Reviews/Short communication

Treatment of Depression in the Elderly: A systematic review

Arash Mirabzadeh, MD.
University of Social Welfare and Rehabilitation Sciences,Social Determinants of Health Research Center, Tehran, Iran

Mohammad Reza Khodaei[1], MD.
University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Introduction: Depression is a common disorder and a major public health problem in the elderly. Despite its prevalence and seriousness, depressive disorder in older people remains under-treated. The optimal treatment of depression in later life is crucial, and requires appreciation of several age-related factors such as comorbidity, polypharmacy, altered drug kinetics, variable treatment responses and increased predisposition to side effects. Discussion: Although sometimes difficult to diagnose because of concurrent stressors, medical illness, or dementia, depression in elderly patients responds readily to appropriate therapy. When untreated, this disorder may result in increased morbidity and mortality or suicide. Effective therapeutic options for late-life depression, as in younger patients, include psychotherapy and pharmacotherapy. Because of their favorable adverse effect profiles and safety in cases of overdose, the selective serotonin reuptake inhibitors have, in most cases, replaced tricyclic antidepressants as first-line therapy when antidepressants are indicated. The SSRIs considered to have the best safety profile in the elderly are citalopram, escitalopram, and sertraline. Finally, electroconvulsive therapy offers a safe and effective alternative for patients refractory to or unable to tolerate antidepressant medication.

Keywords: Polypharmacy, depressive disorder, older people

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Introduction

Depression is common in the elderly and is a major public health problem (1). Major depressive disorder (MDD) is common in the elderly too, with an estimated prevalence of 2% to 3% in the general population and 15% to 25% among nursing home residents (2). Approximately 15% of the community-dwelling elderly have clinically significant depressive symptoms, and such symptoms are present in 25% of elderly patients with a chronic medical illness (3). Despite the high prevalence of depressive illness in this population, it is estimated that clinically significant depression goes untreated in 60% of cases (4,5).

Depression in the elderly can be divided into early-life onset, which recurs in old age, and late-life onset, which begins in old age (6).

Depression in late life is associated with significant morbidity including deficits in a range of cognitive functions and considerable influence on functional impairment and disability (1,2,7). In elders who have co-existing chronic medical conditions, the presence of depressive symptoms increases role impairment, utilization of medical services and treatment costs, decreasing patients' compliance with their medical treatments and altering the course of disease that leads to higher mortality and disability (1,4,5,8).

Evidence regarding outcome and treatment response in relation to age is even less consistent (9,10). Old age has been associated with a slower improvement during treatment and an overall poorer prognosis (9,11-13). However, opposite findings have also been reported (9,14). Elderly patients with late onset of depressive disorder have been characterized by less personality abnormalities and a low incidence of family history of psychiatric illness (9,16), but severity and symptomatology have been observed to be quite similar in early and late onset elderly patients (9,16). Old age at onset has been linked to both better and poorer outcomes. Thus, the impact of age and age at onset of depressive disorder in symptomatology and outcome is still a debated issue. It has been suggested that potential biases may

1- All correspondences to: Dr. Mohammad Reza Khodaei; Email: < kh.ardakani@uswr.ac.ir>

have confounded the above-mentioned study results (17). For example, severity of depression may be influenced by concurrent medical problems and time to remission may be longer. Medical comorbidity more likely occurs in people with late-onset depression without a past psychiatric history (18). The importance of assessing factors related to patient age and not just to age itself in evaluations of risk factors for poor prognosis has been emphasized (9,17).

Obstacles to Treatment

The importance of detecting, diagnosing, treating and following the course of geriatric depression lies in the possibility that, if not recognized, this nosological entity may provoke negative consequences in term of morbidity, potential autonomous life deficits, functional capacities and even death (1). Barriers to proper diagnosis and treatment include attributing depressive symptoms to "normal" aging or physical illness, lack of family support, self-medication (e.g. alcohol use), drug prescription, impoverishment and low socioeconomic status (that confines the accessibility to health care), mourning, social isolation, hypochondriasis, hiding the effects of concomitant medical problems, misdiagnosis of dementia instead of depression, somatization, expense matters, time limitations, and the stigma of mental illness (1,2,4). Clinical experience suggests that physicians who look carefully for symptoms of depression rather than relying on the patient to report mood changes have higher rates of recognition and response to therapy (19). One of the major obstacles to the therapeutic response is the lack of compliance, influenced by several factors such as: cognitive impairment, complexity of dosages, side effects, lack of comprehension of the depressive symptoms, treatment costs, lack of family support, and fear of stigma. On the contrary, factors improving compliance to treatment include: a complete physical and cognitive assessment of the patient, involvement of relatives in the therapeutic program, maintenance of frequent contacts and supply of clear and comprehensible information on diagnosis and therapeutic management, these being, generally, the cardinal points of the so-called good medical practice (1,5,19).

Treatment Modalities

As in younger patients, the goals of treating depression in elderly patients include alleviating depressive symptoms, reducing risk of recurrence and relapse, decreasing morbidity and mortality, and improving quality of life. Because data providing clinical recommendations for depressed elderly patients are limited, treatment recommendations are usually based on data from younger patient populations or from small studies of elderly patients. Treatment options include pharmacotherapy and psychotherapy, in some cases, electroconvulsive therapy (ECT) (20).

Pharmacotherapy

For several reasons, the pharmacologic treatment of depression in elderly patients is particularly challenging. First, reduced 'lean body mass' and increased 'body fat' result in higher concentrations of drugs that distribute in body fluids. One such example is lithium, which increases the distribution and prolongs the elimination half-life of fat-soluble drugs, such as antidepressants (20,21). Second, hepatic and renal drug and metabolite clearance may decrease with age, resulting in slower drug clearance. Third, the presence of medical illness may result in pharmacodynamic changes. For example, the presence of dementia or other brain diseases may increase sensitivity to the central nervous system effects of psychotropic medications. Finally, because elderly patients are often taking multiple medications, drug-drug interactions are a source of concern. For these reasons, elderly patients should initially receive lower antidepressant doses than those recommended for younger patients (20,22-24). The dose can then be slowly titrated upward based on clinical response and emergence of adverse effects. Older patients may take longer to respond to antidepressants, and should receive a 6- to 12-week antidepressant trial, if possible, before assessing for efficacy. Estimates of drug noncompliance in elderly patients range from 40% to 75% (20,25). Simplification of multidrug treatment regimens and dosing schedules and the use of daily dosing pill boxes may facilitate compliance. Lack of medical literacy may also contribute to noncompliance. Patients and significant others should receive verbal and written information outlining dosing schedules and potential adverse effects. Because many elderly patients receive fixed incomes, physicians must consider drug costs as well as the cost of associated risks, such as falls, and follow-up monitoring, such as office visits and laboratory tests, when selecting an antidepressant (20).

