A brief review on the use of antidepressants in palliative care

Wadih Rhondali,[1,2] Michel Reich,[3] Marilene Filbet[2]

Antidepressants are part of the pharmacological management of depressive and anxiety disorders in oncology. In a palliative situation, several properties can enhance their indications, such as hot flushes induced by hormone therapy and neuropathic pain. For frail patients in the palliative stage, pharmacological interactions, their possible side effects and the modalities of their prescription should always be taken into account. In this review, the different classes of antidepressants that can be used in palliative care are described. These classes are briefly compared in terms of efficacy and safety. Suggestions on the best choice according to other symptoms are proposed.

Introduction

This review presents an update of the antidepressants that can be useful in palliative medicine. Antidepressant treatment can be used for several indications—antidepressants, anxiolytics or co-analgesics. In this article, we describe their use in palliative cancer care for depression or major depressive disorder only, and we do not describe the entire management of depression, which should always include education and counselling. This information can be found in a recent article proposing guidelines on the management of depression in palliative cancer care.[1]

Depression is a frequent problem among cancer patients and has been estimated to occur with a frequency of approximately 15% (range 1–77.5%).[2] Often underdiagnosed and undertreated, depression reduces quality of life and aggravates physical symptoms, such as pain and fatigue.[3] Depression has also been reported to reduce adherence with cancer treatment.[4] Moreover, it is an independent predictive risk factor for cancer related mortality.[5]

A recent review of the literature provided evidence that antidepressants are effective in treating depression for patients in

[1]Department of Palliative Care and Rehabilitation Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
[2]Department of Palliative Care, Centre Hospitalier de Lyon-Sud, Hospices Civils de Lyon, Lyon, France
[3]Psycho-Oncology Team, Centre Oscar Lambret, Lille, France

Correspondence to Dr W Rhondali, Department of Palliative Care, Centre Hospitalier de Lyon-Sud, Hospices Civils de Lyon, 165 Chemin du Grand Revoyet, 69495 Pierre-Bénite, France; wadih.rhondali@chu-lyon.fr

palliative care.[6] However, antidepressants are underprescribed in palliative care, probably because of some difficulties in distinguishing 'normal' sadness from major depressive disorder or some reluctance to prescribe another medication for patients already taking several drugs (drug interactions).[7]

Previous studies suggest that for patients with advanced cancer, antidepressants should be reserved for major depressive disorder cases because patients who do not have major depressive disorder will not experience improvement in symptoms, wellbeing or survival.[8]

There are several classes of antidepressant agents: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants. We will not describe the MAOIs as their use should be avoided in palliative care because of the associated side effects (dizziness, dry mouth, diarrhoea, difficulty urinating, headache) and the high risk of serotonin syndrome or hypertensive crisis when associated with medications such as methadone, tramadol or carbamazepine. Except for bupropion, all classes of antidepressant produce their effect by acting via monoaminergic mechanisms (serotonin, norepinephrine or both).[9]

Tricyclic antidepressants (eg, amitriptyline, nortriptyline, doxepin, imipramine)

TCAs inhibit the reuptake of serotonin and inhibit norepinephrine transport in corticolimbic structures. TCAs also inhibit histaminic, cholinergic, and α_1 and α_2 adrenergic receptors, leading to some of the common side effects of these drugs, such as dry mouth, constipation, orthostatic hypotension, drowsiness, dizziness and

cardiovascular toxicity. TCAs are protein bound and are metabolised primarily in the liver. Wide variations of response to antidepressants have been reported between individuals and those variations are mainly explained by patient characteristics such as age, comorbidities and concomitant medication but also by differences in the genetic variant of the enzyme involved in the metabolism of these drugs.

The recommended dosages of TCAs have been proposed empirically, and a recent Cochrane review reported that lower doses of TCAs (75–100 mg/day or less) are equally effective as standard doses but have fewer side effects.[10] When a TCA is prescribed as a co-analgesic, the dose is usually lower (50–75 mg). The long half-life of these drugs enables a 24 h dosing schedule (table 1).

