect profiles are altered in either nature, magnitude or duration compared with the effect of one drug alone (sometimes known as a synergistic interaction). One example is the potential for serotonin syndrome when two serotonin-enhancing antidepressants are combined. Pharmacokinetic drug interactions (the effect the body has on the drug) occur where one drug alters the absorption, distribution, metabolism or elimination (ADME) of another. The majority of the significant pharmacokinetic interactions with antidepressants involve drug-induced changes in hepatic metabolism, which predominantly involve the cytochrome P450 (CYP) isoenzymes. Antidepressants are metabolised through a number of CYP enzymes (most often CYP2D6, 1A2 and 3A4) so can be altered by drugs that inhibit or induce these metabolising routes. In addition, some antidepressants are inhibitors of the CYP enzymes themselves so have the potential to increase levels of other medication. Enzyme inhibition occurs rapidly, within two to three days, due to the offending drug binding to the metabolising enzyme preventing it functioning. Enzyme induction is often a slower process (taking a number of days to a few weeks) as the offending drug is reprogramming the metabolising enzyme to increase production. A common example of an antidepressant kinetic interaction is the addition of fluoxetine to amitriptyline. One would expect the amitriptyline levels and potential toxicity to significantly increase (reportedly by 2.5 to 6.3 times) due to fluoxetine inhibiting the specific isoenzyme CYP2D6. If the extent of the CYP inhibition or induction is known and predictable then a dose adjustment of the affected drug can sometimes be made to counteract the interaction. However, caution must be used because the interaction is likely to become apparent again during dose changes or when discontinuing the enzyme inhibitor or inducer. Other important factors to consider when contemplating drug interactions concern the individual characteristics of the patient. Genetic variances (known as genetic polymorphisms) exist where hepatic enzymes, and hence the ability of the body to metabolise the drug, are altered. For example, around 5% to 10% of Caucasians have a variant of the hepatic isoenzyme CYP2D6. Such individuals are poor metabolisers (have little or no activity) at CYP2D6 so may accumulate and develop toxicity of

Box 1. Examples of drugs significantly affected (increased plasma levels and adverse effects) by fluvoxamine

- Agomelatine (the manufacturer reports a 60-fold increase in exposure)
- Caffeine
- Clozapine (where up to a 10-fold increase in plasma concentrations have been seen), some benzodiazepines such as diazepam, alprazolam and bromazepam
- Duloxetine (a reduction in clearance by 77% was seen in one study)
- Haloperidol
- Melatonin (where plasma levels increased by 12-fold have been reported)
- Olanzapine (increased plasma levels of up to 84% have been reported)
- Phenytoin (one case report highlighted a three-fold increase in levels)
- Proton pump inhibitors (unlikely to be significant)
- Quetiapine
- Theophylline (clearance reduced by up to 70%)
- TCAs (up to eight-fold increases in clomipramine plasma levels have been reported) and warfarin (increased prothrombin times by 28%)

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drugs metabolised through this enzyme.\textsuperscript{5} This varying ability to metabolise certain drugs may in part explain why some patients develop adverse effects and toxicity when exposed to drug interactions while others appear symptom free. Other individual characteristics to consider are age-related changes and comorbidities of individuals, which often increase the risk and worsen the tolerability to drug interactions.

The evidence base supporting drug–drug interactions is often limited, with very few formal interaction studies. Most drug interactions are detected during clinical experience and published either as single case reports or as a case series where proof of causality is rarely available. Where formal studies do exist they often involve a small number of participants who are fit and healthy or they use a low dose of the offending drug.\textsuperscript{6} Therefore, extrapolating this evidence base to complex clients with multiple comorbidities and multiple medication regimens needs to be done with caution. For some, an emerging drug–drug interaction may actually be beneficial while for others the slightest change in drug levels or adverse-effect profiles will not be tolerated or acceptable. As with all prescribing, when determining the relevance and significance of a

