Adults with serious illness have a higher incidence of major depressive disorders than healthy adults, with an estimated incidence of 15% (1). In this Fast Fact, we will provide a clinical framework for selecting pharmacologic agents for seriously ill patients with depression. See Fast Facts # 7, 43 and 146 for assistance in diagnosing and screening for depression in palliative care patients.

**Determine the patient's prognosis**  Because most traditional antidepressants take more than 4 weeks to become effective, they should only be considered in patients expected to live at least that long (2). Use is also limited to patients who are able to swallow oral medications or place them in a feeding tube. For patients with a prognosis < 4 weeks, a psychostimulant such as methylphenidate or dextroamphetamine may act within 1-2 days and be safe in patients without significant cardiovascular disease or delirium. Although the data on psychostimulants are somewhat mixed, controlled trials have shown benefit as both a monotherapy or to augment the effects of another anti-depressant (3-5). See Fast Fact #61.

**Consider co-morbid symptoms** When choosing an antidepressant, consider the patient's other co-morbid symptoms such as insomnia, neuropathic pain, or poor appetite (6). Other considerations include the patient’s past responses to specific agents and possible drug interactions. Common classes of antidepressants include serotonin-selective reuptake inhibitors (SSRIs), serotonin-selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and others.

**SSRIs** Also called “second generation antidepressants”, these are the most commonly prescribed antidepressants. SSRIs should be started at a low dose and then titrated to the minimum effective dose to minimize adverse effects such as QTc prolongation, sexual dysfunction, headaches, nausea and diarrhea. Fluoxetine is associated with emotional activation and may worsen anxiety. Paroxetine can be sedating and lead to withdrawal phenomena with missed doses. Because sertraline, citalopram, and escitalopram have lower side effect profiles and are neither activating nor sedating, they may be better choices for palliative care patients (7). The starting dose of sertraline is 25-50 mg/day with a usual effective dose of 50-200 mg/day; it is available in a concentrated liquid formulation for patients with dysphagia related issues. Both citalopram and escitalopram have been shown to have few drug interactions. The starting dose of citalopram is 20 mg/day with a maximum daily dose of 40 mg. The starting dose of escitalopram is 10 mg/day with a usual effective dose of 10-20 mg/day (8-10).

**SNRIs** Inhibit serotonin and norepinephrine reuptake, two neurotransmitters important in endogenous pain pathways (11). This class may be helpful for neuropathic pain, vasomotor instability, and anxiety-predominant depression. In particular, venlafaxine has shown effectiveness for the amelioration of hot flushes and the prevention of chemotherapy-induced polyneuropathy (CIPN); duloxetine has shown efficacy for the treatment of CIPN (12). SNRIs may prolong bleeding times and therefore may not be safe in patients with active bleeding or intracranial metastases. The starting dose for venlafaxine is 37.5 mg with a usual effective dose of 75-225 mg/day. It requires close monitoring for missed-dose withdrawal and hypertension. The starting dose for duloxetine is 30 mg with a usual effective dose of 60-120 mg/day. It has been associated with hepatic insufficiency and a worsening of acute-angle glaucoma.

**TCAs** are an older class of anti-depressants that can be cost-effective when used at lower doses. They also are proven adjuvant analgesics for neuropathic and chronic low back pain. Unfortunately, their anticholinergic properties can induce delirium, prolong the QTc interval, and be dangerous in overdose. Therefore, their use is limited to heart-healthy patients under the age of 65 with comorbid neuropathic pain and insomnia. Although the preponderance of supporting data for the analgesic effects is for amitriptyline (usual starting dose 10-25 mg/day; usual effective dose is 150 mg/day), nortriptyline is felt to be less sedating (usual starting dose 25 mg/day; usual effective dose is 50-100 mg/day).
Other Medications  Mirtazapine has histaminergic side effects that can be helpful especially for cancer patients who often experience insomnia, poor appetite, and nausea (13). It has few drug interactions but can be associated with orthostatic hypotension. Its usual starting dose is 7.5-15 mg/nightly; usual effective doses are 15-30 mg/day. Bupropion is thought to be less sedating and have a lower incidence of sexual side effects, but it may lower the seizure threshold. The usual starting dose for bupropion is 150 mg/day; the usual effective dose is 150-300 mg/day (14). Single-dose treatment with NMDA antagonist ketamine has shown promise in early investigational studies (15). Aripiprazole may augment the antidepressant effects of SSRIs and SNRIs as early as a week after initiation (16).

Summary Recommendations:
- For patients with prognoses of weeks, consider the use of a psychostimulant like methylphenidate.
- Consider duloxetine or venlafaxine when neuropathic pain is present.
- When polypharmacy is present, consider citalopram, escitalopram or mirtazapine.
- If the patient has insomnia, nausea, or anorexia, consider the use of mirtazapine.
- Closely monitor patients initiated on an antidepressant for adverse effects and dose titration.
- Refer to a mental health clinician for pre-existing major depression, the presence of comorbid psychiatric illness, suicidal ideation, refractory symptoms, or psychiatric polypharmacy.
- Refer to social work and/or spiritual support services if the depression appears to be escalating in relation to social or spiritual factors.

References:


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