Pharmacological Changes

Treatment of depression in the elderly must take into account pharmacokinetic and pharmacodynamic changes in late-life (26). Beyond recognizing the existing clinical variables in patients with late-life depression, aging patients also have changes in key physiologic factors that can influence the pharmacokinetics of antidepressants. These considerations should be applied to all geriatric patients with late-life depression who are about to receive antidepressant therapy (27). The results of studies in younger adult populations cannot be generalized to the elderly people, since drug pharmacokinetics have changed, as well as chronic medical illnesses that may affect their renal, hepatic, and cardiac function. Drug absorption changes, distribution volume is diminished and mean level of drugs are higher in the older ones, all of which may adversely affect their ability to metabolize or excrete some medications (5,28,29).

Pharmacokinetics

Pharmacokinetic changes include decreased absorption, increased volume of distribution, decreased metabolism, and decreased excretion (26). Normal aging results in a number of pharmacokinetic changes that can influence a drug's peak plasma levels and duration of action. Age-related gastrointestinal (GI) changes, like pH alterations and intestinal motility reduction, may reduce the absorption of oral medications; however, the extent of these changes varies among individuals and may not always be clinically significant. Aging patients are at risk of reduction in production of gastric acid and GI motility, decreases in serum albumin, decreases in hepatic blood flow and liver mass, and decreases in renal blood flow (27,30). Reductions in gastric acid production and GI motility may result in reduced absorption of antidepressants (27). Changes in levels of drug-binding plasma proteins, particularly albumin, can alter the fraction of drug that is unbound and thus able to cross the blood-brain barrier and bind to receptor sites (31,32). Changes in the activity level of certain liver enzymes can extend the half-life of many drugs, and decrease in the glomerular filtration rate can decrease renal elimination (31-33). The net result of these pharmacokinetic changes is increased peak plasma levels, prolonged half-life, increased bioavailability and lowered therapeutic dose. Inter-individual genetic variability can magnify these effects. For example, Nortriptyline cured older adults with at least cytochrome P-450 (CYP) 2D6 allele encoding reduced or absent metabolism who had mean drug plasma levels nearly two times more than those of patients with the extensive metabolizer genotype (31-34).

Pharmacodynamics

Patients in later life may have age-related changes in drug sensitivity (26). Elderly patients may have pharmacodynamic changes that make them more vulnerable to anticholinergic and noradrenergic side effects of medication, due to age-related receptor sensitivity and age-related changes in cholinergic and mono-aminergic neurotransmission (25,35). Dosing, therefore, should begin with low doses and be gradually titrated. If administration is a challenge, many antidepressants come in liquid form or have soluble tablets. Despite these concerns, clinicians should be attentive not to under-treat these patients and fail to provide adequate trials at therapeutic dosages (25). Age-related changes in receptor sensitivity and concentration can change the effectiveness of a medication and result in increased adverse effects. Changes in function of acetylcholine receptor can increase the severity of CNS and peripheral anti-cholinergic adverse consequences e.g. confusion, blurred vision, constipation, and urinary retention (31,36,37). Aging alters the serotonergic system, including decreasing serotonin-2A receptors and the serotonin transporter (36). Genetic polymorphisms of the latter may influence treatment response and predispose patients to adverse effects. Functional reserve decreases with age and requires more time to reestablish homeostasis after exposure to a stressor (31-38). The overall effect of these pharmacodynamic changes can worsen adverse effects in elderly patients, even at therapeutic doses (31).

Management Principles

More than 20 antidepressants have been approved by the Food and Drug Administration (FDA) for the treatment of depression in older adults (39). The main target of the anti-depressive treatment is that of obtaining and maintaining a complete remission, i.e. achievement of a complete resolution of depressive symptoms, and a return to the previous level of function. Failure to obtain remission implies a higher risk of relapse with successive episodes characterized by excessive depressive severity, shortened inter-episodic pauses, progressive functional impairment, and an increase in the rates

of suicide and mortality, due to any cause. The pharmacological treatment of geriatric depression is based on the use of anti-depressive drugs, combined with psychotherapy (if needed), antipsychotic drugs in cases of psychotic depression or electroconvulsive therapy in cases of severe depression, non respondent to drug therapy. The duration of treatment depends mainly on the patient anamnesis; generally, the acute treatment of an episode, followed by the continuation and maintenance phases, lasting almost for a year. In patients with two previous episodes, the duration may be prolonged for three years, with successive prolongation beyond three years of treatment in patients with a history of more depressive episodes (1,40).

When selecting an antidepressant it is important to consider the elderly patient's previous response to treatment, the type of depression, the other medical problems of the patient and medications and the potential risk of overdose (41,42). Psychotic depression will likely not respond to antidepressant monotherapy, while treatment of bipolar depression will require a mood stabilizer. Antidepressants are effective in treating depression in the face of medical illnesses, although caution is necessary to prevent worsening of the medical condition or causing adverse events (41,43). For example, dementia, cardiovascular problems, diabetes and Parkinson's disease, which are common in older adults, can worsen with highly anti-cholinergic drugs (41,44). Such drugs can cause postural hypotension and cardiac conduction abnormalities. Minimizing the interactions of drugs is also important especially because of the number of medications that old patients are often taking. Tricyclic antidepressants are lethal in overdose and are avoided for this reason (41).

The pharmacological management of depressive disorder is divided into three phases, namely acute treatment, continuation therapy and maintenance treatment (45). These will be discussed in turn.

Acute Phase

Antidepressants are usually the first-line treatment in patients with moderate and severe depressive episode. In general, no antidepressant drug is clearly more effective than another, but rather antidepressants should be tailored to the patient, taking into account the likely side effects and tolerability. Older antidepressants should be avoided in patients at risk of suicide. The acute phase of major depression treatment is provided with one of the antidepressant drugs, with a first assessment of response after 4-8 weeks. Therapeutic response may occur within 2 weeks. Likewise, if there has been no response within 4 weeks recovery is unlikely (45,46). Once recovery has started it may take up to 12 weeks for a full response (i.e. longer than in younger patients) (45). In case of a positive response, the therapy is carried on in the continuation phase, usually with the same drug and at the same dose. The therapeutic alternatives in the respondent patient include: substitution of the antidepressant drug, combination of drug therapy and psychotherapy or the use of electroconvulsive therapy. More alternatives are present in the partial response patient, including change in antidepressant doses, addition of another antidepressant or no antidepressant drug (lithium, thyroid hormone and etc.). Several factors contribute to the antidepressant drug to be used in the acute phase of treatment (1).