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Significant pharmacokinetic interactions (increased plasma levels and potential adverse effects)</th>
<th>Significant pharmacodynamic interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine – a potent inhibitor of CYP 1A2, 2C19 and weak inhibitor of 3A4 and 2C9</td>
<td>Agomelatine* Some benzodiazepines (eg diazepam, alprazolam and bromazepam) Caffeine + Clozapine* Duloxetine* Haloperidol Melatonin Olanzapine + Proton pump inhibitors Phenotyin* Quetiapine Theophylline* Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotiline and trimipramine) Warfarin*</td>
<td>Potential serotonin syndrome when combined with: Other serotonin-enhancing antidepressants Tramadol Fentanyl Buspirone St John’s Wort Lithium Ondansetron Linezolid Increased risk of bleeding (particularly upper GI bleed) with: NSAIDs Warfarin and other anticoagulants Antiplatelets Other pharmacodynamic interactions to consider: Other drugs which can also cause sexual dysfunction (antipsychotics), GI effects (acetylcholinesterase inhibitors) or hyponatraemia (thiazide diuretics).</td>
</tr>
<tr>
<td>Fluoxetine, paroxetine – potent inhibitor of CYP 2D6</td>
<td>Aripiprazole Atomoxetine Carvedilol Clozapine + Donepezil Galantamine Metoprolol Risperidone + Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotiline and trimipramine)</td>
<td>Other pharmacodynamic interactions to consider: Other drugs which can also cause QT interval.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Clozapine* Unlikely to cause other clinically significant pharmacokinetic drug interactions</td>
<td></td>
</tr>
<tr>
<td>Citalopram, escitalopram</td>
<td>Unlikely to cause clinically significant pharmacokinetic drug interactions but contra-indicated with other drugs which can prolong QT interval.</td>
<td></td>
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</tbody>
</table>

*Avoid – high risk combination either due to the clinical significance or the potential toxicity of the affected drug
+ Use with caution – monitor the combination closely for any adverse effects

Table 1. Summary of significant SSRI drug–drug interactions
potential drug–drug interaction, considering individual patient characteristics is of the utmost importance.

**Selective serotonin reuptake inhibitors (SSRIs)**

Given that the SSRIs are the most widely prescribed antidepressants, reassuringly, they have a low potential for clinically significant drug interactions with a few notable exceptions (see Table 1). Individually, SSRIs differ in their potential to inhibit various metabolising CYP hepatic isoenzymes. Fluvoxamine, for example, is one of the most potent inhibitors of CYP1A2 in clinical use and can reduce the clearance, and hence increase the toxicity, of drugs primarily metabolised by 1A2 (see Box 1). To a lesser extent fluvoxamine is also an inhibitor at CYP2C19, 2C9 and 3A4.5,7,8

As a general rule it would be prudent to monitor closely for adverse effects and drug interactions when co-prescribing fluvoxamine with most drugs and consider using another SSRI that is less likely to interact. Fluoxetine and paroxetine are potent inhibitors of the hepatic isoenzyme CYP2D6 and thus can significantly increase the plasma concentrations of drugs metabolised primarily by this enzyme.5,9 Fluoxetine and paroxetine have been shown to significantly increase the plasma levels of aripiprazole, atomoxetine, carvedilol, clozapine (increases plasma levels by 30–42%), donepezil, galantamine, metoprolol, most tricyclic antidepressants (where a two- to five-fold increase in levels have been reported) and risperidone.5,7,9 In addition, there are reports that paroxetine and possibly fluoxetine may reduce the effectiveness of tamoxifen by reducing the metabolic route to its active metabolite and hence increase the risk of returning breast cancer.5 Sertraline, citalopram and escitalopram are weak inhibitors of CYP2D6 and have little effect on other isoenzymes, so are unlikely to be the cause of significant pharmacokinetic drug interactions. There is one possible exception: there are occasional case reports of sertraline, particularly at higher doses, increasing plasma levels of clozapine, so it would be prudent to monitor this combination closely.5,9 Given the low toxicity of the SSRIs and their multiple routes of metabolism (primarily 2D6 and 3A4)5,9 enzyme inducers or inhibitors are unlikely to cause clinically significant changes in SSRI plasma levels.

