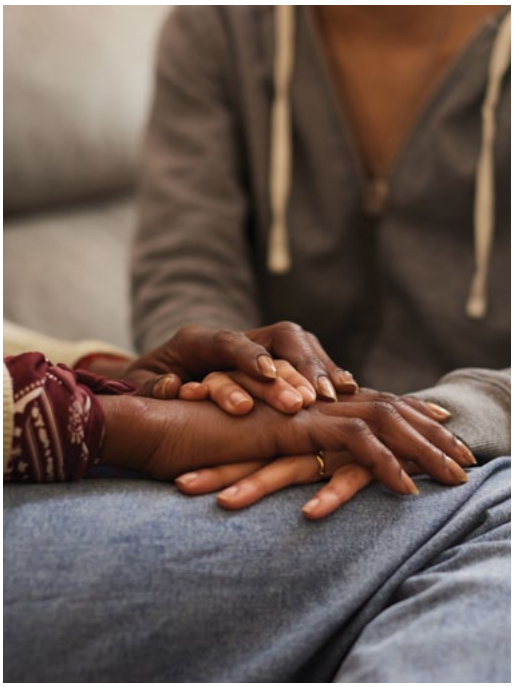
Palliative management of depression in advanced cancer



Taylan Gurgenci, Jones Chen, Benjamin Jull, Claire Stokes, Robert Waugh, Phillip Good

Background
Patients with advanced cancer are often psychologically distressed. Some are depressed, and others might not fit neatly into diagnostic categories. Yet, their suffering is real and worthy of attention.

Objective
This article outlines the evidence-based management of depression in patients with advanced cancer.

Discussion
Throughout this article, the term depression is used loosely, and an approach to patients who might not strictly meet diagnostic criteria is included. The limits of the evidence are emphasised in the hope that general practitioners will feel confident to rely on their own clinical judgement and intimate knowledge of their patients to manage their depression.

DEPRESSION in advanced cancer is hard to diagnose and manage. There are biological mimics of depression that need to be excluded. Once excluded, the clinician then needs to differentiate depression from a normal grief reaction to an emotive diagnosis, existential distress or some other psychological state that is not best characterised as depression. After the diagnosis, the clinician needs to consider drug–drug interactions with oncology treatment as well as other comorbidities.

What is depression?

Defining depression is not the focus of the article, but it is important that we all have the same concept in mind. We accept the standard psychiatric definition that is clearly elucidated in a recent Australian consensus statement.[1] Some difficulty distinguishing depression from other psychological states is inevitable. We agree with the approach outlined in an excellent article by Stone et al previously published in *AJGP*.[2] A quotation from the article summarises their approach well:

> *Psychiatric diagnosis is not a simple act of classification. As Sadler would say, we are not botanists. The GP's* (general practitioner's) *job as a clinician is to behave more like a gardener: understanding botany, but focusing on applying their skills to nurture and support the health of their patients within their rich contexts. To do so, the GP's diagnosis must be accurate, comprehensive and helpful.*

So, in agreement with the approach taken by Stone et al, the focus of the differential diagnosis outlined below is on excluding other physical entities that have well-established, different management approaches to depression. A detailed review of other psychiatric diagnoses is omitted, though managing comorbid anxiety in the setting of terminal illness is discussed.

Biological mimics of depression in the context of cancer

Common mimics of depression relevant to patients with cancer are outlined in Table 1. A discussion about a few of the important points is given below.

One common mimic is hypothyroidism. Approximately 20% of patients who undergo a hemithyroidectomy develop transient hypothyroidism, but only 4% require treatment.[4] Immune checkpoint inhibitor (ICI)-related hypothyroidism can be due to hypophysitis or direct thyroid involvement.[8] Some studies identify thyroid dysfunction as a positive prognostic sign in ICI-treated patients.[8]

Another common mimic is hypercalcaemia. Routine biochemistry

panels (often abbreviated as CHEM-20 or E/LFT) usually report both total calcium and corrected calcium. The corrected calcium might actually be less accurate than the total calcium in some clinical contexts common to the patient with cancer: hypoalbuminaemia, acute kidney injury, acid–base disorders.[9] The ionised calcium is the gold standard in these states and is measured as part of a venous or arterial blood gas.