In cases of neuropathic pain, severe depression with melancholic features or associated symptoms, TCAs might be considered as firstline treatment,[11] especially if a parenteral regimen is required (available in France). However, these drugs will not always be appropriate for frail patients, such as those in palliative care, because of the potential for increasing frequency of constipation, confusion and other side effects.

Selective serotonin reuptake inhibitors (eg, sertraline, escitalopram, citalopram, paroxetine, fluoxetine)

SSRIs inhibit the reuptake of serotonin with a better tolerance than TCAs.[12] In a recent meta-analysis on depression treatment in physically well patients, sertraline and escitalopram demonstrated the best profiles of acceptability but similar efficacy as other SSRIs and several SNRIs.[13] There has been no equivalent study comparing types of

Table 1 Main antidepressants available for palliative care patients

Drug	Recommended dose (mg/day)	CYT P450 enzymes involved in metabolism	Contraindications; all antidepressants are contraindicated in patients with a history of hypersensitivity to any component	Accessory effects	Half-life
Amitriptyline	10–300			Pain, appetite stimulant	10–50
Nortriptyline	25–150		Cardiac arrhythmias, myocardial infarction, glaucoma, urinary retention, prostatic hypertrophy, use of MAOI in the past 14 days	Sedative, anxiety, pain, insomnia	20–100
Doxepin	10–300	1A2, 2C9, 2C19, 2D6, 3A4			17 h
Imipramine	25–200				11–25 h
Fluoxetine	20–80	2C9, 2C19, 2D6, 3A4	Concomitant use of MAOIs, liver impairment	Anxiety, insomnia, borderline personality disorder	1–4 days
Sertraline	50–100	2B6, 2C9, 2C19, 2D6, 3A4		Anxiety, post-traumatic stress disorder	26 h
Escitalopram	10–20	2C19, 2D6, 3A4		Anxiety	27–32 h
Citalopram	20–60				35 h
Paroxetine	20–60	2D6, 3A4		Anxiety, post-traumatic stress disorder	21 h
Duloxetine	30–120	2D6, 1A2	Concomitant use of MAOIs or SSRIs, for duloxetine: chronic alcohol use or liver disease	Pain, hot flushes, fibromyalgia	8–17 h
Venlafaxine	37.5–225	2D6		Anxiety, hot flushes	2.5–7.3 h
Milnacipran	50–100	None		Pain, fibromyalgia	8 h
Trazodone	150–375	3A4	None	Insomnia, anxiety	3–9 h
Mirtazapine	15–45	2D6/1A2, 3A4	Concomitant use of MAOIs	Hypnotic, antiemetic, appetite stimulant	20–40 h
Tianeptine	37.5	IIIA3	Concomitant use of MAOIs	Anxiety, erectile dysfunction	2.5 h
Bupropion	100–450	2B6	History of epilepsy, active brain tumours, anorexia nervosa, bulimia, alcohol or benzodiazepine withdrawal	Stop smoking	12–30 h
Agomelatine	25–50	1A2/2C9	Liver impairment	Insomnia	2.3 h

h, hours; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

antidepressants in physical ill or palliative care populations.

The SSRIs, which are metabolised primarily in the liver, have a variety of pharmacokinetic parameters, including protein binding, half-life, active metabolites, elimination rates and the type of CYP enzymes that are responsible for SSRI biotransformation. Fluoxetine and paroxetine are metabolised by cytochrome P450 2D6 and inhibit this pathway, resulting in some drug interactions, such as decreasing analgesic effect of opioids (hydrocodone and oxycodone) or decreasing efficacy and levels of the tamoxifen metabolite, endoxifen. Citalopram, escitalopram and sertraline are metabolised through the 3A4, 2C19 and 2D6 pathways. Respectively, and are less likely to generate negative drug interactions.