Continuation Phase

Continuation drug therapy reduces the risk of relapse after remission. It is not a fixed period, but in older people a 12-month period of continuation with antidepressants is recommended, in contrast to a 6-month period for younger patients. However, patients with recurrent depression can be treated for 2 years. For patients with delusional depression on antipsychotic medication, it is recommended that this be continued for 6 months before being tapered off (45,47).

Maintenance Phase

Major depression often follows a recurrent course, and older people benefit from maintenance therapy even after a first episode of depression. Evidence comes from several studies. Citalopram, an SSRI, prevented recurrence over a period of 1-2 years, suggesting that a protection effect is not confined to tricyclic antidepressants (48). Extrapolating from studies of younger patients, the risk of relapse is increased if there are residual symptoms or if chronic life stresses exist (49). The case for long-term antidepressant treatment needs to be balanced against adverse effects, which for the older antidepressants can include troublesome weight gain, tooth decay and cardiovascular disturbance (45). Thirty to 40% of geriatric depression cases may be chronic, with recurrence rates of up to 38%, 3 to 6 years after resolution of the initial depression.

Maintenance of treatment regimens for an amount of time sufficient to resolve the depression, as well as adequate full-dose maintenance therapy after remission is critical. Maintenance therapy has been recommended for 6 to 9 months to 2 years after remission of the first depression episode. Some data suggest that antidepressant therapy should continue indefinitely in older persons with late-onset or recurrent depression. In practice, antidepressant therapy is often terminated prematurely due to somatic side effects from the medication, a belief that the patient no longer needs treatment, and other reasons (50).

Choosing an Antidepressant

Fortunately there are several antidepressants that have been shown to be efficacious in elderly patients being treated for a major depressive episode without psychotic features. It is recommended that selection of an antidepressant be based on the least expected side effect profile and lowest risk of drug-drug interactions (41).

A recent meta-analysis of antidepressant use in the elderly found no significant difference in efficacy between drug classes (51). Therefore, selection of an antidepressant is often based on targeting specific symptoms while considering an antidepressant's adverse-effect profile to maximize a patient's overall health and lifestyle (52). Antidepressants are medications that enhance and stabilize serotonin, norepinephrine, and/or dopamine systems in the brain. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are first-line antidepressants for most prescribers, although other antidepressants such as bupropion and mirtazapine could also be used for first-line treatment. The best dosing strategy for late-life depression is to begin the patient's antidepressant at a low starting dose and increase at a rate that is comfortable for the patient. Because it is not possible to predict the antidepressant dose to which a patient will respond to, it is important to assess for tolerability and symptom severity after each dosing increment. The reality of trial and error in antidepressant treatment comes into play when ultimately the patient is either unable to tolerate the medication or does not achieve remission. When patients are already receiving medications that are metabolized through CY P1A2, 2C9, or 2D6, the psychiatrist should recall that there is potential for a drug-drug interaction with certain antidepressants (53). The antidepressants that have a low risk of causing clinically significant CY P450 drug-drug interactions include citalopram, escitalopram, sertraline, venlafaxine, desvenlafaxine and mirtazapine. Fluoxetine, in addition to its CY P450 inhibitory effects, is also noted to have an average half-life of approximately 120 hours. Citalopram and escitalopram have average half-lives of approximately 30 hours. Medications with long elimination half-lives put patients at an increased risk of accumulation, which could manifest as difficulty in tolerating a medication. Given the risk of cognitive decline in elderly patients it is important to avoid the use of antidepressants with anticholinergic properties. Tricyclic antidepressants (TCAs) such as nortriptyline and desipramine are well known to be muscarinic-1 receptor antagonists. Paroxetine also has anticholinergic properties, although many believe that its anticholinergic effects are not as potent as the TCAs. When the psychiatrist is selecting an antidepressant to treat late-life depression, first consideration must be given to the patient for whom it is being prescribed. The patient's history of depression and its treatment is perhaps the initial issue a psychiatrist should consider. Is the patient's current episode of depression the first, or have there been previous episodes? Knowing which antidepressant treatment trials the patient has received in the past can help determine which antidepressants should not be used for the current depressive episode. Furthermore, if a patient has recurrent depression and has received several previous antidepressant treatment trials, it is possible that the antidepressant treatment strategy needed for the current episode maybe more aggressive and associated with a higher degree of safety concerns. For example, for some patients with recurrent depression, the use of higher antidepressant doses or antidepressant combinations or the use of TCAs may be considered. Using any of these strategies, however, should indicate to the psychiatrist that the risk of poor tolerability is greater and that monitoring for appropriate adverse effects in the patient is necessary. The psychiatrist should next consider whether the patient has co-occurring medical or psychiatric conditions. As discussed earlier, comorbidities are likely to be treated with concurrently prescribed medications so the risks of drug-drug interactions, poor treatment adherence, and poor treatment outcomes become magnified (27).

SSRIs

Selective serotonin reuptake inhibitors (SSRIs) inhibit the pre-synaptic reuptake of serotonin. Acute

treatment of depression in the elderly frequently begins with a trial of a selective serotonin reuptake inhibitor (SSRI) for four to twelve weeks with the goal of remission. SSRIs are generally well tolerated in the elderly and have limited drug-drug interactions and are less likely to be discontinued. A good trial is one that has achieved a therapeutic dose in at least eight weeks and about 60-70% of patients have responded. Once there is resolution of depressive symptoms, maintenance treatment should be continued for at least four to six months in order to consolidate remission and recovery (26).

