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Depression in older people often poses challenges, as high rates of comorbid disease combined with changes in pharmacokinetics and pharmacodynamics may complicate designing appropriate pharmacotherapeutic regimens. We wrote this review to provide pharmacists with a concise overview of key concepts in the diagnosis and management of depression in this population.

La dépression chez les patients plus âgés pose souvent des problèmes étant donné qu'un nombre élevé d'états comorbides combinés à un changement au plan des effets pharmacocinétiques et pharmacodynamiques peut compliquer l'élaboration de plans pharmacothérapeutiques. Nous avons rédigé cet examen afin de fournir aux pharmaciens un aperçu concis des principaux concepts touchant le diagnostic et la gestion de la dépression chez les membres de cette population.

Contemporary concepts in the pharmacotherapy of depression in older people

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ABSTRACT

Late-life depression is common in older people. Its incidence increases significantly after age 70 to 85, as well as among those living in long-term care facilities. Depression contributes to excess morbidity and complicates management of comorbid conditions in older people. Diagnosis and management of depression often present clinicians with a challenge. Indeed, symptoms of depression in older people may not always be the same as those associated with depression in younger people. Additionally, age-related

changes in pharmacokinetics and pharmacodynamics also impact selection, dosing, and monitoring of psychopharmacologic regimens. Optimizing management of depression and providing sound advice to older patients with depression requires knowledge and understanding of many clinical factors. The purpose of this review is to highlight salient issues in late-life depression, with a focus on the pharmacotherapy of depression. *Can Pharm J* 2012;145:128-135.e2.

Introduction

Geriatric (or late-life) depression refers to depressive syndromes that develop in people aged 65 years or older.¹ Depressive syndromes commonly affect older people with chronic disease, cognitive impairment or other forms of disability.²⁻⁵ Depression promotes disability in this population and is associated with negative outcomes of chronic disease, such as increased health care utilization and mortality.² Geriatric depression is often undetected or undertreated in primary care settings for various reasons, including the (incorrect) belief that depression is a normal part of aging. It has been predicted by the World Health Organization that by 2020 depression will be second only to heart disease as a cause of disability and premature death in developed countries.⁶ The purpose of this review is to discuss selected issues in geriatric depression, with a focus on pharmacotherapeutic considerations.

Diagnosis

Depression is usually diagnosed using the American Psychiatric Association's *Diagnostic and Statis-*

tical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for major depressive disorder.¹ Specifically, 5 of the following symptoms must be present: diminished interest, loss of pleasure in all or almost all activities, weight loss or gain (>5% of body weight), insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate guilt, reduced ability to concentrate or recurrent thoughts of death or suicide. The diagnosis of depression requires that either depressed mood or anhedonia be present, that the syndrome last at least 2 weeks, that it lead to distress and functional impairment and that it not be a direct effect of substance abuse, a medical condition or bereavement. While the DSM-IV-TR does not specify different symptoms or different diagnostic criteria for geriatric depression, it is important to note that the diagnosis of depression in the older population can be complicated by other disorders (see below) and also by its presentation (Box 1). For example, depressed mood (the hallmark of depression) tends to be under-reported by older patients and thus *appears* to be less prevalent than

other depressive symptoms such as anergia (lack of energy), anhedonia, loss of appetite or sleeplessness.^{7,8} Older patients may report more somatic complaints (e.g., persistent unexplained pain, headache, fatigue, anorexia, gastrointestinal symptoms and weight loss), anxiety or hypochondriasis rather than reporting feeling sad or depressed. Additionally, patients may present with apathy, withdrawal, lack of vigour (i.e., fatigue), psychomotor retardation and cognitive impairment rather than the “usual” symptoms of depression as described above.^{5,9-11} In hospital settings, depression should be suspected in patients who exhibit poor recovery, poor adherence with rehabilitation programs, treatment refusal, functional decline or increased dependency. Depression should also be suspected in those who are high users of health care services or those with persistent but unexplained weight loss, anorexia, pain, headache, fatigue, insomnia or gastrointestinal symptoms. If these subtle differences are appreciated, it will help ensure a proper diagnostic workup, which is essential, as geriatric depression is under-recognized in as many as 50% of patients.¹⁰ Screening tools such as the 9-item Patient Health Questionnaire (PHQ-9) or the Geriatric Depression Scale (GDS) may be helpful in this context.^{12,13}

