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Psychopharmacologic Treatment of Depression in Patients With Cancer: A 2013 Update

Abstract: Depression is highly comorbid with various malignancies, and when present often increases suffering, decreases medical adherence, and can be associated with worse clinical outcomes. High-quality meta-analysis suggests a prevalence rate of major depression in cancer patients of around 16%; men and women are equally afflicted. Widely available screening instruments such as the PHQ-9 have demonstrated reliability in both detecting depression symptoms and measuring response to therapy in cancer patients. Certain cancers and some cancer treatments seem to confer increased risk for new-onset or recurrent depression, and there is a wide range of contemporary antidepressant medications, as well as older agents, that can be helpful. Under some circumstances, novel treatments may also have a role.

Introduction

Depression is widely recognized as a major cause of suffering and disability worldwide (1). When it occurs comorbidly with major medical illness, depression imposes adverse synergy, with overall worse clinical outcomes, greater health care costs, and more distress than in nondepressed patients. Depression in cancer is no exception: depressed cancer patients often demonstrate greater suffering (2), poorer medical adherence (3), longer hospital stays (4), lower quality of life (5), and even reduced cancer survival (6) when compared with nondepressed persons with cancer.

Prevalence

Nearly 5 decades of study have yielded widely varying reports of the prevalence of depressive disorders in cancer patients, ranging from 2%−69% (7–11). A recent careful meta-analysis by Mitchell et al. (12) provides the most useful estimates to date. Of 438 studies in the world literature, this group culled 94 of sufficient quality to allow rigorous analysis. Twenty-four of those studies took place in palliative care settings; the remaining 70 were performed in active-treatment hematology and oncology clinics. In total these analyses encompassed more than 14,000 patients from 20 countries and yielded rates of DSM or ICD major depression of approximately 16%, with no significant difference between active-treatment and palliative care patients. DSM "minor depression" was less prevalent in palliative care settings compared with hematology/oncology settings (9.6 versus 19.2%) as were adjustment disorders (15.4 versus 19.4%) and anxiety disorders (9.8% versus 10.3%). In contrast to studies of general populations without major medical illness in which depression afflicts women 2–3 times more commonly than men, there were no significant associations between mean age or gender and the likelihood of developing depressive illness.

Making the diagnosis

The field of psycho-oncology has benefitted greatly from broad efforts to improve recognition of mood disorders in general medical settings. Combined with widely available evidence-based treatment

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guidelines (13) and consensus screening recommendations (14), it is increasingly possible in a review such as this one to make assertions that are generally representative of majority viewpoints within the field.

SCREENING

Screening for various forms of psychosocial distress is routine in many community cancer clinics and NCI-designated cancer centers. Formal depression screening is an important part of that surveillance, and multiple validated tools are available for that purpose. Since brevity, simplicity, and the option of paper or electronic patient-completion are important elements of a successful screening effort, the PHQ−9 (15) and its shortened counterpart, the PHQ−2 (16) have become "screeners of choice" in many settings. The PHQ−9 has also been validated in cancer patient populations (17) and performs as well or better than other screening measures (18). The PHQ−9 compares favorably to the "gold standard" Structured Clinical Interview for DSM (SCID) and can be used along with clinical follow-up as a measure of response to antidepressant treatments. In a recent longitudinal comparison in a depressed population of cancer patients, The Hopkins Symptom Checklist 20, the Mental Health Inventory, and the PHQ−9 demonstrated similar performance and reliability at baseline and as a measure of change in response to treatment (19).

DIAGNOSTIC CONFIRMATION OF SCREENING RESULTS

Screeners were not designed to make diagnoses, and no screener has demonstrated 100% sensitivity or specificity with subsequent "gold standard" diagnostic evaluations for major depression, even in medically well patients being evaluated exclusively for mood symptoms. Given the added medical complexity of depressed patients with cancer and the attendant considerations necessary to make psychopharmacologic treatment decisions, good care requires a diagnostic evaluation by a duly-trained and capable clinician.