SSRIs have lower anticholinergic effects than older antidepressants and are thus well tolerated by patients with cardiovascular disease (41). A recent meta-analysis of antidepressant use in elderly populations found SSRIs to be as effective as TCAs; the SSRIs were associated with a lower rate of discontinuation as a result of adverse effects. However, SSRIs have several potentially serious side effects, including GI bleeding (especially with concurrent use of aspirin or NSAIDs) and hyponatremia (up to12% of older adults treated with SSRIs may present with clinical symptoms of hyponatremia) (54). Some other common consequences are CNS effects (headache, dizziness and anxiety), high risk of fall and decreased libido. In the elderly, caution should be taken because SSRIs appear both to negatively affect bone marrow density (BMD) and to increase fall risk (55). however, this risk should be considered in context with the decrease in BMD associated with depression itself (31). Owing to renal functioning associated with aging, there is also an increased risk of developing hyponatremia in elderly patients secondary to a syndrome of inappropriate anti-diuretic hormone secretion. This is seen in approximately 10% of patients taking antidepressants and is associated particularly with SSRIs and venlafaxine. It is important to check sodium levels one month after starting treatment on SSRIs, especially in patients on other medications with a propensity to cause hyponatremia, such as diuretics. Of course it is also important to check sodium levels if symptoms of hyponatremia such as fatigue, malaise, and delirium arise. Of the SSRIs, fluoxetine is generally not recommended for use in the elderly because of its long half-life and prolonged side effects. Paroxetine is also typically not recommended for use in the elderly as it has the greatest anticholinergic effect of all the SSRIs, similar to that of tricyclic antidepressants. SSRIs considered to have the best safety profile in the elderly are citalopram, escitalopram, and sertraline (41). It generally is recommended to initiate doses at half the initial dose recommended for younger adults and titrate up slowly to the optimal dose. If adverse effects do occur, one should consider decreasing dosage if the medication is effective or discontinuing the medication if the adverse event is severe or intolerable. If the side effect of the SSRI is minor, one should consider trying another SSRI versus changing to another class of antidepressant. If the side effect is severe, consider switching to another class of antidepressants. An adequate trial of medication is at least 6 weeks of the recommended dosage. If depressive symptoms resolve, continuation of antidepressant therapy for 12 months is recommended to prevent relapse. In older adults with a history of two or more episodes of MDD, long-term indefinite treatment should be considered at the same dose that showed efficacy. Further guidelines for long-term maintenance have not been adequately established (56).

SNRIs

Serotonin–norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine have come to play a role in the treatment of late-life depression. In a specific guideline for geriatric depression, a 2001 expert consensus panel recommended Venlafaxine as an alternative to SSRIs as a first-line treatment for depression in the elderly and as a preferred agent in those who do not respond to SSRIs. A review of the cardiovascular profile of duloxetine reported a low occurrence of cardiovascular adverse events (AEs), suggesting that this agent may be an appropriate choice for the treatment of MDD in the elderly (57). There are also data suggesting that SNRIs may have greater efficacy than SSRIs in the treatment of depression in the general adult population and may have a favorable effect on the pain associated with depression (5,58).

Like TCAs, SNRIs block the synaptic reuptake of both serotonin and norepinephrine. However, SNRIs have respectively lower attachment to cholinergic and histaminic receptors, which gives these agents an adverse-effect profile more similar to that of the SSRIs. Duloxetine appears to increase heart rate and blood pressure slightly. However, a trial of duloxetine in older adults showed no increase in hypertension or orthostatic hypotension relative to placebo. A study of venlafaxine in older adults showed a small but statistically significant increase

in heart rate and decrease in standing blood pressure. However, a review of a large number of National Health Service records from the United Kingdom found no increase in the relative risk of significant cardiac events in patients who received venlafaxine compared with patients who received fluoxetine or citalopram. Venlafaxine has been reported to increase blood pressure with higher doses; however, a study of venlafaxine ER in depressed patients older than 80 years demonstrated no significant changes in blood pressure. A direct comparison of duloxetine and venlafaxine in younger patients suggests that there is a small but significant increase in the number of patients taking venlafaxine in whom elevated systolic blood pressure developed (31-59-60).

Bupropion

Bupropion is the only antidepressant available that inhibits dopamine reuptake and that acts on noradrenergic receptors. Bupropion can cause GI upset and weight loss, which may be a disadvantage in weak seniors. The most medically significant adverse effect linked to bupropion is a dose-dependent increased risk of seizures. In younger patients without a history of seizures, this risk appears to be relatively low, and it is even less in the extended-release preparation. Seizure risk is known to increase with age, and elderly with cerebrovascular disease, dementia, or post-trauma (e.g. a fall) are at high risk for seizures. Use caution when prescribing bupropion for an elderly depressed patient who has any additional risk factors. Bupropion may also exacerbate anxiety extremely and, unlike SSRIs and SNRIs, it is not indicated for the treatment of anxiety disorders (31).

Mirtazapine

Mirtazapine is an antagonist of both norepinephrine and serotonin receptors. Most of the medically serious harmful effects are comparable to those of SSRIs (rare agranulocytosis and hyponatremia, GI bleeding). Some clinicians take advantage of mirtazapine's adverse-effect profile in treating common geriatric depression symptoms of insomnia (antihistaminic effect without anticholinergic toxicity), poor appetite (antihistaminic effect), GI distress (serotonin-2 postsynaptic antagonist effect), and anxiety (31).

Reboxetine

Reboxetine is a specific noradrenaline reuptake inhibitor. It has not been recommended for use in older people in the UK because there are insufficient efficacy data for the elderly. There have been some uncontrolled efficacy studies, and it appears to be well tolerated and safe in this patient group (45).

SARIs (Trazodone & Nefazodone)

Serotonin antagonist and reuptake inhibitors (SARIs) prevent reuptake of serotonin and also have an antagonistic effect on some serotonin receptors, which may help mitigate some of the harmful effects of SSRIs. Both available drugs in this class, trazodone and nefazodone can be sedating. In addition, nefazodone inhibits the CYP3A4 system which is problematic in older adults who may be taking multiple medications for other conditions. Nefazodone has been linked to increased rates of liver failure and is no longer widely used clinically for this purpose (31). Nefazodone is structurally related to trazodone (desyrel) and works well in patients with anxiety and depression but has relatively rare side effects such as agitation and sexual dysfunction. Nefazodone can improve sleep, too. However, the use of nefazodone has been associated with liver failure and the drug has been taken off the market in Europe and Canada (19).

TCAs

Tricyclic antidepressants (TCAs) have significant anticholinergic effects which result in an adverse-effect profile that is undesirable in older adults. Complications may include confusion, blurred vision, dizziness, constipation and urinary retention. TCAs are also linked to cardiovascular effects, such as postural hypotension and prolonged transition, which elevate the risk of fall or cause complications in patients with cardiovascular comorbidities. Due to these significant harmful effects, TCAs are not recommended as first-line treatment of depression in the elderly (31). All TCAs are equally effective, but their adverse effect profiles differ. The secondary amines, nortriptyline and desipramine cause fewer anticholinergic effects than other TCAs. Moreover, nortriptyline causes less postural hypotension than other TCAs, even in patients with reduced left ventricular function. Although age seems to be associated with reduced clearance of imipramine and amitriptyline, clearance of desipramine and nortriptyline does not seem to decrease with age. For these reasons, the secondary amines are preferred over the tertiary amines (imipramine and amitriptyline) for use in elderly patients. Recommended starting doses are 10 mg of desipramine or 10 mg of nortriptyline given at bedtime, with increases of 10 to

25 mg every 3 to 7 days until a total dose of 50 to 75 mg/d is reached (20).