Depression may also present with overlapping symptoms of comorbid medical illnesses (which are common in this age group) and thus must be considered within this context. For example, it is not uncommon for older people to suffer from arthritis, coronary heart disease or heart failure, whose symptoms (e.g., aches and pains, dyspnea, tiredness or fatigue, decreased appetite and/or weight loss, anxiety) overlap with somatic symptoms of depression.^{4,7,9-11} In this high-risk older population, physical illnesses must be ruled out before the presenting symptoms are attributed to depression.

It should also be noted that depression in older people usually occurs against a background of medical disorders. Indeed, there are times when such disorders (e.g., cardiovascular disease leading to a myocardial infarction) predispose or trigger depression in vulnerable individuals and it has been shown that the greater the individual’s overall medical burden, the higher the risk of depression.^{14,15} Additionally, distinctive depressive syndromes are also observed in those with Alzheimer disease, significant cerebrovascular disease and depression-executive dysfunction syndrome.¹⁶⁻²¹

KNOWLEDGE INTO PRACTICE

- In older people, symptoms of depression may be different than in younger patients, and often include memory and concentration problems, various vague somatic complaints, apathy, irritability and more.
- Age-related changes in pharmacokinetics and pharmacodynamics have important implications in terms of selecting appropriate antidepressant medications.
- If treatment with the first antidepressant regimen is unsuccessful, options include switching medications or combining medications.
- This review provides practical information that pharmacists may use to better understand the appropriate treatment of depression in older people.

Medications as potential contributors to depression

Medications are a potential, albeit uncommon, iatrogenic cause of depressive symptoms. Many drugs have been implicated, including, but not limited to, antipsychotics, antiparkinsonian drugs, benzodiazepines, cimetidine, digoxin, clonidine, hydralazine, dextropropoxyphene, methyldopa, propranolol, reserpine, steroids, progesterone, estrogens, vinblastine, vincristine and tamoxifen.²² During the workup of a patient with suspected depression, a complete medical and medication history and physical examination are indicated to assess conditions that may contribute to depression (e.g., hypothyroidism, alcohol, prescription drug abuse).^{4,5,23}

Epidemiology of depression and antidepressant use in older people

Approximately 1% to 4% of the general older population suffers from major depression; women are affected at about twice the rate of men.^{9,10,24} Of particular relevance is the observation that the incidence and prevalence of depression double after the age of 70–85 years.⁴ In medical settings, the prevalence of major depression increases markedly to about 12% for those admitted to hospital and 14% for those residing in nursing homes.¹⁰

BOX 1 Symptoms of depression in older adults

- Anergia
- Anhedonia
- Anxiety
- Apathy
- Early morning awakening
- Hostility
- Irritability
- Loss of appetite
- Self-neglect
- Subjective memory and concentration complaints
- Various somatic symptoms (e.g., persistent unexplained pain, headache, fatigue, gastrointestinal symptoms)
- Withdrawal

- Chez les personnes âgées, les symptômes de dépression diffèrent de ceux qui se manifestent chez les autres patients. On remarque, entre autres, des problèmes de mémoire et de concentration, divers symptômes vagues somatiques, de l'apathie et de l'irritabilité.
- Les changements liés à l'âge dans la pharmacocinétique et la pharmacodynamie ont d'importantes conséquences sur le traitement antidépresseur.
- Si le premier traitement prescrit ne donne pas les effets escomptés, il faut alors changer ou combiner les médicaments.
- Cette analyse donne des renseignements pratiques aux pharmaciens et leur permet de mieux comprendre le traitement approprié de la dépression chez les personnes âgées.