Physical symptoms commonly experienced by cancer patients—particularly fatigue, appetite changes, malaise, and disturbed sleep—overlap with some of the DSM "check list" symptoms of depression, and this led some years ago to the development of many alternative diagnostic schemas. These included rating scales that emphasized emotional and cognitive depression symptoms and de-emphasized physical ones (e.g., the Hospital Anxiety and Depression Scale [20]), the so-called Endicott "substitutive" criteria that a clinician could use to replace physical symptoms found in the DSM checklist with observations such as the appearance of fearfulness or depression, and other approaches. Comparative trials demonstrated high concordance in making the depression diagnosis regardless of which schema was used (21), with predictable differences in sensitivity and specificity based on inclusion or exclusion of overlap symptoms. As the tolerability of treatments for depression has improved, and as the consequences of missed diagnosis or undertreatment of depression have been understood, there is growing consensus that using standard diagnostic criteria is a reasonable strategy

Psychiatrists seeing cancer patients must also remain vigilant to recognize the depressed phase of bipolar disorder, a task which is highly challenging and frequently missed even in medically well mood-disorder patients (22). This is important not only for the purposes of avoiding the risks of antidepressant-induced hypomania/mania or rapid cycling, but also because it is increasingly clear that the depressed phase of bipolar illness typically responds poorly to conventional antidepressant pharmacotherapy even in the absence of induced elevated states (23). Many clinicians find it helpful to inquire with depressed cancer patients about previous periods of spontaneous or medication-related mood elevation, with particular attention to the consequences of any prior exposure to corticosteroids (24).

A more comprehensive review of the management of bipolar disorder-related mood symptoms is beyond the scope of this review, but may be found in the so-called CANMAT Guidelines (25).

For making the diagnosis of a major depressive episode via clinical interview, the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM−5), released in May of 2013, employs a checklist approach familiar to most clinicians (26). It includes requirements for duration (symptoms present for at least 2 weeks), clinically significant distress or impaired functioning, and at least 5 of 9 checklist symptoms, one of which must be depressed mood or anhedonia. A cautionary note directs users not to include symptoms that are "clearly attributable to another medical condition" although such an attribution requires causal inferences and may be irrelevant to treatment decision making.

CANCER BIOLOGY AND DEPRESSION RISK

Some cancers may be more commonly associated with depression, such as pancreatic cancer (27), other GI malignancies, and head and neck tumors (28), and some cancer therapies, such as alpha-interferon, appear to induce depressive symptoms in significant

Table 1. Risk Factors for Depression in Cancer Patients

Factor	Explanation
A. Prior personal history of depressive disorder	
B. Cancer type	Pancreas, head, and neck associated with higher risk than other malignancies
C. Severity of disease	Overall, more advanced disease carries greater depression risk than less advanced disease
D. Chemotherapy regimen	Interferons Interleukin–2 Amphotericin-B Anti-estrogens Clycloserine Glucocorticoids Anti-androgens L-asparaginase Leuprolide Procarbazine Tamoxifen Vinblastine Vincristine

percentages (between 15%−40%) of patients who receive them (29). Chemotherapies that deplete the serotonin precursor L-tryptophan have also been shown in some experimental models to induce depressive symptoms (30).

Table 1 lists cancers and antitumor agents implicated in greater depression risk. These associations have limited clinical value, however; patients don't pick their malignancies, and generally they share their oncologists' preferences to choose chemotherapies based on antitumor efficacy rather than possible neuropsychiatric side effects. Alpha-interferon provides a rare example of what can be done in anticipation of treatment with "depressogenic" chemotherapy: both in the hepatology setting (where interferon is used to treat Hepatitis C) and in the oncology setting (where it is used to treat some melanomas and metastatic renal cell cancers), there is evidence that pretreatment with SSRI-type antidepressants may help prevent the emergence of severe depressive symptoms that could otherwise threaten the patient's ability to complete a course of chemotherapy and induce suicidality (31). Patients, particularly those with premorbid mood disorders, are often now referred to psychiatrists prior to interferon therapy for "clearance," pre-emptive interventions, and closer than usual monitoring during treatment. Pretreatment with SSRIs appears to reduce the incidence of emergent depression during interferon chemotherapy by about 50% (32). A recently published double-blind/placebo-controlled trial of escitalopram in head and neck cancer patients showed a similar 50% reduction in the risk of developing major depression (33).

