Therapeutic brief 5

Antidepressants: Three Steps Towards Safer Use

Antidepressants are among the most commonly prescribed medicines in Australia with considerable growth in usage since the release of the first SSRI, Prozac® (fluoxetine), to the Australian market in June 1990[1]. This increase has also been promoted in part by public health initiatives to facilitate diagnosis and treatment of depression[2,3].

Concurrent use of more than one antidepressant, or use of antidepressants with other medicines creates potential for drug interactions and other adverse effects.

This therapeutic brief asks you to consider ways to achieve safer use of antidepressants for your veteran patients by using a three step approach designed to help identify and address some common drug interactions.

Inside

The three step approach:

1. **Avoid** use of more than one antidepressant at a time.
2. **Check** for additive pharmacologic effects with other medicines *(pharmacodynamic interactions)*.
3. **Assess** for metabolic interactions with other medicines *(pharmacokinetic interactions)*.

Between December 2003 and November 2004, 1 in 4 veterans were dispensed an antidepressant compared to 1 in 6 veterans for the twelve month period January to December 2000.[4] The majority of these veterans were also treated for various other medical conditions.

Antidepressants are used to treat panic disorder, obsessive compulsive disorder, bipolar affective disorder, post-traumatic stress disorder as well as depression. There is a strong association between psychiatric illnesses and other medical conditions.[5-7] This is particularly true for the veteran population.[8]

Key Points

- Using combinations of antidepressants for the treatment of depression is not supported by current evidence and drug-related harm may be substantial.[9-13]
- Antidepressants in combinations with other medicines may cause patients to experience serious pharmacodynamic drug interactions.[14] Important examples include:
  - Selective serotonin reuptake inhibitors (SSRIs) with tramadol causing serotonin syndrome.
  - Tricyclic antidepressants (TCAs) with nitrates causing orthostatic hypotension.
  - TCAs with anticholinergic medicines contributing to blurred vision, dry mouth, constipation and urinary retention.
  - TCAs with selective alpha blockers contributing to postural hypotension.
- SSRIs are the most commonly prescribed antidepressants in Australia.[1] They can influence the hepatic metabolism of many other commonly prescribed drugs[14] and the resulting interaction(s) may cause serious harm.

Step One: Avoid use of more than one antidepressant at a time

Combinations of antidepressants are not recommended for the treatment of depression irrespective of the individual agents involved.[9-11]

There have been no adequate studies to demonstrate additional benefit from the concurrent use of more than one antidepressant.[9-11]

Serious harm associated with combination antidepressant regimens is possible even when dosages of both drugs are modest. Potential adverse consequences include seizures, cardiotoxicity, mania, hyponatraemia, severe hypotension, falls and death.[13]

Many veterans are elderly, have multiple major medical co-morbidities for which they may be treated with drugs of low therapeutic index; these factors compound the risks associated with combination antidepressant regimens.

Even when a low-dose TCA is prescribed concurrently with a SSRI, toxicity may result from high serum concentrations related to the inhibition of TCA metabolism by the SSRI.

Alternatives to TCAs for treating non-mental health conditions.

TCAs are often encountered in antidepressant drug combinations, and in many cases the TCA is added to the drug regimen for reasons other than antidepressant effect. Examples include the use of TCAs (often in low doses) as management strategies for urinary incontinence, sleep disturbance and neuropathic pain. In most cases alternative treatment can be trialed in place of a TCA. The alternatives listed in Table One have some potential for adverse effects; consider individual risk management strategies.

Table One: Alternatives to TCAs for treating non-mental health conditions

Urinary urge incontinence[13]

Oxybutynin, propantheline and tolterodine*

Sleep disturbance

Comprehensive sleep assessment, sleep hygiene measures and short-term hypnosedatives

Neuropathic pain[13]

Gabapentin, carbamazepine and topical capsaicin

*Tolterodine is not presently available on the PBS or RPBS

Serotonin syndrome is a serious adverse effect that can result from combined use of more than one antidepressant agent.

Sometimes fatal, serotonin syndrome can be insidious in onset, but most commonly presents within 2 to 3 days of commencing a drug combination. It may not be possible to monitor patients closely during this initial period of treatment when signs and symptoms may appear. Many features are relatively non-specific and easily missed when dealing with a patient with several medical conditions (see Table Two).

Serotonin syndrome has been reported with antidepressant combinations involving two or more of the following: SSRIs, TCAs, venlafaxine, monoamine oxidase inhibitors (MAOIs) and mirtazapine.[15]

Table Two: Presenting characteristics of serotonin syndrome[15]

Thought to result from over-stimulation of serotonin 5HT1A receptors in the central nervous system, features include:

- mental state changes
- agitation
- myoclonus (twitching)
- hyperreflexia
- fever
- shivering
- tremor
- diaphoresis (sweating)
- ataxia
- diarrhoea

Serious sequelae associated with serotonin syndrome include seizures, disseminated intravascular coagulation, respiratory failure, arrhythmias, coma and death.