The epidemiology of antidepressant use in older people is germane considering the importance of proper drug selection, dosing and treatment duration, yet there are few studies that address this issue.²⁵⁻²⁷ Most recently, Wang et al.²⁵ reported on 12,130 new antidepressant users aged >65 years in the Pennsylvania PACE program during 1994 to 1999. Their main findings were that potentially hazardous regimens (i.e., highly anticholinergic

tricyclic antidepressants [TCAs] or high daily dosages) were used by 11.9% of the sample, low-intensity regimens (i.e., low daily dosages, short [<1 month] duration or inadequate follow-up) by 34.8% and that, overall, 43.3% of subjects had a suboptimal regimen.²⁵ Similar findings have been reported by others, suggesting that much work remains to be done to improve the care of older depressed patients.^{26,27} On the posi-

tive side, these investigators noted a meaningful decrease over time in the use of potentially hazardous antidepressant drugs. Predictors of antidepressant use have also been assessed.^{25,28} For example, some predictors of potentially hazardous regimens have included an age of 65–74 years, nursing home residence, less comorbidity, more physician visits and earlier study years, while predictors of low-intensity regimens included age >85 years, non-white race, greater comorbidity, fewer physician visits and not using other psychotropic medications. While epidemiological studies have limita-

tions, they nevertheless provide useful information that may be used for educational purposes and for planning future studies aimed at improving the pharmacotherapy of depression in the older population.

Pharmacotherapy

There are various treatment goals that are important (e.g., symptom reduction, preventing suicidal ideation, preventing relapse, improving cognitive and functional status), but broadly speaking, there are 2 important overarching constructs that should be kept in mind: response and remission (Box 2).²⁹⁻³¹ The differentiation is an important one; the ultimate goal of treatment should always be remission, as patients who respond but do not achieve remission tend to have worse all-cause outcomes compared to those in remission.³² That said, it can be challenging to obtain remission in a given patient, as demonstrated by the recently published Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in which only about 30% of patients achieved remission after the first level of treatment with citalopram (see below, *Combining and augmenting antidepressants*).³³

Many antidepressant drugs are currently available and it is generally accepted that they demonstrate similar efficacy at the population level; thus, the usual approach is to select a drug based on its tolerability (Table 1), potential for drug interactions (Tables 2 and 3) and cost.³⁴⁻⁴¹ In contemporary practice, selective serotonin reuptake inhibitors (SSRIs) are used as first-line agents due to their ease of use. The most suitable SSRIs for older people are sertraline, citalopram and escitalopram.^{42,43} Fluoxetine is not considered a good choice due to its long half-life and propensity to cause excessive stimulation, sleep disturbance and agitation, while paroxetine has mild, but clinically relevant, anticholinergic properties.^{5,44} SSRI-related adverse effects of particular importance in the older population include dyspepsia or nausea (which usually subside within 7–10 days), hyponatremia, anorexia and weight loss. Clinically relevant drug–drug interactions are few; however, the risk of serotonin toxicity is significant if SSRIs are combined with drugs known to increase intrasynaptic serotonin, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and others (e.g., meperidine, tramadol, some TCAs, linezolid).⁴⁵ Drugs that inhibit the reuptake of norepinephrine and serotonin (e.g., venlafaxine, duloxetine) represent useful alternatives for patients with coexisting pain, especially neuropathic pain.⁴⁶ Important

BOX 2 Definitions of response and remission in depressed older adults

Response: Typically defined as a $\geq 50\%$ decrease in depression rating scale score (regardless of which scale is used).

Remission: Typically defined as a depression scale score below a pre-specified threshold that is consistent with a relative absence of depressive symptoms (i.e., euthymia) and lack of interest/pleasure and includes, at most, 2 other depressive symptoms.