Much research effort has been dedicated to improving our understanding of the roles of immune-activation, inflammation, and the so-called "pro-inflammatory cytokines" (PICs) in the emergence of a wide range of physical and emotional symptoms, including depression, in patients with cancer and other immune-mediated diseases (34). The so-called "sickness syndrome," observed in humans and other mammals exposed to both experimental and environmental immune stimuli, produces a wide range of illness behavior which overlaps dramatically with the signs/symptoms of major depression. These observations have generated new ideas about the pathophysiology and treatment of depression. A recent proof-of-concept trial of the antitumor necrosis factor agent infliximab in medically well adults with treatment-resistant major depression did not improve mood in all patients but showed trends toward efficacy in patients with higher PICs at study baseline (35).

Pharmacotherapies

Do antidepressants work in medically ill adults?

After decades of equivocal studies and confusing metanalyses, Rayner and colleagues produced a definitive 2010 Cochrane review of the utility of antidepressants in medically ill adults (36) that affirmed the superiority of active drug treatments over placebo. That work has been extended to the oncology and palliative care setting with similar results (37), which leaves the field with reason to have generic confidence about the efficacy of antidepressants in cancer patients, but without guidance based on specific malignancies. In general, efforts to discern evidence of efficacy for malignancy-specific depression treatments has fallen short, as outlined in a recent rigorous look at lung cancer (38). Nonetheless, most experts believe that optimal treatment involves both pharmacotherapy and one form or another of evidence-based psychotherapy (39, 40) with sequencing and stepped-therapy approaches based on patient preferences, symptom severity, and the logistics of access (41). A truly scholarly review of the pharmacology of antidepressants is available to readers who wish for greater depth and breadth than is possible in this brief summary (42). Table 2 lists antidepressant drugs available in North America at the time of this writing.

Table 2. Antidepressants Available in the United States, 2013

Type	Dose (mg/day)	Cautions/Contraindications	Monitoring/Special Considerations
SSRIs			All SSRIs have antiplatelet properties and may confer bleeding risk which is compounded by coadministration with NSAIDs, warfarin, clopidogrel
Citalopram	5–20	Dose-dependent QT prolongation risk Avoid in pts c/ familial long QT syndrome; K or Mg abnormal see FDA product insert warning and text	
Escitalopram	5–40		
Fluoxetine	5–80	Potent P450 2D6, 3A4 inhibitor	
Fluvoxamine	25–200	IA2 inhibitor	
Paroxetine	5–60	Potent 2D6 inhibitor	
Sertraline	25–200		
Vilazodone	10–40		
SNRIs			
Desmethylvenlafaxine	50–200		
Duloxetine	20–60	Avoid in pts with alcohol abuse or liver disease	Avoid use if CrCl≤30 or hepatic impairment
Venlafaxine	75–225	May elevate BP at doses>200 mgs/day	
Levomilnacipran	40–120		Renally excreted; avoid use in renal failure
Atypicals			
Bupropion	100–450	Lowers seizure threshold particularly at higher doses in nonsustained release formulations Potent 2D6 inhibitor	Max 100 mg/d in cirrhosis No renal recommendations
Maprotiline	25–225	Potent antihistaminic and anticholinergic	No renal or hepatic recommendations
Mirtazapine	7.5–90		No specific recommendations
Nefazodone	50–300	Rare (1/250,000) fulminant hepatic failure	No renal recommendations Avoid in liver disease
Tricyclics		All TCAs carry risk of: • Cardiac arrhythmia • Orthostatic hypotension • Urinary obstruction • Dry mouth • Constipation	For all TCAs: • Consider TDM to manage safe blood levels • Unmeasured OH- metabolites accumulate in renal failure and may be arrhythmogenic • Suggest d/c or change to non TCA agent in renal or hepatic failure
Amitriptyline	10–300		
Amoxapine	25–600		
Clomipramine	25–250		
Desipramine	25–150		
Doxepin	10–300		
Nortriptyline	10–150		
Imipramine	10–300		
Trimipramine	25–200		
Protriptyline	15–60		
Monoamine oxidase inhibitors		All MAOIs contraindicated for coadministration with SSRIs/SNRIs/Atypicals/ Meperidine/Tramadol/ sympathomimetics/ linezolid	Regular BP checks MedicAlert Bracelets Drug Interaction Cautions in Medical Record
Isocarboxazid	10–60		
Phenelzine	15–90		
Tranylcypromine	10–60		
Selegiline patch	6–12	Fewer dietary restrictions than other MAOIs at FDA-approved low doses	