The most common side effects reported for SSRIs are nausea, diarrhoea, headache, insomnia, jitteriness, fatigue and sexual dysfunction. The most severe adverse effect is the serotonin syndrome, a potentially life threatening adverse drug reaction caused by excess serotonin in the CNS. A recent case report suggested that the risk of this syndrome is increased for patients using strong opioid medications..[14] Recommended doses for SSRIs are summarised in table 1.

Serotonin–norepinephrine reuptake inhibitors (eg, venlafaxine, duloxetine, milnacipran)

SNRIs work by inhibiting the reuptake of serotonin and norepinephrine. They differ from TCAs by their stronger 5-HT effect.[15]

Compared with SSRIs, the efficacy of SNRIs on neuropathic pain is higher and has been reported to be equivalent to that of TCAs.[16]

Similar to SSRIs, SNRIs are metabolised primarily in the liver and are transformed by cytochrome enzymes. Cytochrome enzymes involved in SNRI biotransformation as well as recommended doses are summarised in table 1.

The most common side effects of SNRIs are headache, somnolence, dizziness, insomnia, nausea, dry mouth, constipation, anorexia, mydriasis, sexual dysfunction and weakness. Because elevated blood pressure can also occur, patients at risk of hypertension and heart disease who are taking SNRIs should have their blood pressure monitored.

Atypical antidepressants (eg, trazodone, mirtazapine, tianeptine, bupropion, agomelatine)

Trazodone is a serotonin antagonist and reuptake inhibitor. Trazodone also has anxiolytic and hypnotic effects. It has no anticholinergic activity, weak α_1 adrenergic activity and moderate antihistaminic activity. The main side effects of trazodone are sedation and orthostatic hypotension. Trazodone is empirically used in geriatric patients with agitation and insomnia.[17] The most common side effects are dry mouth and orthostatic hypotension; priapism occurs rarely.

Mirtazapine is a tetracyclic antidepressant that acts by increasing norepinephrine and serotonin levels (noradrenergic and specific serotoninergic antidepressants). It is a strong antagonist of

histaminic (H_1) adrenergic and muscarinic receptors. The most common side effects are sedation, constipation, dry mouth, dizziness and weight gain. Mirtazapine was recently reported to be one of the most effective antidepressant drugs for non-physically ill patients.[13] In a meta-analysis which compared the efficacy and tolerability of 12 common antidepressants (including SSRIs and SNRIs), mirtazapine had superior efficacy and tolerability. An expert opinion (using a Delphi process) reported mirtazapine as one of the best antidepressants for treating depression in the palliative care setting (along with citalopram), probably because of its accessory effects (eg, appetite stimulant and sedative qualities).[18]

Tianeptine is an antidepressant that probably involves glutamate in its mechanism of action.[19] It has strong antidepressant and anxiolytic effects with good tolerance (eg, less sedative effect, few anticholinergic and cardiovascular adverse effects).[19] Tianeptine is metabolised in the liver and has a half-life of only 2.5 h. The recommended dose is 3 tablets per day (morning, midday and evening). It is frequently used for elderly patients. The most reported side effects of tianeptine are dry mouth, constipation, dizziness, drowsiness and insomnia.

Bupropion have a specific mechanism of action; it is not fully understood but it seems to work by binding and inhibiting the dopamine and norepinephrine uptake pumps.[20][21] Bupropion is metabolised in the liver into several active metabolites. The most reported side effects are dizziness, headache, insomnia, nausea and dry mouth, and it is associated with an increased risk

of seizure. Bupropion has a lower risk than other antidepressants for causing sexual dysfunction and weight gain. There are no studies on its use in cancer patients in palliative care.

Agomelatine is a melatonin (MT) analogue drug with a specific mechanism of action. It acts as an MT1/MT2 melatonergic receptor agonist and as a 5-HT2C antagonist. Because it does not bind to 5-HT2A receptors, agomelatine has a more favourable side effect profile than SSRIs. Agomelatine is metabolised in the liver. A recent review reported a similar efficacy to venlafaxine and sertraline, and a higher efficacy than fluoxetine.[22] There are no studies on its use in cancer patients in palliative care.