TABLE 1 Selected antidepressant drugs, doses and adverse effects^{40,41}

Drug	Starting daily dosage	Maximum daily dosage	Therapeutic dosage range	Common adverse effects in clinical trials (% drug vs % placebo)
SSRIs	Adverse effects common to this class are diarrhea, headache, insomnia, nausea, nervousness, sexual dysfunction, somnolence, increased risk of gastrointestinal bleed, dizziness, dry mouth, SIADH			
Citalopram (Celexa)	10 mg daily	40 mg	20–40 mg daily	Anxiety (3.3% vs 2.1%), tremor (8.4% vs 6.3%), dose-dependent QT prolongation
Escitalopram (Ciprallex)	5 mg daily	20 mg	10–20 mg daily	Nasopharyngitis (5% vs 1.2%), constipation (3.5% vs 1.2%), dyspepsia (5.9% vs 1.6%), pharyngolaryngeal pain (5.9% vs 0%), dose-dependent QT prolongation
Sertraline (Zoloft)	25 mg daily	200 mg	50–100 mg daily	Dyspepsia (6% vs 2.8%), tremor (10.7% vs 2.7%), anorexia (2.8% vs 1.6%)
SNRIs	Adverse effects common to this class are nausea, dry mouth, headache, somnolence			
Duloxetine (Cymbalta)	30 mg daily	120 mg	30–60 mg daily	Constipation (11% vs 4%), decreased appetite (8% vs 2%), fatigue (8% vs 4%), hyperhidrosis (6% vs 2%), diarrhea (8% vs 6%)
Venlafaxine XR (Effexor)	37.5 mg daily	225 mg	75–225 mg daily	Abnormal dreams (7% vs 2%), anorexia (8% vs 4%), dizziness (20% vs 9%), nervousness (10% vs 5%), sweating (14% vs 3%), tremor (5% vs 2%), sexual dysfunction
Desvenlafaxine ER (Pristiq)	50 mg daily	100 mg	50–100 mg daily	Hyperhidrosis (10% vs 4%), dizziness (13% vs 6%), insomnia (9% vs 6%), constipation (9% vs 4%), decreased appetite (5% vs 2%), fatigue (7% vs 4%), vomiting (3% vs 2%), sexual dysfunction
TCAs*	Adverse effects common to this class are sedation, weight gain, dry mouth/and or eyes, urinary retention, constipation, blurred vision, orthostatic hypotension, impairment of cardiac conduction, sexual dysfunction			
Desipramine (Norpramin)	10 mg at bedtime	150 mg	75–100 mg at bedtime	Abdominal cramps, nausea, vomiting, asthenia, insomnia, weakness, headache, lethargy, agitation
Nortriptyline (Aventyl)	10 mg at bedtime	200 mg	50–75 mg at bedtime	Sedation, weight gain, lowered seizure threshold, fatigue. Least hypotensive TCA.
Norepinephrine dopamine reuptake inhibitors				
Bupropion (Wellbutrin)†	SR: 100 mg XL: 150 mg	SR and XL: 300 mg	SR:100–150 mg daily XL: 150–300 mg daily	Headache (27.5% vs 23.4%), dry mouth (13.1% vs 7%), nausea (10.7% vs 7.5%), dizziness (7.1% vs 5.5%), insomnia (7.9% vs 6.5%), tremor (3.1% vs 0.8%), tinnitus (3.9% vs 1.8%), anorexia (3.1% vs 1.6%)
Noradrenergic/specific serotonergic antidepressants (NaSSAs)				
Mirtazapine (Remeron and Remeron RD)‡	7.5 mg at bedtime	45 mg at bedtime	15–30 mg at bedtime	Dry mouth (25% vs 15%), sedation, arthralgia, somnolence (54% vs 18%), increased appetite (17% vs 2%), weight gain (12% vs 2%), dizziness (7% vs 3%), constipation (13% vs 7%)
Reversible inhibitors of MAO-A				
Moclobemide (Manerix)	75 mg twice daily	600 mg	300–600 mg in divided doses	Sleep disturbances (7.3% vs 4.8%), increased anxiety (2.8% vs 2.2%), restlessness (4.1% vs 2.6%), tremor (5% vs 3%), vomiting (1.6% vs 0.4%), hypotension (3% vs 0.4%)

SIADH: syndrome of inappropriate antidiuretic hormone secretion.

* Amitriptyline, clomipramine, doxepin and imipramine are not drugs of choice for the elderly due to their anticholinergic and sedating effects as well as their pronounced effects on the cardiovascular system; hence, it is best to avoid them in the elderly.

† Bupropion should not be used in patients with a seizure disorder or with anorexia nervosa.