MAOIs

Monoamine oxidase inhibitors (MAOIs) inhibit the degradation of neurotransmitters and hinder their effect. The primary drawback of the MAOIs for patients is the dietary restrictions required to prevent a hypertensive crisis. Use of an MAOI also limits a clinician's opportunities to augment antidepressant therapy with SSRIs and TCAs, which cannot be used concomitantly with MAOIs. More common is the risk of hypotension with MAOI use in the elderly. According to limited evidence on adverse effects in the elderly and the accessibility of more preserved- and not necessarily more effective alternative treatments, MAOIs are not widely used to treat geriatric depression (31). Although MAOIs are thought to be dangerous and difficult to use, drugs such as phenelzine (nardil) are to some degrees safe and effective in older patients. A full therapeutic response can be achieved after five to seven weeks of treatment. Hypotension, hypertension and food-drug interactions are the most likely problems with MAOI use. Taking agents from more than one drug class can increase a patient's risk for developing serotonin syndrome (i.e. mental status changes, hyperreflexia, agitation, myoclonus, diaphoresis, shivering, tremor, diarrhea, incoordination and fever (19).

Drug interactions

Drug interactions are a major concern in the selection of an appropriate antidepressant. Most drugs are metabolized in the liver by the cytochrome P-450 system. Inhibition of one of these enzymes results in higher blood levels of any drug that is metabolized by that enzyme, and induction of that enzyme results in lower levels of such drugs. Two of these enzymes, CYP2D6 and CYP3A4, have particular relevance to the treatment of depression (61). Many antidepressants such as bupropion, duloxetine, fluoxetine and paroxetine inhibit the CYP2D6 enzyme, which metabolizes a numerous variety of drugs, including β-blockers such as propranolol; antipsychotics such as haloperidol and clozapine and many antidepressants—TCAs such as nortriptyline and other SSRIs. Erythromycin and grapefruit juice both inhibit the CYP3A4 enzyme, which metabolizes citalopram, sertraline, mirtazapine, and venlafaxine (62). Start these medications at low doses to allow for appropriate adjustments in response to increased or inhibited enzymatic activity. Caution patients who start taking an antidepressant about drugs such as antibiotics that could inhibit or induce the metabolism of the antidepressant. This is especially serious with antidepressants that have a narrow therapeutic window. MAOIs interact with a wide variety of medications including antihypertensives, anesthetics, pain relievers (especially meperidine) and monoamines (such as levo-dopa) (63). Non prescription supplements and herbs can also interact with the CYP system or otherwise interfere with antidepressants (31). Venlafaxine, mirtazapine and bupropion are also considered to have good safety profiles in terms of drug-drug interactions (64). SSRIs such as fluoxetine, paroxetine and fluvoxamine have higher risks of drug-drug interactions (41).

Treatment-Resistant Depression

An important chapter in the management of elderly depression is that of treatment-resistance, the definition of which states that it is an incomplete or absent response, or high tendency to recur in patients adequately treated with at least 2 antidepressant drugs at adequate doses and times of treatment. Several factors contribute to the occurrence of treatment-resistance especially in elderly depressive patients with medical comorbidities (1). Various factors have been discussed that may increase the probability of not responding to antidepressant treatment. The presence of a comorbid psychiatric or general medical disorder is very important. Keitner and colleagues reported that 53% of patients hospitalised with major depression have coexisting axis I, II, or III conditions, stated as "compound depression" (65). Other factors that guarantee consideration in the evaluation of treatment-resistant depression include female gender, family history, early or late age of onset, severity of illness, and course chronicity. Assessment of treatment-resistant depression (TRD) should include careful attention to the possibility of pseudoresistance. Causes of pseudoresistance include prescribing an inadequate dose or duration of treatment, patient noncompliance or unusual pharmacokinetics, and misdiagnosis of the primary disorder by not recognizing a secondary mood disorder or a depressive subtype. Of the clinical variables reviewed, the presence of a comorbid psychiatric or general medical disorder, older age, greater severity of illness, and chronicity of course show the strongest evidence as risk factors

for treatment-resistant depression. Clearly, more research is essential to investigate the characteristics and predictors of treatment-resistant depression by means of using controlled trial designs and standardized definitions of treatment resistance (66).

Strategies of Treatment

Treatment options for refractory depression are: the switching option, the augmentation or the combination one. The switching option, the substitution of an antidepressant with another one, is used in cases of lack of tolerance or poor symptomatic reduction. The advantages of this option include better compliance, less drug interaction and reduced costs. The other two options, the combination method (association of another antidepressant to the first one) or the augmentation one (association of a non antidepressant drug) are used in cases of partial remission; the advantages of these two methods are a more rapid response, lack of necessity of titration and maintenance of the initial improvement (1,67).

Switching

The decision to switch a medication should be made on the basis of its effectiveness and adverse effects. If the harmful effects of a drug create significant discomfort, switching to another drug may be beneficial. A medication should be immediately stopped or tapered off if it produces medically serious adverse effects, such as hyponatremia or seizures (31).

Add-On Treatments

Augmentation: Continued treatment with antidepressants comparing to placebo is more efficacious in preventing relapses and recurrences. In absence of maintenance treatment, 30-90% who achieve recovery will experience recurrence in 8 to 48 months. Unfortunately, failure of response to SSRIs may be as high as 77%. Therefore, augmentation of the SSRI with buproprion, lithium or nortriptyline can be considered. For lithium, drug levels and renal function should be closely monitored. Furthermore, augmentation using other antidepressants such as mirtazapine and venlafaxine may also be effective. There are several atypical antipsychotics that are FDA approved as augmentation strategies. The data on treatment of non-remission of depressive symptoms is limited and results are not optimal. This will hopefully be an area of greater clinical investigation in the future (26).

Combination: The aim of combining antidepressants is to combine two or more mechanisms of action in an attempt to obtain a synergy (enhancement of efficacy) or enhanced tolerability (by opposing or blocking side effects) (68). Concurrent administration of two or more antidepressant agents (e.g., adding trazodone [desyrel], desipramine [norpramine] or bupropion [wellbutrin] to fluoxetine) may result in a different therapeutic response than that produced by use of either drug alone (68).

Treatment of Comorbidity

In the cognitively impaired: Despite the high prevalence of depression in patients with dementia, there are limited trials of antidepressants in this population. However, placebo-controlled trials of citalopram, fluoxetine, and sertraline as well as some TCAs have demonstrated efficacy in this group (30). The compromised ability of the patient to report adverse effects and the fact that s/he has stopped taking the medication is of concern, which points to the need to rely on caregivers' reports, which may be incomplete. Moreover, confusion or cognitive impairment from anticholinergic antidepressants such as TCAs may be misinterpreted as worsening dementia, and it may go undetected.