Underappreciated issues in antidepressant prescribing for patients with cancer

After biological mimics are excluded and depression is diagnosed, the question becomes how is it best to manage the condition. Non-pharmacological management is outlined in a subsequent section. This section focuses on pharamacological management.

Tamoxifen

One common scenario is prescribing antidepressants to patients on tamoxifen. Tamoxifen is a selective estrogen-receptor modulator used to treat some breast cancers. It is metabolised into the active metabolite, endoxifen, by CYP2D6 (cytochrome P450, family 2, sub-family D, polypeptide 6).

Many researchers have expressed concern that CYP2D6 inhibition could reduce tamoxifen efficacy, in part by reducing endoxifen levels.[10] Others have plausibly argued the risk is overstated.[11] The prudent course is to treat this interaction as being clinically significant until there is more certainty, but not to overstate the significance in situations where it might cause anxiety.

As such, venlafaxine, venlafaxine-XR (extended release), mirtazapine, citalopram and escitalopram represent good prescribing options for patients on tamoxifen. Conversely, fluoxetine, paroxetine and bupropion should be avoided where possible. Where the patient is taking a medication from the latter group, switching to a drug from the former group is recommended. An excellent Australian reference exists to guide the switching.[12]

Dysphagia

Patients with cancer often develop temporary or permanent dysphagia or odynophagia. Oropharyngeal mucositis caused by systemic therapy and radiation oesophagitis are common causes of this. Citalopram, escitalopram and mirtazapine can be crushed before administration, which can make them easier for patients to take. Furthermore, escitalopram is available as an oral solution and mirtazapine in a disintegrating tablet form, both of which might be easier to administer.

Benzodiazepines in anxiety

Antidepressants are often used to treat anxiety disorders as well, particularly as the downsides to the routine use of benzodiazepines are increasingly acknowledged.[13] Some potential risks include tolerance, addiction, withdrawal reactions at high doses and long-term cognitive impairment and dementia risk. As these are less problematic in patients receiving palliative care, the benefits – namely, that the class is widely accepted to have an anxiolytic effect – are more compelling. Were patients to end up on high oral doses, benzodiazepines can be given subcutaneously to avoid precipitating withdrawal during the terminal phase.

When to refer

A referral to a psychiatrist might be warranted if there is concern about medication interactions, ambiguity around the diagnosis (eg depression vs bipolar affective disorder), the clinician feels a request for voluntary assisted dying is being driven by an untreated mental health disorder rather than an expression of autonomy or the prognosis is very short, in which case a psychostimulant

Table 1. Differential diagnosis of depression

Diagnosis	Investigations	Oncology-specific notes
Hypothyroidism	TSH±TFTs	• Expected after thyroidectomy; 1 in 25 patients need replacement after hemithyroidectomy • Occurs in ~44% of patients treated with immune checkpoint inhibitors[3,4]
Hypercalcaemia	Routine biochemistry, ideally confirmed with ionised calcium (ie venous blood gas)	• Most common mechanism is PTHrP mediated • Others include osteolytic metastases, overproduction of 1,25-dihydroxyvitamin D and PTH-mediated hypercalcaemia[5]
Steroid-induced	History	• Corticosteroids (might not be dose related)[6]
Parkinsonism	History and examination	• Consider commonly used anti-nausea medications (metoclopramide, haloperidol, olanzapine) as unmasking or causing this
Anaemia	Full blood count	• Treatment-induced myelosuppression; marrow failure due to infiltration; decreased dietary intake of iron and folate
Cerebral metastases	MRI is gold standard. Contrast-CT is a practical alternative	• Treatment options might include dexamethasone 8 mg orally or subcutaneously twice daily (short term), radiotherapy or surgery[7]

CT, computed tomography; MRI, magnetic resonance imaging; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; TSH, thryoid-stimulating hormone; TFTs, thyroid function tests.

might be indicated. Furthermore, psychiatric referral might be of value in more straightforward cases that nevertheless do not respond to first-line treatment.