Overview on drug interactions

Much has been written in the last two decades about pharmacokinetic and pharmacodynamic drug interactions associated with antidepressant medications. Although a review of these issues is beyond the scope of this article, sophisticated oncology drug interactions databases (43) and computer-assisted studies of large populations have begun to sort out the question of whether antidepressant pharmacotherapies are actually associated with drug-drug interactions (DDIs) in patients being simultaneously treated for a variety of cancers. For example, in a recent retrospective analysis of nearly 9000 patients and nearly 40,000 prescriptions for oral anticancer drugs in Singapore, an overall potential DDI rate of about 5% was noted (44). Age, male gender, and prednisolone seemed to increase risk for theoretical DDIs, and only one antidepressant (paroxetine) appeared in the analysis, specifically in relation to coprescription with tamoxifen, a rare event. A thorough discussion of P450 2D6-mediated drug interactions with tamoxifen follows in the section titled "Special Considerations."

In another digital analysis of a smaller cohort of 910 cancer patients on antidepressants, Chan et al (45) identified 281 (31%) simultaneously being treated with oral anticancer drugs. Their database identified a potential DDI rate of 21% among 17 drug pairs. However only three of those drug pairs (tamoxifen/paroxetine, tamoxifen/fluoxetine, and tamoxifen/fluvoxamine) corresponded to documented DDIs considered of significance, all involving the now-controversial question of whether inhibition of tamoxifen biotransformation to endoxifen meaningfully reduces tamoxifen's efficacy. (Please also see "Special Considerations.")

Riechelmann et al. (46) reported on 100 hospitalized Brazilian cancer patients, whose charts were abstracted for potential DDIs. Of 180 potential drug interactions, 18% were judged "severe," 57% "moderate", and 25% "minor." SSRI coadministration with tramadol, which has occasionally been linked to serotonin syndrome, was described as one of the more common findings. In a study of palliative care patients, the same group of investigators identified two other potential interactions implicating antidepressants: SSRIs plus risperidone (serotonin syndrome risk) and SSRIs plus NSAIDs (increased GI bleeding risk).

SSRIs. SSRI antidepressants are generally the agents of first-choice in both medically well and medically ill adults with depression. Over the 25 years since the introduction of fluoxetine to the U.S. market, SSRIs as a class have demonstrated their overall safety, tolerability, and efficacy—both in medically well and medically ill populations—and have earned worldwide first line status and preferability over the older, better established tricyclics (47). In general populations, all SSRIs are more or less equally effective as antidepressants and it is reasonable to infer the same to be true in cancer patients. Their utility in a specific situation often devolves to side effect profile (of which there are small differences among agents); potential for drug interactions (see below); dose formulations (cuttable pill versus capsule versus liquid); multidetermined individual responses (the single strongest predictor of therapeutic drug response is prior response to that agent); pharmacy insurance benefits considerations (what drug the patient can actually get access to); patient/clinician beliefs, and other matters.

By virtue of their shared mechanism of selectively inhibiting the reuptake of serotonin, all SSRIs have some common side effects. The acute inhibition of serotonin reuptake in peripheral and central tissues is responsible for many of the acute side effects associated with treatment initiation: nausea, loose stools, tremulousness, diaphoresis, and appetite suppression, sleep changes, and libido changes and delayed orgasm both in men and women. Many of these symptoms attenuate with time. Some of the more serious class side-effects of note in an oncology population include SIADH/hyponatremia, platelet dysfunction characterized by petechiae or bruising, and serotonin syndrome.