There are many potential pharmacodynamic drug interactions with the SSRIs. Few are absolute contraindications but all require close monitoring for increased adverse effects of the interacting drug. For example, SSRIs increase serotonergic neurotransmission so have the potential to cause serotonin syndrome when combined with other similarly acting drugs, when used on their own in high doses or following an overdose. Symptoms of serotonin syndrome include sweating, diarrhoea, myoclonus and confusion and although rare it can be potentially life threatening (see Figure 1).10 Drugs that have been implicated in serotonin syndrome when combined with SSRIs or another serotonin enhancing antidepressant include buspirone, linezolid, lithium, fentanyl, tramadol, pethidine and St John’s Wort.10,11 While triptans might also be expected to incur a risk of serotonin syndrome with SSRIs and other antidepressants the clinical significance is hotly debated.11 Some of the most severe cases of serotonin syndrome have been reported following combinations of monoamine oxidase inhibitors with either TCAs or SSRIs and this should particularly be avoided.5 SSRIs have also been associated with an increased risk of bleeding, particularly upper gastrointestinal bleeding (GI). While the bleeding risk associated with the SSRIs alone appears low the risk substantially increases when SSRIs are combined with nonsteroidal anti-inflammatory drugs, oral anticoagulants or antiplatelet drugs.11,12 The mechanism behind the bleeding risk has been proposed as an SSRI-induced increase in gastric secretion12 or a depletion in platelet serotonin.7,12 This GI bleeding risk may be reduced by the addition of a proton pump inhibitor.12 It would be prudent to be cautious when prescribing SSRIs in those at a high risk of a bleed such as people with acid-peptic disease, those with a previous history of bleeds or anyone undergoing invasive surgery.7,12 Other pharmacodynamic interactions to consider with the SSRIs are sometimes evident when co-prescribing drugs with similar adverse reactions. Examples may include drugs that also cause sexual dysfunction (eg antipsychotics), the addition of medication that causes GI effects such as nausea, vomiting and diarrhoea (such as the acetylcholinesterase inhibitors) or the rare but potentially serious consequence of hyponatraemia (eg thiazide diuretics). Of additional note is that both citalopram and escitalopram have been associated with a dose-related increase in QT prolongation, so are contraindicated with other medicines known to prolong QT intervals (such as most antipsychotics and TCAs).5

![Figure 1. The spectrum of symptoms associated with serotonin syndrome](image-url)
Tricyclic antidepressants (TCAs)

TCAs are primarily metabolised through the hepatic isoenzyme CYP2D6 with 1A2 and 3A4 as secondary routes.\(^4,5\) Although they themselves do not cause enzyme inhibition or induction, because of their narrow therapeutic index they are susceptible to significant interactions when combined with inhibitors or inducers of these CYP enzymes (see Table 2).

There are also a number of pharmacodynamic interactions to consider with the TCAs, many of which can be potentially serious. For example TCAs have multiple effects on cardiac function (e.g. postural hypotension, QT prolongation, arrhythmias and are cardiotoxic in overdose) so are best avoided in anyone with pre-existing cardiac disease. Other drugs that alter cardiac conduction either directly (e.g. antiarrhythmics or phenothiazines) or indirectly (e.g. diuretics via electrolyte disturbances) should be used with caution.\(^7\) The SSRIs or mirtazapine are safer alternatives in cardiac disease.\(^7\) Tricyclic antidepressants can also lower the seizure threshold (caution with other proconvulsant drugs, e.g. antipsychotics), may be serotonergic (see serotonin syndrome above) and have pronounced sedative and anticholinergic properties (such as constipation, blurred vision and confusion).\(^7\)

Monoamine oxidase inhibitors (MAOIs)

Although MAOIs are rarely used in clinical practice they are associated with some of the most profound and clinically significant drug interactions of all the antidepressants. Three MAOIs are currently available (phenelzine, tranylcypromine and isocarboxazid) and each irreversibly binds to the MAO enzyme disrupting its function. This is associated with one of the most famous drug–food interactions in medicine, the commonly quoted ‘cheese reaction’. Tyramine (a biogenic amine found in food) is a potent releaser of systemic noradrenaline and can thus elevate blood pressure.\(^13\) Normally tyramine cannot accumulate because it is broken down by MAO-A in the intestinal wall and liver before it is absorbed. Furthermore if tyramine does make it to the systemic circulation any noradrenaline released is destroyed by the circulating MAO-A.\(^12\) MAOIs compromise this protective system and therefore any food high in tyramine has the potential to cause a hypertensive crisis. Which foods are high enough in tyramine is open to some debate but historically an over-cautious diet is often imposed. In reality most foods can be safely consumed if bought fresh and immediately cooked and consumed in modest quantities.\(^14\) Over time, as food degrades or is stored incorrectly, the biogenic amine content, including tyramine, increases.\(^14\) Table 3 highlights the dietary restrictions associated with MAOIs. The reversible monoamine oxidase inhibitor, moclobemide, incurs a much lower risk of dietary interactions because it is displaced by circulating noradrenaline enabling the MAO-A to retain some function. As long as the patient is not consuming large amounts of high tyramine-rich foods a restricted diet is not required with moclobemide.\(^15\)