‡ Mirtazapine dose may require adjustment in patients with renal impairment.

adverse effects of SNRIs include nausea, agitation, insomnia and increases in diastolic blood pressure, particularly at higher (e.g., >300 mg venlafaxine) doses.^{47,48} Mirtazapine possesses serotonergic and noradrenergic properties and is associated with sedation, increased appetite and weight gain.⁴⁶ It can be a useful drug for patients suffering from significant insomnia and/or weight loss. Bupropion has noradrenergic properties and can be stimulating, which may be beneficial for patients with sig-

nificant lethargy, daytime sedation, apathy or lack of energy.⁴⁶ Neither bupropion or mirtazapine are associated with sexual side effects, making them good choices for those who have experienced these effects from other drugs. Bupropion may lower the seizure threshold and should not be used in those with a seizure disorder or a history of seizures. TCAs are effective medications, although they are not usually considered first-line agents due to their toxicity (e.g., anticholinergic properties, potential

TABLE 2 Antidepressant metabolism and selected drug interactions^{40,41,83,84}

Drug	CYP 450 isoenzymes responsible for metabolism of drug	CYP 450 isoenzymes which may be inhibited by the drug	Potential interactions related to CYP 450 inhibition by the antidepressant	Other relevant drug interactions
SSRIs*				
Citalopram (Celexa)	CYP2C19 CYP2D6 CYP3A4	CYP2D6 (Weak)	None	
Escitalopram (Cipralex)	CYP2C19 CYP2D6 CYP3A4	CYP2D6 (Weak)	None	
Sertraline (Zoloft)	CYP2D6 CYP2B6 CYP2C19 CYP3A4 CYP2C9	CYP2D6 (Moderate; strongly inhibits at higher doses)	CYP2D6: Increased levels of amiodarone, amphetamine, atomoxetine, aripiprazole, bupropion, chlorpheniramine, chlorpromazine, clozapine, codeine, dextromethorphan, duloxetine, encainide, flecainide, fluvoxamine, haloperidol, metoclopramide, mexiletine, ondansetron, oxycodone, perphenazine, promethazine, propafenone, risperidone, tamoxifen, vinblastine and zuclopenthixol when co-administered.	Warfarin: Monitor INR when initiating or stopping sertraline.
SNRIs*				
Duloxetine (Cymbalta)	CYP1A2 CYP2D6	CYP2D6 (Strong)	CYP2D6: Same as sertraline.	
Venlafaxine (Effexor)	CYP2D6 CYP3A4	CYP2D6 (Weak)	CYP2D6: Same as sertraline.	Warfarin: Monitor INR when initiating or stopping venlafaxine.
Desvenlafaxine (Pristiq)	CYP3A4	CYP3A4 (Weak)	Increase in desvenlafaxine levels may be seen when co-administered with potent CYP3A4 inhibitors.	Warfarin: Monitor INR when initiating or stopping desvenlafaxine.
TCAs*				
Desipramine (Norpramin)	CYP2D6	CYP2D6 (Strong)	CYP2D6: Same as sertraline.	Epinephrine/norepinephrine. Avoid concomitant use of anticholinergics or QTc-prolonging agents.†
Nortriptyline (Aventyl)	CYP2D6 CYP1A2	CYP2D6 (Weak) CYP1A2 (Weak)	Increase in nortriptyline levels may be seen when co-administered with potent CYP2D6 or CYP1A2 inhibitors.	

for hypotension) and cardiac risk in the event of an overdose.⁴³ Cardiac arrest may result from an overdose, while arrhythmias may occur even at therapeutic doses. These drugs are contraindicated in patients with a history of narrow angle glaucoma, recent history (<2 weeks) of myocardial infarction, cognitive impairment, cardiac conduction disturbances, orthostatic hypotension, urinary retention or prostatic hypertrophy. Nevertheless, some TCAs may be considered for those who have responded favourably in the past or for those with coexisting neuropathic pain. Among TCAs, amitriptyline and doxepin (and many others) are generally considered unsuitable for use in geriatric depression due to their potent anticholinergic properties, while nortriptyline and desipramine may be acceptable options.⁴⁴ It is important to note that dosing of

nortriptyline and desipramine, unlike other antidepressants, needs to be guided by monitoring plasma concentrations, with target therapeutic ranges of 60–120 µg/L and >115 µg/L, respectively. Lastly, MAOIs are a class of antidepressants that are not extensively used in older people, mostly due to the required dietary modifications and potential for drug–drug interactions.⁴⁹

