Antidepressants and Analgesics
Jennifer Chen, Pharm.D.

Introduction

Depression is a commonly encountered psychological issue in terminally ill patients who suffer from chronic pain and it often complicates the patient’s conditions and treatment. A common sign of depression in the terminally ill patient is pain that is not responding to treatment as expected. Therefore, being aware of potential drug-drug interactions between antidepressants and pain medications not only can help avoid serious adverse effects but also provide a better overall care for terminally ill patients. This article will review different classes of antidepressants and discuss choices of antidepressants with different pain medications based on pharmacokinetic properties of antidepressants and opiates.

Antidepressants

In hospice, SSRIs are typically the first choice in patients with depression. Currently available SSRIs include citalopram (Celexa), escitalopram (Lexapro), Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine (Paxil), and Sertraline (Zoloft). Although there are minor differences between these medications, they all have the same overall mechanism of action, which is the inhibition of reuptake at serotonin transporters and potentiation of serotonin in the central nervous system. The primary metabolic pathways for SSRIs are the cytochrome P450 (CYP) 2D6 isoenzymes and the magnitude of their CYP inhibition has been shown to be dose and concentration dependent.

SNRIs are usually considered in patients who have coexisting neuropathic pain and in patients without severe or uncontrolled heart disease. Currently available SNRIs indicated for depression include venlafaxine (Effexor), desvenlafaxine (Pristiq) and duloxetine (Cymbalta) and most recent levomilnacipran (Fetzima). The primary metabolic pathways for SNRIs are CYP 1A2 and CYP 2D6.
SSRI (serotonin-selective re-uptake inhibitor) Antidepressant Drugs
Fluoxetine (Prozac)
Paroxetine (Paxil)
Sertraline (Zoloft)
Fluoxetine (Luvox)
Citalopram (Celexa)
Escitalopram (Lexapro)

SNRI (serotonin & norepinephrine re-uptake inhibitor) Antidepressant Drugs
Venlafaxine (Effexor)
Duloxetine (Cymbalta)
Desvenlafaxine (Pristiq)
Levomilnacipran (Fetzima)

TCAs are older antidepressants and are usually not a first-choice treatment because of numerous side effects. Many medical conditions seen in the elderly, such as dementia, Parkinson disease and cardiovascular problems can be worsened by a tricyclic antidepressant. In general, the secondary amines (desipramine and nortriptyline) are better choices than the tertiary amines (imipramine, amitriptyline and doxepine) because they have fewer side effects, such as sedation and anticholinergic effects. The primary metabolic pathways for TCAs are CYP 2D6 and CYP 2C19.

MAOIs (Isocarboxazid, Phenelzine, Tranylcypromine, Selegiline) can cause serious adverse events with various drugs and have numerous clinically significant drug interactions, which may result in hypertensive crises and serotonin toxicity. Therefore, MAOIs are rarely used and generally not recommended for geriatric patients.

Atypical antidepressants (Bupropion, Trazodone, Mirtazapine) are relatively safe in the elderly. They have lower anticholinergic effects than older antidepressants and are well tolerated by patients with cardiovascular disease. Depressed patients with anxiety and insomnia may benefit from a sedating antidepressant such as trazodone or mirtazapine given at bedtime.

Oxycodone
Oxycodone is metabolized via both CYP 3A4 and 2D6. However, a study showed that inhibition of 2D6 alone had no significant effect on oxycodone concentration, but the inhibition of both 2D6 and 3A4\(^2\). The combination of CYP 3A4 and 2D6 inhibitor has shown to result a substantial increase in oxycodone concentration and increased drowsiness in these patients were observed when compared with placebo. Most SSRI and SNRI are 2D6 inhibitors with less effect on CYP 3A4 metabolism; therefore, they are generally safe except fluoxetine and fluvoxamine, which are also moderate 3A4 inhibitors.
Methadone

Methadone is metabolized primarily by CYP 3A4, with 2D6 playing a smaller role. Both fluoxetine and fluvoxamine inhibit CYP 3A4 and 2D6 and studies had showed both antidepressants to be associated with decreased metabolism of methadone. Among the SSRIs, citalopram, escitalopram and sertraline have relatively minimal CYP interactions. Besides CYP interactions, methadone also has the potential to prolong QTc interval. TCAs are known to cause prolongation QTc interval and therefore, should be avoided or used cautiously in patients taking methadone. Other than TCAs, citalopram, paroxetine and sertraline have also shown the potential to prolong QTc interval. With regards to which antidepressant is safe to use while using methadone, venlafaxine appears to only mildly inhibit 2D6 and cause QTc prolongation to a lesser degree. Mirtazapine may increase the risk of CNS depression due to its sedating effect but it does not prolong QTc interval and has minimal CYP interactions with methadone. For more information on Methadone drug interactions, see the July edition of our newsletter, The Clinician: Volume 9, Issue 3.

Fentanyl

Fentanyl is also metabolized primarily by CYP 3A4. Inhibitors of 3A4 such as fluoxetine and fluvoxamine can cause fentanyl to build up in the system leading to adverse effects and should be used cautiously in patients taking Fentanyl.

Tramadol

Tramadol is metabolized by CYP 2D6 to an active metabolite which is much stronger than its parent drug. Paroxetine was shown to decrease the analgesic effect of tramadol via the inhibition of CYP 2D6 and reduced concentration of its active metabolite was observed. In addition to pharmacokinetic interactions, tramadol inhibits serotonin and norepinephrine reuptake, which may increase the risk of serotonin syndrome when used concurrently with antidepressants.

Hydrocodone and Codeine

Hydrocodone and codeine are metabolized by CYP 2D6 to their active metabolites, hydromorphine and morphine, respectively. Since the analgesic effect of codeine is dependent on the CYP 2D6 metabolism, co-administration of antidepressants strongly inhibit CYP2D6 such as paroxetine and fluoxetine with codeine may prevent the conversion of codeine to morphine and thus lead to loss of efficacy.

<table>
<thead>
<tr>
<th>Atypical Antidepressant Drugs</th>
<th>Tricyclic Antidepressant Drugs (TCAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazadone (Desyrel)</td>
<td>Amitriptyline (Elavil)</td>
</tr>
<tr>
<td>Mirtazepine (Remeron)</td>
<td>Nortriptyline (Pamelor)</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>Desipramine (Norpramin)</td>
</tr>
<tr>
<td></td>
<td>Doxepin (Sinequan)</td>
</tr>
<tr>
<td></td>
<td>Imipramine (Tofranil)</td>
</tr>
</tbody>
</table>
Citalopram and sertraline, which inhibit CYP 2D6 to a lesser degree, may be better antidepressant choices in these patients. Unlike codeine and tramadol, CYP 2D6 inhibition seems to have little effect on hydrocodone’s analgesic properties as shown in both animal and human studies so hydrocodone may be a better choice for patients taking paroxetine or fluoxetine⁴.

Morphine and Hydromorphone

Finally, morphine and hydromorphone are metabolized by phase 2 glucuronidation so they have little potential for metabolically based drug interactions.

Recommendations

When selecting an antidepressant it is important to consider the patient’s previous response to treatment, the type of depression, the patient’s other medical problems, and the patient’s other medications. Depression may magnify pain and pain can provoke an emotional response. It is also important to minimize the drug interactions and carefully assess the patient’s overall medication regimen before increasing pain medication or changing the antidepressants.

References:


Mark Your Calendar! – “Pathways to Success: Conference By The Bay”
November 12 - 13, 2014 – Claremont Hotel Club & Spa, Berkeley, CA
Watch the website for details as they develop – http://outcomeresources.com