Citalopram is among the most widely prescribed antidepressants in North America. It is generally well tolerated, is available in pill and liquid forms, and is dosed once daily. Citalopram is a weak inhibitor of P450 2D6 with low likelihood for altering the pharmacokinetics of other agents. In 2011 the FDA issued a warning that citalopram was associated with dose-dependent QT prolongation and risk for Torsades des Pointes; daily dose recommendations were reduced to a maximum dose of 40 mg (48). The FDA caution identified Familial Prolonged QT Syndrome as a primary risk factor but also identified hypokalemia and hypomagnesemia as risk factors needing correction if the agent were to be used. Since these electrolyte abnormalities are not uncommon in patients undergoing cancer chemotherapy, the FDA's warning might argue against de novo selection of citalopram in a patient undergoing systemic therapies for cancer. A more difficult question, for which there is no available answer, is whether a patient on maintenance therapy with citalopram who now comes to cancer chemotherapy should be switched to a different antidepressant medication. Since the FDA issued its warning two large trials have been

published casting doubt on the Torsades risk findings (49, 50) but clinical psycho-oncology is probably not the best venue in which to resolve the matter.

Escitalopram, one of the two stereoisomer metabolites of citalopram, has also been widely prescribed. It, too, comes in pill and liquid forms for once daily dosing. Available since 2002, escitalopram was marketed as potentially more effective and with more rapid onset of efficacy than its parent molecule, citalopram. In the FDA's safety reanalyses mentioned above, escitalopram did not appear to be associated with increased cardiac rhythm risk and carries no product warnings in this area. Escitalopram is a weak inhibitor of P450 2D6 with low likelihood for altering the pharmacokinetics of other agents.

Fluoxetine is the first of the SSRI class, arriving in the United States in 1987. It is available in capsule, tablet, liquid, and once-weekly capsule forms. The once-weekly delivery mode is feasible because of the very long half-life of the parent molecule and its active metabolite norfluoxetine (4 and 9 days, respectively). This characteristic may make fluoxetine an effective antidepressant pharmacotherapy for cancer patients with intermittent bowel obstruction or other circumstances that may require extended NPO periods. Among SSRIs, fluoxetine is one of the more potent inhibitors of the liver isoenzymes P450 2D6 and 3A3/4, which confers upon it the potential to significantly alter the pharmacokinetics of other prescribed agents.

Paroxetine is available in capsule, tablet, liquid, and once-daily controlled release forms. Paroxetine is experienced by many patients as the most sedating of the SSRIs, which can be beneficial in highly anxious patients, and which makes bedtime dosing advantageous. Among SSRIs it is the most potent inhibitor of P450 2D6. Paroxetine cessation often requires lengthy and cautious downward titration to avoid an uncomfortable discontinuation syndrome. This may make it a poor choice for patients with unreliable GI function, intermittent obstruction, and anticipated surgeries requiring more than a day of NPO status. In June 2013, paroxetine was approved by the U.S. FDA as a once-daily treatment for menopause-related hot flashes in women (51).

Sertraline is available in tablet and liquid forms. Aside from often more intense gastrointestinal side effects at the start of treatment, sertraline is generally well tolerated by patients. Sertraline is a weak inhibitor of P450 2D6 and is generally "neutral" re: activation versus sedation.

Vilazodone is the newest drug in the SSRI class and is only available in once-daily tablets. In addition to its "standard" SSRI properties, vilazodone also activates 5HT1a receptors, conferring theoretical anxiolytic action shared with buspirone. Vilazodone is an unimportant inhibitor of any P450 isoenzymes.

SNRIs. Until recently, there were three drugs from the SNRI (serotonin-norepinephrine reuptake inhibitor) category approved by the U.S. FDA as antidepressants: duloxetine, venlafaxine, and desmethylvenlafaxine. A fourth, levomilnacipran, was approved in July 2013.

Duloxetine is available in capsules. It is an effective antidepressant and anxiolytic which also carries FDA indications for diabetic peripheral neuropathic pain (DPNP), fibromyalgia, and chronic musculoskeletal pain. It is a midpotency inhibitor of P450 2D6. The label suggests duloxetine should be avoided or used with caution in patients with hepatic dysfunction and/or significant alcohol abuse. By virtue of its multiple analgesic effects, there may be a special role for duloxetine in depressed cancer patients with pain.

Venlafaxine is available in pills, capsules, and extended-release versions of both. Unmodified venlafaxine requires at minimum twice-a-day dosing, whereas the extended-release versions can be given once daily. A serotonin inhibitor at low dose, venlafaxine does not become a dual-action (SNRI) agent until daily dose exceeds 75-100 mgs, and some patients find it difficult to achieve adequate dosing due to agitation or gastrointestinal effects. It is an unimportant P450 inhibitor. Venlafaxine is associated with a very challenging discontinuation syndrome following abrupt cessation, so it may not be a good choice for cancer patients with unreliable or intermittent bowel function, or who may be facing surgery or other extended NPO periods. Although it does not possess an FDA pain indication, venlafaxine has been shown to be effective for both fibromyalgia and neuropathic pain. Venlafaxine was among the first modern antidepressants to be shown effective in reducing menopause-related hot flashes, although it does not have an FDA indication for this use.

