Pharmacologic treatment of depression in late life

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Abstract

A NUMBER OF AGE-RELATED FACTORS, including changes in pharmacokinetics and pharmacodynamics, medical comorbidity and an increased risk of drug–drug interaction, can complicate the pharmacologic management of depression in late life. Nevertheless, over 80% of elderly depressed patients will eventually respond to vigorous treatment and, when treated over 2 years, up to 75% of those will not have a relapse or recurrence of depression. This article reviews a number of issues relating to the pharmacotherapy of depression in elderly people. In particular, it discusses the similarities and differences between various antidepressant medications, issues pertaining to dosing and length of treatment, and management of the patient who does not respond to first-line treatment. The author emphasizes that, because of the high risk of relapse and recurrence, a long-term collaboration between the patient and the physician is required to successfully manage depression in late life.

Résumé

DE NOMBREUX FACTEURS LIÉS À L'ÂGE, y compris des changements de la pharmacocinétique et de la pharmacodynamique, la comorbidité médicale et un risque accru d'interactions entre les médicaments, peuvent compliquer le traitement pharmacologique de la dépression chez les personnes âgées. Néanmoins, plus de 80 % des patients âgés déprimés finiront par répondre à un traitement énergique et, s'ils sont traités pendant plus de 2 ans, il n'y aura pas de rechute ou de réapparition de la dépression chez 75 % d'entre eux. Dans cet article, on passe en revue un certain nombre de questions liées à la pharmacothérapie de la dépression chez les personnes âgées. On y discute plus particulièrement de similitudes et de différences entre divers antidépresseurs, de problèmes qui ont trait au dosage et à la durée du traitement, ainsi que de la prise en charge du patient qui ne réagit pas au traitement de premier choix. L'auteur souligne qu'à cause du risque élevé de rechute et de récurrence, une collaboration à long terme entre le patient et le médecin s'impose si l'on veut traiter avec succès la dépression chez les personnes âgées.

Depression in late life is a common but treatable illness. Although less than 3% of people 65 years and older who live in the community have major depression (defined in Table 1[1]), up to 15% report clinically significant subsyndromal depressive symptoms.[2] Prevalence rates of depression are higher in institutional settings: 10%–15% of elderly people in nursing homes or hospitals have major depression, and another 20%–30% have significant depressive symptoms.[2]

In elderly people, the consequences of untreated depression include suffering and despair, increased rates of death from medical illnesses and suicide, medical morbidity and utilization of medical services, exaggerated cognitive impairment, inappropriate institutionalization and caregiver burden.[3] The rate of suicide in the elderly population is higher than in the general population, and elderly men are at highest risk.[3] Approximately 75% of elderly people visited a primary care physician in the month before they committed suicide,[3] which indicates that these people could have been treated.

Despite the significant rates of morbidity and mortality associated with depression, most depressive illness goes undetected and, therefore, untreated.[3] Even

Body and mind

Corps et esprit

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when symptoms are recognized, patients often receive inappropriate or inadequate treatment.[3] Of particular concern is the tendency of physicians to overuse benzodiazepines and to underprescribe antidepressants.[4] Although benzodiazepines may help alleviate the symptoms of anxiety and insomnia, which frequently accompany depression, they do not effectively treat the core depressive illness. The appropriate *primary* pharmacotherapy for depression, regardless of whether there are associated symptoms of anxiety, is an antidepressant not a benzodiazepine.

In people of all ages, depression is characterized by exacerbations and remissions, and by its chronicity.[5] Most elderly people with major depression are at risk of recurrence.[5] Therefore, the goals of treatment are not only to eliminate symptoms but also to prevent relapse (the reemergence of symptoms of the acute or index episode of depression) and recurrence (a new episode of depression). Treatment can improve the quality of life of patients and their caregivers, enhance function, improve physical health status, reduce the rate of death from medical illnesses and suicide, and lower health care costs.[3]

Treatment of depression in late life involves pharmacotherapy, psychotherapy and electroconvulsive therapy. Most research on the treatment of depression in elderly people has concerned pharmacotherapy, which is the focus of this article. Most treatment studies have involved medically stable outpatients who do not have dementia and who are less than 80 years of age. There have been few studies involving very old people (80 years of age and older), patients with significant medical illnesses and patients with dementia or other neurological problems. The findings of studies involving relatively healthy "young old" patients cannot necessarily be extrapolated to these special groups. This point needs to be kept in mind when reading this paper.