Effectiveness of pharmacotherapy for depression in advanced cancer

Investigators have studied stimulants, antidepressants or a combination of the two; there are excellent contemporary review papers available as well as a 2023 Cochrane review.[14,15] The authors of the Cochrane review were at pains to stress how poor quality the evidence was and the limits of generalising from it. The general consensus is that it is reasonable to try antidepressants but there is little high-quality evidence to support their use.

This is a difficult clinical problem for which to get high-quality evidence. Selective-serotonin reuptake inhibitors (SSRIs), to take one class, are expected to have an effect in weeks to months after commencement.[16] The expected attrition rate due to ill health or death for just a two-week trial in palliative patients with advanced cancer is at least 20%.[17] Clinical trials going for months would have a higher attrition rate. They would therefore be criticised for missing data, irrespective of their methodology for dealing with it. Furthermore, minimum clinically important differences in psychiatric outcome measures are not well established in this population.[18] This makes it hard to know how clinically relevant statistical differences between intervention arms truly are.

Non-pharmacological management of depression in advanced cancer

There is no non-pharmacological treatment for depression that is unequivocally beneficial in patients with advanced cancer.[14] Treatments include cognitive behavioural therapy (CBT), counselling, hypnosis, dignity therapy, psychotherapy, mindfulness, group therapy, meaning-centred therapy, music and aromatherapy, among others.[14]

Clinicians should recognise the opportunity cost of attending such treatments for patients with limited life expectancy.[19] Keeping this concept of time toxicity in mind, our approach is to offer those modalities we think are relevant to the patient. Patients tend to make it quite clear whether they are finding these sorts of treatments helpful; given the evidence is not compelling, we do not push them very hard to continue if they are not getting a benefit.

Putting it all together

We try to fix things we are good at fixing. Untreated pain that interrupts sleep and prohibits social activity will make anyone feel down.[20] Patients often worry their symptoms will become severe, and so we regularly check if they are worried about the future.[21] We are often surprised how often patients worry about a specific symptom that is both unlikely to occur and easy to manage. Mood often improves after addressing these, but not always.

We ask tactfully about how patients and their loved ones are faring. Often patients with young children are stressed about how their children will cope when they are gone. Appropriately trained counsellors can effectively help children before and after their parent dies.[22] They can also help partners and other family members. Financial stress is often significant, and time away from work for both patient and carer adds to this.[23] We prioritise any paperwork that relieves financial stress.

We explore what people mean by depression and where they are coming from. We attend to their psychological and spiritual distress. We also offer them an appointment with a psychologist, other non-pharmacological modalities that we think are relevant to the patient (refer above) and/or medication (refer above).

Patients who regularly practise their faith often have good pastoral support from their religious communities. We offer pastoral care support to all patients. This is easier in a hospital setting and particularly in a faith-based health service where many of the authors work. We have had patients who have rekindled their religious practice and others who have practised for the first time. Sometimes, the opposite happens and terminal illness triggers a crisis of faith. Finally, atheists and agnostics sometimes appreciate dialogue from a different perspective, even if they do not share a common religious tradition with the pastoral care representative.

Responding to a patient who wishes to hasten death

Studies have shown that common reasons for patients who wishes to hasten death are:[24]

- fear of being a burden
- loss of independence
- loss of control
- fear of the dying process
- a desire to live well.

A desire to hasten death does not always mean a request for voluntary assisted dying (VAD). When a patient makes a statement such as 'I just want to die', a clinician should empathetically explore. Communication skills such as 'tell me more' allow us to understand where the patient is coming from. Empathic statements that acknowledge the patient's emotions can connect us with the patient.