Desmethylvenlafaxine, an active metabolite of venlafaxine, is available only in extended-release tablets. It is an unimportant P450 inhibitor. Like venlafaxine, desmethylvenlafaxine has been shown to be effective in reducing menopause-related hot flashes, although it has not received an FDA indication for this use.

Levomilnacipran, a metabolite of milnacipran, is available in once-daily extended-release tablets. It is reportedly the most noradrenergic of the SNRIs. The most common side effects reported in the FDA trials were nausea, constipation, and sweating. It is not an important P450 substrate or inhibitor.

Atypical Agents. *Bupropion* is available in multiple generic and brand name pill formulations. An aminoketone that inhibits neuronal uptake of norepinephrine and dopamine, bupropion is activating for many patients and can be valuable for the fatigued or apathetic depressed cancer patient. It is also FDA approved to aid in smoking cessation, which is sometimes of value in the cancer setting. Bupropion has been demonstrated to have no adverse impact on cardiac conduction. It is a potent inhibitor of P450 2D6 and will likely significantly elevate blood levels of coprescribed 2D6 substrates. Bupropion lowers seizure threshold more than other antidepressants (52) and should probably be avoided in patients with primary brain tumors or metastases, or other factors that might increase seizure risk.

Maprotiline is an older tetracyclic compound with potent norepinephrine reuptake inhibiting properties. It is also a strong H1 agonist and thus is very sedating; it can be a good choice for cancer patients who are insomnic and anxious. Combined with its anticholinergic properties, however, maprotiline carries many of the liabilities of conventional tricyclic antidepressants, causing dry mouth, sluggish bowel and bladder motility, orthostatic hypotension, and occasionally urinary obstruction in men with prostatic hypertrophy. These side effects, and the other caveats pertaining to cardiac conduction effects associated with conventional tricyclics (see below) significantly limit maprotiline's utility in medically ill adults.

Mirtazapine is a noradrenergic and specific-serotonergic antidepressant. It is available in pills and effervescent dissolving sublingual tablets. Its receptor pharmacology is believed to be responsible for its clinical profile: it is potently sedating, rapidly effective as an anxiolytic and antidepressant, and also has significant antiemetic and appetite stimulating properties. These features have made it widely used in clinical oncology for depressed patients with appetite concerns, insomnia, and anxiety, a trend confirmed in a recent expert opinion (53). The chief treatment limiting problem is sedation, which can be a truly debilitating "first dose" effect that generally attenuates with repeat doses over days. In contrast to the tricyclic and tetracyclic agents with which it shares clinical features, mirtazapine has very benign effects on cardiac conduction, even in overdose (54), and thus can be used confidently in medically ill adults.

Nefazodone is available in pill form only, weakly inhibits norepinephrine, serotonin, and dopamine reuptake and is therefore sometimes referred to as a SNDRI. Perhaps more relevant to its clinical profile is that it potently blocks 5HT1a, 5HT2, and alpha-adrenergic receptors. It is sedating for most patients, and generally lacks the negative effects on libido and sexual functioning associated with SSRIs, and avoids the appetite stimulation associated with mirtazapine. Rare (1 per 250,000 patient years) fulminant hepatic failure led its original manufacturer to withdraw it from the U.S. market. Nefazodone is a potent inhibitor of P4503A3/4 and can therefore alter the pharmacokinetics of a number of other prescribed drugs, including some chemotherapies. It is prescribed uncommonly and probably has very limited utility in cancer patients.