Using appropriate dosing strategies in order to maximize the chance of success and minimize the risk of side effects is of paramount importance. Specifically, lower starting doses should be used (see Table 1), yet final doses should be in the same range as for the adult population to increase the chance of an adequate response and remission.^{50,51} If a patient is not adequately responding to an antidepressant, there are various options avail-

TABLE 2 Antidepressant metabolism and selected drug interactions^{40,41,83,84} (cont.)

Drug	CYP 450 isoenzymes responsible for metabolism of drug	CYP 450 isoenzymes which may be inhibited by the drug	Potential interactions related to CYP 450 inhibition by the antidepressant	Other relevant drug interactions
Norepinephrine dopamine reuptake inhibitors				
Bupropion (Wellbutrin)	CYP2B6 CYP2D6	CYP2D6 (Moderate)	CYP2D6: Same as sertraline.	
Noradrenergic/specific serotonergic antidepressants (NaSSAs)*				
Mirtazapine (Remeron and Remeron RD)†	CYP2D6 CYP3A4	None	Increase in mirtazapine levels when co-administered with potent inhibitors of CYP2D6 or CYP3A4.	Warfarin: Monitor INR when initiating or stopping mirtazapine.
Reversible inhibitor of MAO-A*				
Moclobemide (Manerix)	CYP2D6 CYP2C19	CYP2D6 (Weak) CYP2C19 (Weak) CYP1A2 (Weak)	Increase in moclobemide levels may be seen when co-administered with potent CYP2D6, CYP2C19 or CYP1A2 inhibitors.	Alcohol, alpha 1 and 2 agonists, amphetamines, atomoxetine, bupropion, buspirone, carbamazepine, cyclobenzaprine, dexamethylphenidate, dextromethorphan, fentanyl, lithium, linezolid, MAOIs, maprotiline, meperidine, methotrimeprazine, methyl dopa, methylphenidate, mirtazapine, opioids, phenylephrine, phenylpropanolamine, pseudoephedrine, reserpine, sibutramine, SNRIs, SSRIs, tamoxifen, TCAs, tetrabenazine, tetrahydrozoline, thioridazine, tramadol, trazodone, triptans, tyramine-containing products.

N.B. The metabolism of most antidepressant drugs is at least partially dependent on hepatic microsomal cytochrome P450 isoenzymes. Any drug or natural health product that is a substrate, inducer or inhibitor of these CYP isoenzymes may also interact.

* Risk of developing serotonin syndrome in combination with buspirone, linezolid, L-tryptophan, MAOIs, sibutramine, St. John's wort, tramadol, TCAs, triptans, SNRIs and SSRIs.

† Risk of QTc prolongation in combination with dronedarone, nilotinib, pimozide, quinine, tetrabenazine, thioridazine and ziprasidone. QTc-prolonging agents include amiodarone, chlorpromazine, clarithromycin, domperidone, erythromycin, haloperidol, methadone, pimozide, quinidine, quinine, sotalol and ziprasidone.

‡ Mirtazapine dose may need to be increased when given concomitantly with phenytoin or carbamazepine. Monitor INR when concomitantly given with warfarin.

able, such as switching to another antidepressant, combining antidepressants, using adjunctive pharmacological treatments or electroconvulsive therapy.⁵²⁻⁵⁴ If a patient's therapy is to be switched, a key consideration may involve the gradual tapering of the existing antidepressant in order to avoid withdrawal syndromes with short half-life drugs (e.g., paroxetine, venlafaxine) and drugs possessing significant anticholinergic properties.^{50,53} There are several different ways to do this, including using a complete washout period (gradually tapering one before starting another — appropriate when switching from an irreversible MAOI to another antidepressant) or using the crossover technique (gradually reducing the dose of 1 drug while slowly starting the new agent). In all cases, individual patient tolerance must be considered.