Step Two: Check for additive pharmacological effects with other medicines *(pharmacodynamic interactions)*

Combined use of two or more agents with similar pharmacology can result in an interaction, where each drug can potentiate the effects of the other, resulting in serious adverse effects.

Serotonin syndrome is the most serious of the pharmacodynamic interactions involving combinations of antidepressants (see Table Two).

Antidepressants and tramadol

Serotonin syndrome may be precipitated by the concurrent use of antidepressants with tramadol (a serotonergic analgesic agent). The combined use of antidepressants and tramadol should be avoided and an alternative analgesic considered.

As well as the pharmacodynamic interaction, SSRIs inhibit the metabolism of tramadol. This may increase the likelihood of serotonin syndrome.

TCA interactions

TCAs are often involved in pharmacodynamic drug interactions because they block alpha-adrenergic, muscarinic and histaminic receptors. These drug interactions can be largely avoided by either replacing a TCA (when used for depression) with an antidepressant that does not have the interacting potential, or replacing the TCA with an alternate agent when used for other indications such as urinary urge incontinence, sleep disturbance or neuropathic pain (see Table One).

Avoid concurrent use of TCAs with selective alpha blockers, nitrates and drugs with anticholinergic or antihistaminic effects (see Table Three).

Reserve TCAs for clinical circumstances where there has been excellent previous treatment response, or where alternate treatment is ineffective or poorly tolerated.

Table Three: Avoiding TCA interactions

Alpha-adrenergic blockade

Potentiation of alpha-adrenergic blockade can result in hypotension (especially postural hypotension), reflex tachycardia and urinary incontinence.

Caution with concurrent use of TCAs and alpha blockers (e.g. prazosin, terazosin). Nitrates, diuretics and antipsychotics may increase the likelihood of orthostasis .

Anticholinergic effects

Potentiation of anticholinergic effects can result in tachycardia, cognitive impairment, constipation and urinary hesitancy (especially in the presence of prostatic hypertrophy).

Caution with concurrent use of TCA and antipsychotics, antihistamines, oxybutynin and some antiarrythmics.

Antihistamine effects

Sedation, respiratory depression and increased risk of falls.

Caution with concurrent use of TCAs and antipsychotics, hypnosedatives, opioids, antihistamines and alcohol use.

Step Three: Assess for metabolic interactions with other medicines *(pharmacokinetic interactions)*

SSRIs are implicated in clinically important drug interactions caused by inhibition of hepatic enzymes that metabolise other drugs. [13]

Different SSRIs inhibit different metabolic pathways, thereby interacting with a variety of medicines. The expression of the interaction will depend upon an individual's genetic profile. In some cases an interaction may be important because a patient is genetically predisposed to poor metabolism of certain medicines.

The dose of both the SSRI and the potentially interacting drug may be important – high dose SSRIs will influence drug metabolism more profoundly (see Table Four, page 4).

Citalopram has the least effect on hepatic enzymes and should be regarded as the SSRI of first choice for most veterans, particularly those with complex medication regimens.

Table Four: SSRI pharmacokinetic interactions[13,16]

HMG Co-A Reductase Inhibitors (statins)

- Increased risk of myopathy, particularly with fluvoxamine and fluoxetine.
- Assess for myalgia, consider monitoring plasma creatine kinase.
- Avoid simvastatin and atorvastatin.

Beta blockers (specifically metoprolol & propranolol)

- Potentiation of beta blockade, bradycardia and hypotension, particularly with paroxetine and fluoxetine.
- Consider alternative beta blockers such as atenolol or carvedilol.

Perhexiline

- Interaction most pronounced with paroxetine and fluoxetine.
- Potential for perhexiline toxicity with features including hepatotoxicity, peripheral neuropathy, hypoglycaemia and papilloedema.
- Avoid SRRIs for patients requiring perhexiline.

Antipsychotics

- Interaction most pronounced with paroxetine and fluoxetine. Often manifested as potentiation of extrapyramidal side effects.
- Also potential for over sedation when used with olanzapine.

Drugs used for patients with cognitive impairment (donepezil)

- May increase incidence of gastrointestinal side effects such as nausea, vomiting and anorexia.

What to tell my patient

- Ask patients to discuss with you any new medicines they may be taking because of the risk of interactions and unwanted effects.
- Inform patients that some medicines bought from pharmacies, health food shops, and supermarkets may cause unwanted effects when used with antidepressants.

  One of the most clinically important examples is St John's Wort, which induces the metabolism of other drugs, and can contribute to the serotonin syndrome.
- Suggest the patient keep a complete list of their medicines including all prescription and non-prescription medicines (MediList).
- Educate patients on the importance of reporting any unwanted effects from ALL medicines, including antidepressant medicines.
- Useful websites, for patients and carers, about depression and its treatment include:

  www.sane.org.au

  www.depressionet.com.au

  www.beyondblue.org.au

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