Advance care planning empowers the patient to have control. Well-resourced carer support for families can relieve a person's fear of being a burden. Discussion of how a person's symptoms can be well managed can alleviate the fear of the dying process. Listening to the patient's narrative allows a clinician to sit in the space of being a healer. Discussing how palliative care can improve a person's quality of life can bring hope to the person and their family.

The current law around initiating discussions about VAD varies between states. In Victoria and South Australia, a clinician cannot initiate conversations about VAD. In New South Wales, Queensland, Western Australia and Tasmania, a clinician can initiate a VAD conversation, but only if the clinician gives information about palliative care and other available treatments in the same conversation.[25]

Detailed exploration of eligibility criteria, assessment and other components of the VAD process are outside the scope of this paper.

Conclusion

Patients with terminal cancer are often depressed or unhappy or both. We do not advocate routine screening for depression because the screening tools are not validated for this population and the best management for positive cases is ambiguous.

Two of the better known non-pharmacological treatment modalities are CBT and dignity therapy. Most trials assessing pharmacological management

have used either antidepressants or psychostimulants. A recent Cochrane review said published trials were of low quality.

In this context, we suggest a patient-centred approach in which the clinician attends to a person's physical, psychosocial and spiritual needs. Patients can be offered various treatments, but they should not be pushed if they decline or discontinue them.

Authors

Taylan Gurgenci FRACGP, FAChPM, Palliative Care Specialist, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; Mater Research Institute, University of Queensland, Brisbane, Qld

Jones Chen FRACGP, FAChPM, Palliative Care Specialist, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld

Benjamin Jull MPharm, FANZCAP (Generalist, MentalHlth), Acting Senior Mental Health Pharmacist, Pharmacy Department, Gold Coast Hospital and Health Service, Gold Coast, Qld

Claire Stokes FRACGP, Palliative Care Research Fellow, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; General Practitioner, Camp Hill Medical Centre, Brisbane, Qld

Robert Waugh MBBS, Psychiatry Registrar, Consultation Liaison Psychiatry Service, Mater Adult Hospital, Brisbane, Qld

Phillip Good FRACP, PhD, Director of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; Director, Palliative Care, St Vincent's Private Hospital, Brisbane, Qld; Professor, Faculty of Medicine, Mater Research Institute, The University of Queensland, Brisbane, Qld

Competing interests: None.

Funding: None.

Provenance and peer review: Commissioned, externally peer reviewed.