Addressing depression in older adults with dementia without using an antidepressant can be difficult and requires additional effort to consider their individual circumstances and to engage them. But psychosocial interventions that focus on helping people with dementia and their caregivers coping with the consequences of cognitive loss would be the best first step (69). In past studies, depression associated with dementia has been safely treated with SSRIs and tricyclics. These recent studies also demonstrated antidepressant efficacy in patients with dementia; patients whose depression lifts may also be associated with modest improvement in cognitive function (70).

Comorbid physical illness

Depression is commonly associated with medical illness in the elderly. Although trials of antidepressants in older adults are generally safe and well tolerated different from healthy people, many elderly patients have considerable medical comorbidities. A recent analysis of a large cohort in elderly patients for whom an antidepressant was prescribed found a median of 5 comorbid conditions in more than 40% of patients: hypertension,

hyperlipidemia, ischemic heart disease, and gastro-esophageal reflux. While the cardiovascular adverse effects of TCAs make them undesirable to use in patients with significant cardiac disease, SSRIs with their convenient cardiovascular profile appear safe for use in this population. SSRIs also appear to be both safe and effective in the treatment of post-stroke depression. Pain was a frequent comorbid condition, and occurred in 24% of patients in the cohort mentioned above. The use of antidepressants with NSAIDs or opioids can lead to an increased risk of complications, such as GI bleeding or serotonin toxicity (70). The adverse-effect profile of SSRIs may be preferable to those of TCAs in older adults because these agents generally lack cardiovascular and anticholinergic effects (except Paroxetine, which has some anticholinergic properties). A randomized controlled trial of sertraline in patients who experienced depression after hospitalization for a myocardial infarction or unstable angina showed no difference in cardiac safety parameters or in adverse cardiac events compared with placebo. This study suggests that SSRIs are well tolerated, even in patients with significant cardiovascular comorbidities. (11). Untreated depressed persons with comorbidities (e.g. diabetes, arthritis) are at risk for further health deterioration. Awareness of the key presenting and comparatively atypical signs of irritability and anxiety, unintended weight loss, and preoccupation with death can help identify patients so that appropriate treatments can be discussed and initiated (50). Because depression in the elderly is associated with unfavorable medical outcomes and suicide, treatment should generally be instituted (71). Although depression has been recognized as detrimental to cancer prognosis, treatment, and related quality of life not much is known about the treatment of depression among the elderly with cancer (72).

Psychotherapy

Psychotherapy alone is as efficacious as antidepressant medication in patients with mild to moderate major depression and may be used as first-line treatment (73). For many years it was thought that elderly patients could not benefit from psychotherapy because they were "no longer educable and, on the other hand, the numerous issues to be dealt with would prolong the duration of the treatment indefinitely". This shows that the same highly focused types of psychotherapy that are effective in younger persons are also effective in elderly patients (20). Cognitive behavioral therapy (CBT), reminiscence therapy (i.e. an intervention that uses recall of former events, quality of life, feelings and thoughts to facilitate pleasure and adaption to the present), and general psychotherapy were compared in their effectiveness in treating depressive symptoms. All three types of psychotherapy were found to be effective treatments for depression in elderly people. Particularly, each format of individual therapy was significantly more effective than no intervention or placebo. CBT and reminiscence therapy had similar efficacy in treating depression in the elderly patients.. The results altogether confirm the efficacy of psychotherapy for treating depression in the elderly (74). Psychotherapy alone or in combination with other modalities of treatment is effective in treating late-life mood disorders depending on the severity and nature of the illness and patient characteristics. The duration and the choice of therapy depend on several factors, including disease severity, presence of a support system, individual patient variability and use of combination treatment modalities.

Cognitive behavioral therapy:

CBT is a structured, goal-directed, problem-focused, and time-limited approach focusing simultaneously on the environment, behavior, and cognition. Patients learn how their thoughts contribute to symptoms of their affect and how to change these thoughts. Elevated cognitive awareness is combined with specific behavioral techniques. It is the form of psychotherapy most often used with depressed older adults and has shown to be highly effective with patients who have depression in hospital and community settings and in individual and group formats. CBT also seems to be of benefit in the management of bipolar disorder in lowering the rate of relapse, improving medication compliance, and decreasing hospitalizations.

Interpersonal therapy:

Interpersonal therapy (IPT) is a practical, focused, brief, and manual-based therapy applicable in the treatment of depression in older adults in acute phase and in relapse prevention. It focuses on disturbance of patients' current relationships in the domains of role transition, role disparity, abnormal distress, and interpersonal deficit. The aim is to improve communication, express affect, and support renegotiated roles in relationships with the effect of

symptom reduction and improvement in functionality. Interpersonal therapy has shown clear benefits in depressed older adults. Interpersonal psychotherapy is a highly precise type of psychotherapy specifically developed for the treatment of depression (20).

Systemic (family) therapy:
Systemic therapy attempts to correct distorted communications and relationships as a means of helping the entire family or system, including the identified patient. Late life depression is sometimes complicated by enmeshed and high expressed emotional family or systemic relationships. It will be present if at least some part of the system (crucial members of the family) can be engaged in it. Controlled outcome studies of family therapies for depression suggest that the addition of problem-centered, family-based interventions may improve family function and enhance patient recovery from depressive symptoms. Cognitive analytical therapy or brief dynamic therapy CAT or brief dynamic therapy represents a modern integration of analytic and cognitive therapy traditions to offer a brief, structured, and collaborative therapeutic experience in a coherent way of linking the past and present. It shows that later life is the period when coping mechanisms are challenged by disability, losses, and changes in social role which can easily resurface pre-existing trauma and low self-esteem that lead to affect deregulation and interpersonal difficulty. Patients who have personality disorders and past traumatic experiences living in highly dysfunctional relationships or isolation can get help from a dynamic or CAT approach (75).

Brief psychodynamic therapy:
From a brief dynamic perspective, depression is often conceptualized from a psychodynamic perspective as being the result of unresolved, unconscious conflicts, usually stemming from childhood. The goal of this therapy for the patient is to understand and cope better with these feelings. As such, brief psychodynamic therapies focus on the reflection of past experiences, clarification of affect, the therapeutic relationship, and the confrontation of maladaptive interpersonal patterns, wishes, or conflicts (75,76)

Psychoeducation:
Psycho-education provides patients and families with information about their diagnosis, its treatment, how to recognize relapse signs to prevent it, and strategies to cope with the reality of prolonged emotional or behavioral difficulties. It can be a component of or an adjunct to other forms of therapy and may be directed toward the patient or the patient's family. The main goal is to reduce confusion, distress, and anxiety within the patient or the patient's family to facilitate treatment compliance and reduce the risk of relapse. In combination with primary treatments, psycho-education is particularly helpful for patients and the families of patients who have bipolar disorder (56).