A number of age-related factors can adversely affect pharmacotherapy in elderly people. Pharmacokinetic changes, particularly reduced hepatic metabolism and reduced renal clearance, can result in higher plasma concentrations and prolonged elimination half-lives of some antidepressants and their metabolites. These pharmacokinetic changes are often magnified by the presence of comorbid medical conditions. Antidepressant medications may adversely affect disorders associated with age, such as cardiac arrhythmias, postural hypotension, postural instability, prostatic hypertrophy, constipation, impaired vision and cognitive impairment. Elderly people take more prescribed and over-the-counter medications than younger people and, as a result, are at a greater risk of drug–drug interactions.[6] Taking combinations of medications, forgetfulness, sensory impairment, social isolation and financial hardship can all interfere with a patient's compliance with treatment.[6] These factors present a challenge to physicians prescribing antidepressant medication to elderly patients. Nevertheless, elderly depressed patients can benefit from treatment as much as their younger counterparts.[7] Patience and persistence are key to managing depression in late life.

Table 1: Symptoms of major depression*

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss or gain, or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death, or suicidal ideation or attempt

*Major depression is defined as the presence of symptom 1 or 2, or both, plus enough of symptoms 3–9 to make a total of 5 or more symptoms with a minimum duration of 2 weeks.

Selecting an antidepressant

Several classes of antidepressants are commercially available in Canada: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), serotonin and norepinephrine reuptake inhibitors (venlafaxine), phenylpiperazines (nefazodone) and triazolopyridines (trazodone). Controlled studies have found that the efficacy of TCAs, SSRIs, MAOIs and trazodone as first-line treatments of major depression in late life is comparable.[8] As yet, there have been no controlled studies of the newer antidepressants nefazodone (Serzone) and venlafaxine (Effexor) that include elderly depressed patients, although trials that have included patients of mixed ages report that young and old subjects have similar rates of response to venlafaxine.[9] The selection of a specific antidepressant is guided by the following factors: the tolerability and safety of the drug, the pharmacokinetics of the drug, the patient's previous response to the drug and the cost of the drug. These factors need to be considered within the context of the patient's medical and neurological status and concomitant drug use. Because MAOIs, especially first-generation agents such as phenelzine (Nardil) and tranylcypromine (Parnate), tend to be used only in specialist psychiatric practice, this class of antidepressant will not be reviewed in this article.

Tricyclic antidepressants

The side effects of TCAs result from their blockade of central and peripheral cholinergic receptors (dry mouth, blurred vision, constipation, urinary hesitancy or retention, cognitive impairment, tachycardia), histaminergic receptors (sedation, weight gain) and α-adrenergic receptors (orthostatic hypotension). The secondary amine

TCAs nortriptyline (Aventyl) and desipramine (Norpramin) are less likely to induce these effects than tertiary amine drugs such as amitriptyline (Elavil) and imipramine (Tofranil) and therefore are the preferred tricyclics in elderly patients.[3,10] Of the TCAs, nortriptyline is the least likely to cause orthostatic hypotension.[11] It has been extensively studied in elderly depressed patients and is well tolerated by "young old" individuals who are medically stable and who do not have dementia.[12,13] Nortriptyline has been found to be less well tolerated in very old or frail nursing home residents,[14] patients who have had a stroke[15] and people who are medically ill.[16] It is worth noting that many patients wrongfully attribute the somatic symptoms of depression to the antidepressant medication.[13] Careful documentation of the patient's somatic complaints before the antidepressant is started can help clarify whether subsequent symptoms are related to the illness or the medication.

All TCAs, including nortriptyline, slow cardiac conduction and therefore are not safe for patients with bundle branch block.[11] TCAs also have significant antiarrhythmic activity resembling that of class 1 antiarrhythmic compounds such as quinidine.[17] Class 1 antiarrhythmics increase the risk of death in patients with moderate to severe ischemic heart disease,[17] and therefore TCAs should not be given to these patients.[17]

Monitoring plasma TCA levels in elderly patients can help maximize clinical response and minimize adverse effects.[18] There is a curvilinear relation between the plasma level of nortriptyline and its therapeutic effect; clinical response is most likely to occur in the range of 200–500 nmol/L.[18] For patients aged 60–80 years, a nortriptyline dose of 1 mg/kg of body weight will usually produce a plasma level in the therapeutic range. Monitoring TCA plasma levels is also useful for evaluating patient compliance.