Extreme caution is also warranted when MAOIs are co-prescribed with drugs that are metabolised or have effects at the MAO enzyme. Examples include the sympathomimetics, levodopa, amphetamine, ephedrine and dextromethorphan (which is occasionally found in cough mixtures). The risk of serotonin syndrome is also potentially profound if an MAOI is combined with another serotonin enhancing agent (e.g. TCAs, SSRIs, pethidine, venlafaxine, duloxetine). These combinations are best avoided. Furthermore, this concern has led to a recommendation of waiting two weeks after stopping the MAOI before initiating another serotonin acting antidepressant.

Serotonin and noradrenaline reuptake inhibitors (SNRIs)

Venlafaxine is an SNRI, which at lower doses acts as a serotonin reuptake inhibitor, with noradrenaline reuptake inhibition developing at higher doses.\(^11\) Venlafaxine is extensively metabolised in the liver, primarily by CYP2D6 to O-desmethylvenlafaxine (known as

<table>
<thead>
<tr>
<th>Significant pharmacokinetic interactions</th>
<th>Significant pharmacodynamic interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>May increase the plasma levels of TCAs</td>
<td>Potential serotonin syndrome when combined with:</td>
</tr>
<tr>
<td>Bupropion (can double the plasma levels of desipramine)</td>
<td>Other serotonin-enhancing antidepressants</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Buspirone</td>
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<tr>
<td>Fluconazole</td>
<td>St John’s Wort</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Duloxetine (a 2.9-fold increase in desipramine has been demonstrated)</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Caution in pre-existing cardiac disease or with other drugs which effect cardiac function (antiarrhythmics)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Caution in epilepsy and with other drugs which lower the seizure threshold (e.g. antipsychotics)</td>
</tr>
<tr>
<td>Venlafaxine (largely theoretical)</td>
<td>Caution with other drugs which are sedative and have anticholinergic properties (e.g. constipation, blurred vision, confusion)</td>
</tr>
<tr>
<td>Terbinafine</td>
<td></td>
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<tr>
<td>Ritonavir (at higher doses only)</td>
<td></td>
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<tr>
<td>May reduce the plasma levels of TCAs</td>
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<tr>
<td>Carbamazepine</td>
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</table>

Table 2. Summary of significant TCA drug–drug interactions
Antidepressant drug interactions

**Table 3. Dietary restrictions with MAOIs**

<table>
<thead>
<tr>
<th>Foods to avoid</th>
<th>Foods which can be eaten in modest amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged cheeses (eg English Stilton, Cheshire, Danish Blue)</td>
<td>Processed, cottage and cream cheese, ricotta cheese, yogurt (including commercially available pizzas from large chains)</td>
</tr>
<tr>
<td>Dried, aged, smoked, fermented fish or poultry</td>
<td>Fresh or processed meat, fish or poultry</td>
</tr>
<tr>
<td>Broad bean pods, banana peel</td>
<td>All other fruit and vegetables</td>
</tr>
<tr>
<td>Tap and unpasteurised beers</td>
<td>Canned or bottled beers and alcohol (including wine and chianti)</td>
</tr>
<tr>
<td>Marmite and sauerkraut</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Soya products / tofu</td>
<td></td>
</tr>
</tbody>
</table>

desvenlafaxine) and desvenlafaxine is itself marketed in some countries for depressive disorders. Cytchrome 3A4 is also involved in venlafaxine metabolism to a lesser extent. Venlafaxine is thought to be a (probably not significant) CYP 2D6 inhibitor and is not known to be an inhibitor or inducer of 1A2, 2C9 or 3A4. Drugs that may increase venlafaxine plasma levels, predominantly via 2D6 enzyme inhibition, include diphenhydramine, terbinafine, bupropion and, theoretically, fluoxetine and paroxetine. As with other serotonergic antidepressants venlafaxine has been associated with the risk of serotonin syndrome when combined with similarly acting drugs and has the same risk of bleeding as the SSRIs. Dose-related increases in blood pressure are also commonly reported with venlafaxine, so it may cause or worsen hypertension and potentially reverse the benefits of antihypertensives.