Exercise Programs:
Several randomized, controlled trials suggest that short-term (e.g. 12-week) supervised, group-based physical-exercise programs involving walking or other forms of aerobic exercise can reduce depression in older adults; 45 to 65% of program participants have a substantial reduction in symptoms of depression as compared to 25-30% of controls. A physical-exercise program could be a first-line strategy for patients with mild-to- moderate depression who prefer this approach, but it may be difficult for patients with depression to engage in such a program, and additional treatment with antidepressants or psychotherapy may be needed (39).

ECT *(Electroconvulsive Therapy)*
Several randomized, controlled trials have established the efficacy of ECT for severe late-life depression, with efficacy rates ranging from 60 to 80% (78). ECT is particularly indicated for patients with depression that is resistant to other treatments and for patients at risk for serious harm because of psychotic depression, suicidal ideation or severe malnutrition. ECT is usually administered as a series of 6 to 12 treatments in an inpatient psychiatric setting over a period of 2 to 4 weeks. Common side effects include headache that usually responds to analgesics and temporary confusion or memory impairment. Less common side effects include memory loss for events during the period surrounding treatment and falls immediately after treatment sessions. The mortality associated with ECT is less than 1 death in 10,000 patients. A successful course of ECT should be followed by maintenance pharmacologic treatment because of high rates of relapse. In a randomized trial involving patients with depression that had improved after ECT, 6-month relapse rates were 84% among patients receiving placebo, 60% among patients receiving nortriptyline, and 39% among patients

receiving lithium plus nortriptyline (39,79). Contraindications include recent myocardial infarction, brain tumor and uncontrolled heart failure (19). ECT is also considered as an alternate treatment for severe depression, specifically in cases where a patient has failed to respond to two antidepressants or is acutely suicidal such that a quick improvement in symptoms is required for the patient's safety or if the patient is unable to take medications owing to medical problems. In the elderly it has been associated with better treatment outcomes and fewer side effects than medications. In the case of treating psychotic and severe depression with ECT, another advantage is that an antidepressant typically exists in maintenance treatment to avoid the use of an antipsychotic medication and its potential side effects with long-term use (41). Geriatric patients obtained more benefit from education, as shown by their greater improvement in decisional capacity after education (80). With respect to the goal of maximizing efficacy plus minimizing cognitive side effects, dispute continues about unilateral vs. bilateral electrode position. It is thought that Right unilateral (RUL) ECT causes less cognitive impairment than bitemporal, but bitemporal ECT is believed to be more effective than unilateral ECT (80). The relation between electrode position and electrical dose relative to a patient's seizure threshold is controvertial.Seizure threshold is the minimum electrical intensity required to induce an adequate generalized grand mal seizure. It is well known that a generalized tonic-clonic seizure is necessary for ECT to exert the expected antidepressant effect (41). However, several studies have shown that, while a generalized seizure is sufficient for the efficacy of bilateral ECT, the patient should not categorized for RUL treatment (41,80). ECT, however, had greater memory impairment at 1 week and 2 months after finishing ECT. These results led to this conclusion that "right unilateral ECT at high dose is as efficacious as a robust form of bilateral ECT but produces less severe and persistent cognitive effects" (80).

Length of seizure, beyond the widely quoted minimum criterion of 20 seconds of motor or 25 seconds of electroencephalographic manifestation, is not related to ECT efficacy (80). Many clinicians recommend avoiding the use of benzodiazepines in elderly patients during ECT, if possible. If a benzodiazepine is required, lorazepam at a dose of 0.5 to 1.0 mg daily is the most appropriate choice. Antipsychotic medications, which can lower seizure threshold, can be an effective alternative to benzodiazepines in the acute management of agitation or severe anxiety associated with late-life depression. In patients with seizure disorder, antiepileptic medication should initially be maintained at a therapeutic dosage, because dosage reduction or discontinuation increases the patient's risk of experiencing seizures between ECT treatments (41). The dosage should be cautiously reduced only if an adequate seizure cannot be elicited. In the case of patients taking antiepileptic medications as mood stabilizers, it is preferable to withdraw the medications prior to ECT (80).

Controlled studies have established that bitemporal ECT administered 3 times weekly results in more rapid improvement than treatment twice weekly, but there is no difference between the 2 schedules in the total number of treatments required to achieve response or in the percentage rate of response. Conversely, the more frequent schedule is associated with more retrograde amnesia, both immediately after finishing the course of ECT and at 1-month follow-up. Thus, twice-weekly administration may be the optimal schedule for bitemporal ECT in the elderly, unless clinical indications or other considerations (for example, length of hospitalization) require the more rapid antidepressant effect of thrice-weekly treatment. Comparable data on the frequency of RUL ECT are not available (80).

There is considerable variability in the number of ECT treatments required for eliciting response. As a result, the number of treatments in a course of ECT should be decided on a case-by-case basis. ECT is typically discontinued once symptoms remit or when symptoms reach a plateau of improvement after 2 consecutive treatments. Among elderly patients with major depression, 6 to 12 treatments are often required to achieve maximal benefit, but some patients may need more than 12 treatments. In the case of no response or minimal response many experts recommend at least 10 to 12 bitemporal treatments before the depressive episode is labeled nonresponsive (78,80).

The mortality rate associated with ECT is only 0.2 to 0.4 per 10000 treatments, no higher than that expected with general anesthesia alone. Cardiovascular complications constitute the principal cause of ECT-related morbidity. Delivery of the ECT stimulus induces a brief parasympathetic

response that can result in sinus bradycardia and hypotension. Not infrequently, transient asystole occurs. As the patient starts to seize, a discharge in catecholamines from the adrenal medulla results in increased heart rate and blood pressure. In patients with ischemic heart disease, this period of increased myocardial oxygen demand may increase the risk of cardiac ischemia. In turn, ischemia is the main cause of arrhythmias. ECT use in medically ill patients has been extensively reviewed elsewhere, and a detailed discussion is beyond the scope of this article. ECT has been safely and effectively performed in the presence of a wide range of serious medical conditions, including: severe ischemic heart disease, aortic stenosis, chronic airways disease, osteoporosis, aortic and cerebral aneurysms, brain tumors, epilepsy, and recent stroke. Patients with pacemakers and patients taking anticoagulants can safely undergo ECT. As with any treatment, the risks of ECT must be balanced against its potential benefit and the risks and benefits of alternative treatments or no treatment. It is worth emphasizing that untreated depression can have severe medical consequences in the elderly, including dehydration, malnutrition, skin breakdown or deep venous thrombosis secondary to prolonged immobility and an increased risk of mortality. Further, untreated depression can adversely affect recovery from various medical and neurological conditions (78-80).