Psychostimulants (eg, methylphenidate, modafinil)

For patients with a short life expectancy, depression can be managed with psychostimulants, which take effect quickly (within 24–48 h). Psychostimulants are reported to be generally well tolerated although common side effects include agitation, confusion and insomnia.[11 23] Clinicians should be alert to cognitive disturbances such as delirium. In cases of severe depression, patients with longer life expectancy can benefit from starting a psychostimulant while waiting for a prescribed antidepressant agent to be fully effective (4–6 weeks).

Efficacy

Among the antidepressant drugs available, mirtazapine, escitalopram, venlafaxine and sertraline have been reported as the most effective for physically well patients.[13] For palliative cancer care, a recent literature review reported that there was still not enough evidence to answer the question of which antidepressant clinicians should choose for their patients.[6]

All antidepressants have a delayed onset of clinical effect (4–6 weeks) but they are not equivalent regarding their accessory effects or functions.[6] The side effects should be assessed in the first week of treatment and depression should be reassessed (eventually using a specific tool) every 2 weeks. Regarding the assessment, choice of antidepressant in palliative care should be dictated by the patient's symptoms, presented by the patient (eg, pain, poor appetite, insomnia, hot flushes, etc), as well as the potential toxicity.[6] Furthermore, patients with limited life expectancy (less than 4 weeks) should probably received psychostimulants rather than antidepressants.

Tolerability and safety

In the general population, as for cancer patients, SSRIs are reported to be safer and better tolerated than TCAs, especially by the elderly.[6 24] However, the review from Rayner et al showed little difference between the two classes of drug regarding adverse events.[6] TCAs are associated with a higher risk of dry mouth, blurred vision, dizziness, constipation and tremor whereas SSRIs are associated with a higher frequency of nausea, diarrhoea, insomnia and headache.[25]

Clinical practice propositions

Treatment should be started as soon as the diagnosis of major depressive disorder is made. The patient should be regularly reassessed and treatment efficacy should be assessed at least 4 weeks after initiation of the antidepressants (a first assessment can be done at 2 weeks looking for a partial response). In the case of a partial or no response at 4–6 weeks of antidepressant medication at an adequate dosage, increasing the dose should be considered. Cases of non-response should be discussed on a case by case basis (switching to an antidepressant from a different class, switching to another antidepressant from the same class or combining antidepressants from different classes). Treatment should be continued for 6–9 months.

Palliative care patients often develop multiple severe symptoms. They are more likely than patients not in palliative care to present with depression associated with symptoms such as pain and fatigue. Thus firstline treatment should be chosen after considering not only the associated symptoms but also the potential side effects.

If a patient presents with both depression and anxiety, SSRIs such as citalopram, escitalopram and paroxetine or NSRIs such as venlafaxine should be favoured.

Venlafaxine has been reported to be effective in treating depression that has not previously responded to SSRIs. Agomelatine and mirtazapine are favoured for cases of insomnia, mirtazapine for anorexia or nausea, mirtazapine and fluoxetine for fatigue, duloxetine and milnacipran for pain, venlafaxine for hot flushes and nortriptyline for agitation or suicidal ideation. In cases of severe liver failure, tianeptine or milnacipran can still be used.

In the case of severe liver failure, we can still use tianeptine or milnacipran. Venlafaxine has been reported to be effective in treating depression that has not previously responded to SSRIs.

Conclusion

Antidepressant prescription must follow a logical and rational protocol and cannot be prescribed without a thorough assessment of the medical and psychosocial situation, especially in the palliative care setting. The patient's comorbidities, potential pharmacological interactions and benefit–toxicity ratio must be taken into account. Antidepressants, prescription, if well prescribed, can alleviate patient suffering and, to optimise efficiency, should be used in combination with psychotherapeutic interventions.

> # Key message
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> Antidepressant drugs have a place in palliative care and the best effectiveness will be achieved by experts who know their pharmacology, clinical effects, side effects and contraindications in this category of patients.

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