Combining and augmenting antidepressants

Only about 40% to 50% of older adults with non-psychotic major depressive disorder will respond to the first prescribed antidepressant within 2–3 months, making it clear that alternative strategies are necessary for many patients.^{50,51} As previously noted, combinations of drugs are often required to increase response/remissions rates. There are 2 main objectives when considering combination therapy. The first is to increase response or remission rates and the second is to reduce the rate of relapse or recurrence.⁵⁵ When combining antidepressants, it is important to combine agents with different mechanisms of action, for example, SSRIs with bupropion, SSRIs with selected TCAs (desipramine or nortriptyline) or SSRIs with mirtazapine.⁵⁵⁻⁶⁰

Augmentation strategies differ from combination therapy in that they involve the use of medica-

TABLE 3 Cytochrome P450 enzyme-inducing agents⁸³

P450 enzyme	Inducing agent
CYP1A2	Carbamazepine, charbroiled meat, chlorpromazine, clozapine, cruciferous vegetables, modafinil, morphine, omeprazole, pethidine, phenobarbital, phenytoin, primidone, rifampin, smoking
CYP2D6	Dexamethasone?, phenobarbital?, phenytoin?, rifampin?, ritonavir?
CYP3A3/4	Amiodarone, carbamazepine, clofibrate?, clozapine, ethosuximide, felbamate, high-potency glucocorticoids?, griseofulvin, isoniazid, modafinil, oxcarbazepine, pethidine, phenytoin, phenobarbital, primidone, rifampin, rifabutin, ritonavir, topiramate
CYP2C9	Carbamazepine, phenobarbital, phenytoin, rifampin
CYP2C19	Carbamazepine, norethindrone, phenobarbital, phenytoin, rifampin
CYP2B6	Clozapine, modafinil

Induction of CYP 450 isoenzymes could lead to suboptimal response and/or therapeutic failure and thus should be considered when CYP-inducing agents are co-prescribed with antidepressants. Higher doses of the antidepressant may be necessary. ? = possible inducing agent.

tions that are not typically considered antidepressants (Box 3) in order to enhance the therapeutic effect of a known antidepressant.⁵⁶ Along these lines, the STAR*D trial was the first large-scale study that examined the effectiveness of different treatment strategies, including augmentation with lithium, triiodothyronine (T₃), buspirone or bupropion, for patients who did not achieve remission after initial therapy with citalopram. This study included a population (mean age 40 years, with 741 [25%] of the sample >51 years, with medical and psychiatric comorbidities) of patients with major depressive disorder who initially received citalopram and subsequently received up to 3 additional steps if remission was not achieved or the medication was intolerable.⁵⁵ The study's primary outcome measure was remission, defined as a score of ≤7 on the 17-item Hamilton Rating Scale

for Depression. A key finding from the study was that lower remission rates were observed when multiple treatment steps were required. The observed remission rates were 37%, 31%, 14% and 13% following treatment steps 1 through 4, respectively (see Rush et al. for a detailed review of STAR*D results).⁵⁶ With regard to tolerability, significantly more patients taking lithium exited the study due to side effects compared to those taking T₃ (23% vs 9%, $p < 0.05$), while sustained-release bupropion was better tolerated, as demonstrated by a lower rate of discontinuation (12.5%) compared with buspirone (20.6%).

Some antipsychotics, specifically aripiprazole, olanzapine and quetiapine, have been well studied as augmenting agents in patients with depres-

sion who have failed to remit with more than 1 prior antidepressant trial.⁶¹⁻⁷⁰ In fact, in the United States, aripiprazole and quetiapine are both FDA approved for use as adjuncts to antidepressants for patients with unipolar, nonpsychotic depression.^{71,72} In studies of these drugs, remission rates have been consistently (and significantly) higher when antipsychotics are used as adjuncts to antidepressants versus antidepressants alone.^{65,70} For a more detailed discussion, the reader is referred to a recent review and meta-analysis of this strategy.^{73,74} It is worth mentioning that the aforementioned augmentation strategies are not well studied in older people. Nevertheless, this should not dissuade clinicians from using selected augmentation strategies to help patients achieve remission. In general, medications that are well tolerated in this population for this purpose include bupropion, T₃, aripiprazole and mirtazapine.