Depression relapse in response to ECT is a significant problem. Several studies suggested that despite continuing antidepressant medication, the relapse rate during the 6 to 12 months exceeds 50% following acute ECT . Preventing the relapse still is a major challenge for the field. A primary indication for ECT is to obtain an adequate response of antidepressant medication, yet these medications are usually prescribed as supplementary treatment following ECT. Thus, after responding to ECT, patients generaly switch back to a treatment modality that had shown ineffectiveness. Therefore, the resistance to antidepressant medication predicting post-ECT relapse is not surprising. To solve this problem, ECT after response is better to be continued. Currently available, albeit limited, data suggest that continuing ECT (C-ECT) is a safe, efficacious and cost-effective way to prevent relapse (78-80).

Newer Modalities

Vagus nerve stimulation:

Vagus nerve stimulation (VNS) was initially used and finally approved for treatment of refractory epilepsy in 1997. Noticing its mood-brightening effect on epileptic patients, anatomic afferent connections of the left vagus nerve to the CNS and to structures relevant to mood regulation lead to studies conducted to determine the effectiveness for depression. Many of these studies demonstrated its long-term benefit for treatment-resistant depression, which resulted in its FDA approval in 2005 for the same indication. So far studies have failed to show its effectiveness as monotherapy or in the acute setting. VNS may be more promising as a long-term maintenance treatment to sustain remission than as an initial treatment to bring someone out of depression. Under general anesthesia, a pulse generator is implanted in the left chest wall and a wire threaded into the neck and around the left vagus nerve. The stimulator, similar to a cardiac pacemaker, is programmed through an external hand held device. This procedure is safe (the only common adverse effect is hoarseness) and causes fewer side effects than antidepressant medications and ECT. Performing a surgical procedure under general anesthesia is a disadvantage as is the one-time high cost. Its safety and low side-effect profile makes it a good modality for selected elderly patients, although there is no adequate controlled data in this age group (56,81,82).

Transcranial magnetic stimulation (TMS):

Repetitive transcranial magnetic stimulation (rTMS) uses an electric coil to generate a magnetic field that stimulates the cerebral cortex. It is well tolerated by patients and, in contrast to ECT, does not require the use of anesthesia and does not appear to cause cognitive impairment. Randomized controlled and meta-analytic studies of rTMS have produced conflicting results. A subsequent randomized trial of rTMS in 60 patients who had TRD did show a significantly higher rate of response in two active treatment groups (high-frequency left-sided rTMS and low-frequency stimulation to the right prefrontal cortex) compared with placebo. The absolute benefit, however, appeared to be relatively small. rTMS seems most promising to those with depression who have not responded to medication before going on to ECT. Once its benefit is established this is another safe and potential treatment option in the geriatric group. One study showed no significant benefit for TRD in the elderly, however rTMS is not FDA approved at the present time (56,83,84).

Deep brain stimulation:
Deep brain stimulation (DBS) is an FDA-approved treatment of refractory Parkinson's disease and other movement disorders. Stimulating electrodes (*w*1 mm in diameter) are implanted stereotactically, through a scalp burr hole and under MRI visualization into the subgenual cingulate region (Brodmann area 25), one lead on each side. The leads are connected to pulse generators placed in the chest. The stimulators are programmed using telemetry. Electrodes are directed to this metabolically overactive region in TRD. The high-frequency stimulation in DBS is believed to work by inhibiting neuronal activity. Patients selected for this procedure are severely and chronically ill and have not responded to any of the available treatment modalities, in most cases, ECT. Mayberg et al study results in March 2005 showed a remarkable outcome. Five of 6 patients experienced substantial respite from their depressive symptoms, and in follow up 4 patients remained well after 6 months of treatment. So far, fewer than 20 patients who have depression worldwide have undergone DBS. Given its invasiveness and the need for more data, DBS would be reserved for patients who have been severely impaired by depression and have been refractory to all other treatment modalities (56-85-86).

Conclusion

Finally, as already said, one of the major obstacles to the therapeutic response is the lack of compliance influenced by several factors such as: cognitive impairment, complexity of dosages, side effects, lack of comprehension of the depressive symptoms, treatment costs and lack of family support, and finally, fear of stigma. On the contrary, factors improving compliance to treatment include a complete physical and cognitive assessment of the patient, involvement of relatives in the therapeutic program, maintenance of frequent contacts and supply of clear and comprehensible information on diagnosis and therapeutic management, these being generally, the cardinal points of the so-called good medical practice. The fact that depressed individuals do not receive the necessary treatment may lead to significant negative consequences such as a reduction in their quality of life, the chronification of emotional problems, an increase in the use of health services or an increase in the risk of suicide. Therefore, the application of an adequate intervention for the problems of depression must be an essential objective for assistance at the primary health care level and thus, important efforts in this direction are needed (87). In the oldest group of community-dwelling patients to be studied, medication was not more effective than placebo for depression treatment. However, according to the considerable psychosocial support received by all patients, the placebo condition shows more efficacy than the ingestion of an inactive pill. There was a remarkable range across sites in response to medication, 18% to 82%, and to placebo, 16% to 80% (88). Late-life depression represents an important opportunity for pharmacists to participate in the care of their aging patients. This common psychiatric illness leads to poor quality of life and is associated with a significant mortality risk, and can adversely influence the outcomes of comorbid medical illnesses. Late-life depression can be part of an unreported bipolar illness; it can also be associated with symptoms of psychosis and/or anxiety. The resulting psychiatric pharmacotherapy may therefore include various combinations of psychotropic medications. Pharmacists know that patients receiving multiple concurrent medications are at increased risk for adverse effects, drug interactions, treatment non-adherence and poor treatment outcomes. Taken together, this makes late-life depression an important illness for which pharmacists should screen their patients'situation forrecommending the use of rating scales such as the PHQ-9 or GDS. Elderly patients being considered for antidepressant treatment should have several factors evaluated prior to the selection of an antidepressant. History of depressive episodes and corresponding antidepressant treatment, as well as current pharmacotherapy are among the most important pre-treatment considerations. Once a patient is receiving an antidepressant the psychiatrist should help the patient use rating scales to measure depression symptom severity. Antidepressant dose and treatment durations are also important concerns for the psychiatrist to reinforce with the patient. The goal of the psychiatrist is to help the patient safely achieve remission (27).

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