Duloxetine, another SNRI, is extensively metabolised by CYP1A2, as its primary route and 2D6 as a secondary route. It is itself considered to be a moderate inhibitor of CYP2D6 so can potentially increase the levels of drugs mainly metabolised through this route (eg TCAs, tolterodine, metoprolol, risperidone and aripiprazole). Cigarette smoking is associated with lower duloxetine plasma levels (via 1A2 induction) and fluvoxamine and paroxetine have been shown to increase duloxetine levels: for example, fluvoxamine increases the area under the plasma concentration/time curve of duloxetine by 460%. Similarly to venlafaxine, duloxetine incurs a risk of serotonin syndrome, increased bleeding and can increase blood pressure.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant often used as a second-line antidepressant when sedation and appetite stimulation are required. Mirtazapine has three main metabolic pathways via CYP2D6, 1A2 and 3A4 and this suggests that the kinetic interaction profile is low as multiple routes of metabolism are available should an individual pathway be inhibited. Mirtazapine also has no appreciable inhibitory or inducing effects itself on CYP enzymes. However, of the few interaction studies available cimetidine, fluvoxamine and ketoconazole have been shown to markedly increase mirtazapine plasma concentrations while carbamazepine and phenytoin (CYP3A4 inducers) reduce mirtazapine plasma concentrations. Mirtazapine commonly causes sedation so may potentiate the pharmacological effects of other sedatives (e.g. alcohol, benzodiazepines and antipsychotics) and, in particular, next day sedation and a falls risk in the elderly should be monitored for. Weight gain is another common adverse effect of mirtazapine, which occasionally can be problematic when the drug is combined with antipsychotics. Mirtazapine probably has a lower risk of serotonin syndrome and bleeding risk than the SSRIs although this is open to some debate.

Agomelatine was first approved in Europe in 2009 and has a novel mechanism of action with melatonergic agonist (MT1 and MT2 receptors) and 5-HT2c antagonist properties. It is extensively metabolised in the liver with CYP1A2 accounting for around 90% of the biotransformation and the remaining 10% due to 2C9 and 2C19. Agomelatine is not known to induce or inhibit CYP isoenzymes but it can be profoundly affected by other drugs or substances that affect CYP1A2. For example, fluvoxamine can increase the exposure of agomelatine 60-fold (range: 12- to 412-fold). Ciprofloxacin and oestrogens are also expected to increase agomelatine plasma levels. Conversely cigarette smoking (especially in heavy smokers [≥15 per day]) would be expected to reduce plasma concentrations by inducing CYP1A2.

There are few pharmacodynamic interactions with agomelatine with the exception that it has been associated with raising liver enzymes and has the potential for hepatic injury, particularly in the first few months of treatment. Patients and prescribers are advised to closely monitor liver enzymes (at baseline, 3, 6, 12 and 24 weeks after initiation) and watch for any signs of liver impairment. Presumably this would also be a concern if co-prescribed with other medication that can potentially cause liver impairment (eg clozapine and TCAs).

Vortioxetine is a relatively recent addition to the antidepressant market, first authorised in Europe in December 2013. It is described as a multimodal antidepressant.

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with a variety of serotonin-specific agonist and antagonist mechanisms of action (5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B partial agonist, a 5-HT1A agonist and inhibitor of 5-HT transporter). Vortioxetine is metabolised to its major carboxylic acid metabolite via the CYP2D6 pathway with CYP3A4/5 and 2C9 as secondary routes. Vortioxetine itself does not show any induction or inhibition at cytochrome P450 isoenzymes but may be significantly affected by inhibitors of CYP2D6 such as bupropion, fluoxetine and paroxetine (where increased levels would be expected). Other 3A4 inhibitors (eg ketoconazole, fluconazole, itraconazole and clarithromycin) may be expected to increase vortioxetine levels while 3A4 inducers (eg carbamazepine, rifampicin and phenytoin) may be expected to decrease vortioxetine levels. The clinical significance of the 3A4 interaction is yet to be established. Along with many other antidepressants there is risk of serotonin syndrome when combining vortioxetine with other serotonin-enhancing agents.

Reboxetine and trazodone are mainly metabolised by CYP3A4 so are subject to inhibitors of 3A4 (eg erythromycin, ketoconazole and ritonivir) and inducers such as carbamazepine and St John’s Wort. Neither reboxetine nor trazodone is considered to be a CYP inducer or inhibitor on its own but trazodone may incur a risk of serotonin syndrome when combined with similar agents.