Time to response and treatment duration

Older patients may respond as well as younger patients, but may require longer for the full response to be observed (i.e., 8–12 weeks of treatment).^{50,51} Interestingly, recent data suggest that early improvement may be a good predictor of subsequent response. For example, Mulsant et al. found that a full response can be expected in two-thirds of patients who have partial improvement after 4 weeks of treatment.⁷⁵ Close monitoring of the patient is of paramount importance during the first 8–10 weeks of treatment. For example, weekly or biweekly contacts either in person or by telephone should occur to monitor for adverse effects, drug interactions, worsening or improvement of depressive symptoms and to further adjust the regimen if necessary. Monitoring can be improved by using rating scales such as the PHQ-9, with the goal being remission (i.e., PHQ-9 score <5). Minor depression and dysthymia may exhibit a greater and faster improvement in symptoms when treated with pharmacotherapy compared to placebo, although remission rates are not significantly different.⁷⁶

An adequate duration of treatment is a key factor for successful long-term management of depression. In the absence of long-term treatment, high rates of relapse and recurrence are observed.⁷⁷ In a recent study of community-dwelling elderly people with major depression, approximately 60% became depressed again within 2 years unless they were maintained on antidepressant therapy.⁷⁸ Similarly, a study on maintenance therapies in recurrent depression found that even when an antidepressant was prescribed for at least 3 years

BOX 3 Drugs used to augment antidepressants

- Aripiprazole
- Bupropion
- Buspirone
- Lithium*
- Olanzapine*
- Quetiapine*
- Triiodothyronine (T₃)

*Not well tolerated in older people; thus their use is not generally recommended.

after remission, 43% of patients still experienced recurrence.⁷⁹ The beneficial impact of long-term antidepressant treatment has been supported by results of the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT).⁸⁰ It was noted that, in the geriatric population, patients had lower mortality rates after more than 4 years of a structured depression intervention (with medication and psychotherapy components) compared to those receiving usual care. In fact, up to 75% of elderly patients who remitted from an episode of depression and were maintained on full-dose antidepressant treatment remained free of relapse and recurrence when followed for 2 years. Maintenance therapy should therefore be considered for any patient with a history of 1 or more episodes of major depression or who is otherwise at high risk of recurrence (e.g., onset of the first episode of depression after age 60).⁸¹ For patients with a first episode of depression, initial treatment durations of up to 24 months are not unreasonable. In contrast, lifelong treatment should be considered for those who have had 3 or more lifetime episodes. Reducing the dose of the antidepressant appears to increase the risk of relapse and recurrence. Thus, the consensus is that patients should be maintained on the dose to which they responded. Patients who are stabilized on drugs should be followed on an individualized basis (e.g., every 1–6 months) to monitor efficacy, adverse effects and adherence.

Pharmacist's role and conclusions

Pharmacists can play a significant role in depression management as they are readily accessible to patients and are able to maintain trusting relation-

BOX 4 Opportunities for pharmacists in the care of depressed individuals

- Educate patients about depression as a biological disease.
- Help to destigmatize depression.
- Address common misconceptions about depression and its treatment.
- Educate patients about the expected course of symptom improvement.
- Educate patients about possible adverse effects and management strategies.
- Provide patients with additional resources (handouts, websites).
- Provide patients with self-rating scales (e.g., 9-item Patient Health Questionnaire, the Geriatric Depression Scale, the Cornell Scale for Depression in Dementia) to aid in monitoring progress.
- Stress the importance of adherence to antidepressants.
- Provide a call-back service to patients to assess their progress.
- Provide support to the patient and their caregiver.

ships.⁸² These factors enable pharmacists to provide several services important to depression care (Box 4). It is also clear that depression in older people can be a complex illness that transcends many usual medical, pharmacological and psychosocial considerations. Pharmacists and other health care professionals who work with older people must be vigilant in order to ensure that patients at risk for depression are appropriately screened, assessed and treated. Likewise, patients with known depression must be carefully followed and managed in order to ensure positive outcomes. It is paramount that pharmacists have an understanding of the many considerations discussed in this review in order to be able to improve the care of older patients with depression. ■

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