Correspondence to:
t.gurgenci@uq.edu.au

References

1. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021;55(1):7–117. doi: 10.1177/0004867420979353.
2. Stone L, Waldron E, Nowak H. Making a good mental health diagnosis: Science, art and ethics. Aust J Gen Pract 2020;49(12):797–802. doi: 10.31128/AJGP-08-20-5606.
3. Iwamoto Y, Kimura T, Dan K, et al. Immune checkpoint inhibitor-induced hypothyroidism predicts treatment response in Japanese subjects. Front Endocrinol (Lausanne) 2023;14:1221723. doi: 10.3389/fendo.2023.1221723.
4. Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: Systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 2012;97(7):2243–55. doi: 10.1210/jc.2012-1063.
5. Mirrakhimov AE. Hypercalcemia of malignancy: An update on pathogenesis and management. N Am J Med Sci 2015;7(11):483–93. doi: 10.4103/1947-2714.170600.
6. Yagi Y, Takahashi Y, Ogata Y, et al. Oral corticosteroid dosage and clinical presentation of psychiatric conditions after steroid use: A consultation-liaison psychiatry service's experience. Neuropsychopharmacol Rep 2021;41(4):471–75. doi: 10.1002/npr2.12204.
7. Sharma A, Das AK, Jain A, Purohit DK, Solanki RK, Gupta A. Study of association of various psychiatric disorders in brain tumors. Asian J Neurosurg 2022;17(4):621–30. doi: 10.1055/s-0042-1757437.
8. Chera A, Stancu AL, Bucur O. Thyroid-related adverse events induced by immune checkpoint inhibitors. Front Endocrinol (Lausanne) 2022;13:1010279. doi: 10.3389/fendo.2022.1010279.
9. Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J. Things We Do for No Reason™: Calculating a "Corrected Calcium" level. J Hosp Med 2021;16(8):499–501. doi: 10.12788/jhm.3619.
10. Hansten PD. The underrated risks of tamoxifen drug interactions. Eur J Drug Metab Pharmacokinet 2018;43(5):495–508. doi: 10.1007/s13318-018-0475-9.
11. Bradbury M, Hutton B, Beltran-Bless AA, et al. Time to update evidence-based guideline recommendations about concurrent tamoxifen and antidepressant use? A systematic review. Clin Breast Cancer 2022;22(3):e362–73. doi: 10.1016/j.clbc.2021.10.003.
12. Keks N, Hope J, Keogh S. Switching and stopping antidepressants. Aust Prescr 2016;39(3):76–83.
13. Hirschtritt ME, Olfson M, Kroenke K. Balancing the risks and benefits of benzodiazepines. JAMA 2021;325(4):347–48. doi: 10.1001/jama.2020.22106.
14. Perusinghe M, Chen KY, McDermott B. Evidence-based management of depression in palliative care: A systematic review. J Palliat Med 2021;24(5):767–81. doi: 10.1089/jpm.2020.0659.
15. Vita G, Compri B, Matcham F, Barbui C, Ostuzzi G. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev 2023;3(3):CD011006.
16. Boschloo L, Hieronymus F, Lisinski A, Cuijpers P, Eriksson E. The complex clinical response to selective serotonin reuptake inhibitors in depression: A network perspective. Transl Psychiatry 2023;13(1):19. doi: 10.1038/s41398-022-02285-2.
17. Shelby-James TM, Hardy J, Agar M, et al. Designing and conducting randomized controlled trials in palliative care: A summary of discussions from the 2010 clinical research forum of the Australian Palliative Care Clinical Studies Collaborative. Palliat Med 2012;26(8):1042–47. doi: 10.1177/0269216311417036.
18. Chyr LC, Sauers EG, Dy SM, Waldfogel JM. The application of minimal clinically important differences in palliative research: Interpretation of results of a systematic review. J Pain Symptom Manage 2022;64(6):e363–71. doi: 10.1016/j.jpainsymman.2022.08.008.
19. Gupta A, Eisenhauer EA, Booth CM. The time toxicity of cancer treatment. J Clin Oncol 2022;40(15):1611–15. doi: 10.1200/JCO.21.02810.
20. Ko HJ, Seo SJ, Youn CH, Kim HM, Chung SE. The association between pain and depression, anxiety, and cognitive function among advanced cancer patients in the hospice ward. Korean J Fam Med 2013;34(5):347–56. doi: 10.4082/kjfm.2013.34.5.347.
21. Parry R, Land V, Seymour J. How to communicate with patients about future illness progression and end of life: A systematic review. BMJ Support Palliat Care 2014;4(4):331–41. doi: 10.1136/bmjspcare-2014-000649.
22. Haine RA, Ayers TS, Sandler IN, Wolchik SA. Evidence-based practices for parentally bereaved children and their families. Prof Psychol Res Pr 2008;39(2):113–21. doi: 10.1037/0735-7028.39.2.113.
23. Khan HM, Ramsey S, Shankaran V. Financial toxicity in cancer care: Implications for clinical care and potential practice solutions. J Clin Oncol 2023;41(16):3051–58. doi: 10.1200/JCO.22.01799.
24. Monforte-Royo C, Villavicencio-Chávez C, Tomás-Sábado J, Balaguer A. The wish to hasten death: A review of clinical studies. Psychooncology 2011;20(8):795–804. doi: 10.1002/pon.1839.
25. Waller K, Del Villar K, Willmott L, White BP. Voluntary assisted dying in Australia: A comparative and critical analysis of state laws. UNSWLJ 2023;46(4):1421–70.

correspondence **ajgp@racgp.org.au**