TCAs. Tricyclic antidepressants were first synthesized in the 1950s as derivatives of chlorpromazine. They are available in a variety of pill, tablet, and capsule forms. All tricyclics inhibit serotonin and norepinephrine reuptake to some degree, and unfortunately share anticholinergic, alpha-adrenergic, antihistaminic, and fast Na-channel blocking effects that create a similar overall side effect profile that generally limits utility in medically ill adults. These include dry mouth, orthostasis, sedation, exacerbation of urinary outflow/obstructive problems, and potential cardiac conduction effects even at therapeutic doses. It is this latter feature that has led some experts to argue that tricyclics should simply not be prescribed in medically ill adults (55). However tricyclics are effective antidepressants, widely available, inexpensive, and are also proven adjuvant analgesic drugs, with broad efficacy in a variety of neuropathic and somatic pain states. Because of safety, drug interaction, and side effect concerns, however, they should be used with great caution, and rarely if ever as first-line agents in medically complex adults. TCAs have been administered parenterally in clinical trials (56) but the increased awareness of their potential arrhythmogenicity suggests this is an unwise strategy in most clinical settings, and it should not be undertaken for patients who require antidepressant pharmacotherapy but who lack GI absorptive function.

MAOIs. Monoamine oxidase inhibitor antidepressants can be life-saving for patients who have not benefitted from conventional TCA, SSRI, SNRI, or atypical agents. They have fallen out of favor in contemporary practice due to the complexity of their use: because they inhibit the metabolism of dietary amines, patients taking them must practice dietary caution to avoid potentially life-threatening tyramine reactions that include hypertension, tachycardia, and autonomic instability. Likewise, MAOI patients must not be coadministered serotonergic compounds (including opioids with serotonergic properties, such as meperidine), which can precipitate lethal serotonergic syndrome. Potential drug and diet interactions make the use of MAOIs highly

problematic in medically ill patients undergoing complex treatments such as chemotherapies and argue against their de novo initiation. For patients who have benefitted importantly from MAOIs and who then come to cancer treatment on maintenance therapy with them, a careful risk/benefit assessment by an experienced psychopharmacologist is in order. In the United States, the MAOIs available for clinical use are isocarboxazid, phenelzine, tranylcypromine, and the selective MAO-B inhibitor selegiline. Selegiline is available in tablets, orally dissolving pills, and is the only antidepressant in the United States marketed as a transdermal patch, which may have special utility in a cancer patient who lacks GI function for extended periods. By virtue of its MAO-B selectivity at the FDA-approved dosing, selegiline requires much less dietary vigilance and is also theoretically safer for use with medically complex patients. However clinical experience shows that many patients require higher daily doses, at which point selegiline's MAO-B selectivity is lost. In that situation "standard" MAOI dietary and drug-interaction cautions are necessary for safe use.

Psychostimulants. *Methylphenidate* and *Dextroamphetamine* are available in various pill and transdermal patch forms and have been used and studied extensively in medically ill patients as rapidly acting treatments for fatigue, apathy, and depressed mood. They are generally safe and effective but because they are inotropic and chronotropic, special attention must be paid to their potential cardiovascular effects. They can also cause appetite suppression, insomnia, increased anxiety, jitteriness, or can worsen unrecognized delirium. They typically work within hours and can be dramatically helpful. For depressed cancer patients in the last days of their lives, stimulants are often the only pharmacologic therapies likely to provide benefit soon enough to help. Where there is likely more time for conventional antidepressants to achieve a fuller antidepressant effect (most experts assert 4 weeks is required) initiation of treatment simultaneously with a psychostimulant and a conventional agent can confer early relief and serve as a "bridge" to antidepressant efficacy. Two newer nonsympathomimetic drugs, modafinil and armodafinil, have become available in the last decade and are now occasionally used second-line in the management of fatigue and mood in cancer patients (57). These agents are FDA approved for daytime somnolence associated with narcolepsy, obstructive sleep apnea, shift-work sleep disorder, and fatigue associated with MS. They are believed to work via orexin pathways to enhance CNS dopamine levels, thereby promoting wakefulness. They have not been well-studied as antidepressants but are sometimes substituted for conventional stimulants, particularly in patients who cannot tolerate the cardiovascular effects of the conventional agents.

Ketamine. Ketamine is an agent used historically to induce general anesthesia and as a veterinary anesthetic. It has potent NMDA antagonist properties, which may explain its analgesic efficacy. In recent years low-dose intravenous ketamine has been shown to have rapid efficacy in relieving treatment-resistant depression (58, 59).