St John’s Wort
When considering drug interactions with antidepressants it would be appropriate to mention the herbal product St John’s Wort (SJW). Although there is no licensed or approved product in the UK it is widely self-prescribed for mild-to-moderate depression. SJW has been shown to cause some dramatic interactions mainly as a result of its ability to induce CYP3A4, 2E1, 2C9 and P-glycoproteins. Examples of significant drug–SJW interactions include reducing cyclosporine and tacrolimus levels, which in some cases has resulted in transplant rejections, reducing the effectiveness of oral contraceptives causing unintended pregnancies, and studies demonstrate reduced levels and effectiveness of warfarin, digoxin, methadone and some benzodiazepines. It would be advisable to monitor carefully most other drugs when faced with a patient using SJW and consider alternative antidepressant choices.

Conclusions
Antidepressants are widely used in the general population and a few have the potential for significant and even potentially fatal drug interactions. If one were to rank the antidepressants in order of drug interaction risk most clinicians would agree that the MAOIs would rank first due to the concern about a hypertensive crisis with foods high in tyramine and the profound risk of serotonin syndrome with other serotonergic agents. The TCAs are likely to rank second due to their narrow therapeutic index and potential for cardiototoxicity, with fluvoxamine ranking third because of its profound CYP1A2 inhibition. Following these the clinical relevance of drug interactions with the antidepressants becomes low as long as a few basic pharmacological parameters are considered. Of the SSRIs, fluoxetine and paroxetine are worthy of caution because of their tendency to increase plasma concentrations and adverse effects of drugs predominantly metabolised through CYP2D6.

Mirtazapine, citalopram, escitalopram and sertraline incur lower risks of drug kinetic interactions but, similar to most antidepressants, have pharmacodynamic considerations such as the risk of serotonin syndrome and increased bleeding (less likely with mirtazapine). In addition, caution and potential cardiac monitoring should be considered when using citalopram or escitalopram with other drugs that can prolong QT intervals.

Declarations of interest
No conflicts of interest were declared.

References

Stephen Bleakley is Chief Pharmacist at Salisbury NHS Foundation Trust and Director and Fellow of the College of Mental Health Pharmacy.
Mindfulness-based stress reduction training effective for chronic low back pain

Clinical question
Is mindfulness-based stress reduction training useful in the treatment of chronic low back pain in adults?

Bottom line
Both mindfulness-based stress reduction (MBSR) training and cognitive behavioral therapy (CBT) are superior to usual care alone in reducing pain and improving function in adults with chronic low back pain. The difference in effectiveness, if any, between MBSR and CBT is minimal. (LOE = 1b)

Reference

Study design: Randomized controlled trial (single-blinded)  Funding source: Foundation
Allocation: Concealed Setting: Population-based

Synopsis
MBSR training focuses on increasing awareness and acceptance of moment-to-moment life experiences. These investigators identified adults, aged 20 to 70 years, with nonspecific low back pain persisting for at least 3 months. Eligible patients were randomly assigned (concealed allocation) to 1 of 3 groups: (1) usual care consisting of a $50 stipend and recommendation to seek whatever treatment, if any, they choose; (2) MBSR training; or (3) CBT. The MBSR and CBT training included 2 hours of instruction sessions per week for 8 weeks and an optional 6-hour retreat for the MBSR program only. MBSR classes included mindfulness practice (body scan, yoga, and meditation focusing on awareness of the present moment). CBT training focused on education about chronic pain, relationships between the body and mind and physical reactions, sleep hygiene, practice in changing dysfunctional thoughts, and pain-coping strategies. Individuals masked to treatment group assignment assessed outcomes by telephone interviews using validated pain and function scoring tools. Complete follow-up occurred for approximately 90% of participants at 52 weeks. Using intention-to-treat analyses, an overall clinically meaningful improvement (a greater than or equal to 30% improvement from baseline in functional limitations and self-reported back pain) occurred significantly more often in patients who received either MBSR training or CBT than in patients who received usual care (60.5% and 57.7% vs 44.1%; numbers needed to treat = 6 and 7). There were no significant differences in outcomes between the MBSR and CBT groups.

However, the benefit of functional improvement and pain reduction compared with usual care seen at 26 weeks was maintained at 52 weeks for MBSR but not CBT. The study was 80% powered to detect a predetermined clinically meaningful difference in the MBSR and CBT groups.

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