The nearly immediate antidepressant benefit, which may be of particular utility in depressed patients with cancer nearing the end of life, is countered by reports of a widely varying duration of the effect, which generally attenuates over days to weeks (59). Based on an individual patient's length of antidepressant benefit, weekly maintenance treatments are sometimes arranged, similar to maintenance ECT treatments. Since many patients undergoing antitumor therapies are often in infusion center settings and have permanent intravenous access, some of the logistical barriers to maintenance ketamine infusion are removed. However there are no published data on maintenance intravenous ketamine for depression in cancer patients undergoing systemic chemotherapies. The anxiolytic and dissociative properties of ketamine have led some investigators to study its potential to help patients cope with existential end-of-life concerns, and, most recently, to pilot oral ketamine for end-of-life depression and anxiety (60, 61). This proof-of-concept trial showed robust benefits and few side effects in a small, open-label population. Although preliminary, this work warrants close attention and may inform clinical decision making under special circumstances.

Special considerations

Women receiving tamoxifen

Tamoxifen is one in a class of antiestrogen drugs used for adjuvant therapy in breast cancer. A series of observations in the last decade have elucidated the steps of tamoxifen biotransformation, and suggest that its active metabolite *n*-desmethyltamoxifen (endoxifen) plays an important role in the drug's efficacy (62). Endoxifen is produced via hepatic oxidative metabolism of tamoxifen mediated by the P450 2D6 isoenzyme. Clinical studies in women who are genetically poor 2D6 metabolizers suggested that they may produce lower levels of endoxifen than extensive metabolizers, an effect replicated by coadministration of potent 2D6 inhibitor antidepressants (63). This was followed in

2010 by a trial suggesting women receiving tamoxifen had greater breast cancer recurrence and mortality associated with paroxetine, but not sertraline, citalopram, venlafaxine, fluoxetine, or fluvoxamine coadministration (64). Although subsequent reports have produced contradictory results (65) and a recent meta-analysis downplays the importance of 2D6 genotype in clinical outcomes (66), the most prudent strategy for now is to err on the side of caution and to choose (or perhaps even transition tamoxifen patients to) antidepressants that have no or minimal impact on P450 2D6, such as venlafaxine, desmethylvenlafaxine, citalopram, escitalopram, or sertraline.

Patients with complex cancer pain

Antidepressants can be useful adjuvant analgesics entirely separate from their effects on mood disorders. The evidence is most robust for the tricyclics, duloxetine, and venlafaxine, which share SNRI properties and which are clearly effective in neuropathic pain states, fibromyalgia, and other painful conditions. Much early enthusiasm that the SSRIs would also prove to be effective adjuvant analgesics was dashed by clinical trials demonstrating their failure to separate from placebo. While there will always be individuals who report pain relief benefits from them, SSRIs should not generally be expected to deliver predictable or reliable coanalgesia. Conversely it is reasonable to choose tricyclics and SNRIs for depressed cancer patients with pain problems incompletely responsive to opioid analgesics, and it is entirely consistent with the evidence base to emphasize their potential coanalgesic benefits when educating patients.

Patients who cannot swallow or absorb pills

The selective monamine oxidase inhibitor selegiline is the only FDA-approved antidepressant available in a transdermal patch. Oral dietary concerns are generally a moot issue in cancer patients who cannot swallow or absorb pills, which reduces an important source of MAOI-related safety concerns. The potential for dangerous pharmacodynamic interactions with coprescribed medications—predominantly with serotonergic agents—remains, however, and any hospitalized or medically complex patient on a selegiline patch should wear an allergy/Medic alert bracelet and should have clear "no serotonergics; no Demerol" orders and safety stickers in his/her electronic or paper medical record. Some of the SSRIs are available in elixir forms, which can be administered conveniently via a gastrostomy tube. Alternative approaches have included rectally administered fluoxetine (67), which demonstrated low but measurable circulating levels of the drug in a small trial of normal volunteers, and buccal administration of some antidepressants (68). The latter approach is often limited by bitter taste, poor dissolvability, and lack of effectiveness. For the severely depressed cancer patient with anticipated long-term or permanent loss of bowel absorptive capacity, other psychotherapeutic and somatic therapies should be considered, including ECT, IV ketamine, TMS, and other evolving techniques.

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