Selective serotonin reuptake inhibitors

With the exception of paroxetine, which has a moderate effect on cholinergic receptors (and therefore the potential for anticholinergic side effects),[19,20] the SSRIs have little affinity for adrenergic, histaminergic, cholinergic or dopaminergic receptors.[21] The side effects of SSRIs, which primarily reflect central and peripheral serotonin reuptake inhibition, include gastrointestinal upset (nausea, anorexia, frequent and loose stools), central nervous system dysfunction (insomnia, sedation, apathy, nervousness, restlessness, dizziness, tremor and headaches) and sexual dysfunction (decreased libido, anorgasmia, delayed ejaculation and impotence).[21] SSRIs can also induce postural instability in older people, increasing the risk of falls.[22] An infrequent but potentially dangerous side effect is the syndrome of inappropriate secretion of antidiuretic hormone and hyponatremia.[23] Virtually all cases of SSRI-induced hyponatremia have occurred in elderly people, usually within the first month after the start of therapy.[23] The hyponatremia will resolve once the SSRI is discontinued but may recur if the patient starts taking the same, or a different, SSRI.[24] In healthy volunteers, SSRIs produce no significant cardiac effects and do not produce postural hypotension,[21] although their use in patients with cardiac disease has not been well studied.[25] In contrast to TCAs and first-generation MAOIs, SSRIs taken alone in an overdose do not cause death.[21,25] Side effects tend to be dose related[26] and are often transient. Patients who cannot tolerate one SSRI may well be able to tolerate another.[27] Although the side effects of SSRIs and TCAs differ and SSRIs are the safer of the 2 drugs, it has not been established whether elderly people tolerate SSRIs better than secondary amine TCAs. In all published studies comparing the effects of an SSRI with a TCA in patients with late-life depression, the TCA drug was a tertiary amine TCA (such as amitriptyline or imipramine), which would not normally be used in elderly people.[8] To my knowledge only 1 trial has compared an SSRI (sertraline) with a secondary amine TCA (nortriptyline), and both drugs were equally well tolerated.[28]

SSRIs are a structurally heterogeneous group of drugs; this is reflected in their different pharmacokinetics.[21] Fluoxetine (Prozac) has an elimination half-life of 70 hours, and its pharmacologically active metabolite, norfluoxetine, has a half-life of 330 hours.[26] This means that there is a delay of several weeks before steady-state plasma concentrations are reached and that there is a risk of ongoing side effects and drug interactions for 5 to 6 weeks after the drug is discontinued. Therefore, fluoxetine is potentially more problematic in elderly people than the other 3 SSRIs available (fluvoxamine [Luvox], paroxetine [Paxil], and sertraline [Zoloft]), which have half lives of 26 hours or less and no clinically active metabolites.[21]

The SSRIs inhibit isoenzymes of the hepatic P-450 cytochrome system, which is involved in the metabolism of a large number of drugs (Table 2).[29,30] Although SSRIs are not the only psychotropics with this property, the potency of their inhibition and their potential to increase the plasma concentration of a variety of medications has led to concern.[30] The isoenzymes primarily affected are 1A2, 2C, 2D6 and 3A. The potency of inhibition of these enzymes differs among the SSRIs (Table 3).[29,31,32] It is important to note that the clinical significance of many potential SSRI-drug interactions is not known. Even when such interactions are significant, there is tremendous variability in the severity of the clinical sequelae. Therefore, a potential drug interaction does not normally preclude the use of an SSRI, but doses may need to be adjusted and the patient should be carefully monitored.[30] Particular caution should be exercised when any SSRI is prescribed with

drugs that have a narrow therapeutic window (margin between a therapeutic dose and a toxic dose), such as tricyclic antidepressants, antipsychotics, theophylline, phenytoin, carbamazepine and tolbutamide.[29] The administration of an SSRI with the antihistamine terfenadine or astemizole is contraindicated because of the risk of fatal ventricular arrhythmias resulting from P-450 3A4 inhibition.[29] Also, SSRIs should be administered with caution, if at all, to patients taking type 1C antiarrhythmics (encainide, flecainide, propafenone).[29] Like TCAs, SSRIs are highly protein bound and therefore have the ability to displace and thereby enhance the effect of other protein-bound drugs (e.g., warfarin and digoxin).[29,30]

The SSRIs have a flat dose-response curve.[33] This means that, for the majority of patients, increasing the amount beyond the minimum effective dose does not increase efficacy but can cause more side effects. Consistent with the flat dose-response curve, there is no relation between plasma SSRI concentrations and clinical response.[33] To date, there have been no studies published that have determined the minimum effective dose of SSRIs in elderly people; therefore, we have to be guided by data obtained from studies involving younger people. Since paroxetine has a higher plasma concentration and longer elimination half-life in older people than it does in younger people,[34] the starting and maximum doses of this drug should be reduced in elderly patients (Table 4). Aging has not been shown to have a clinically significant effect on the pharmacokinetics of fluoxetine,[35] fluvoxamine[36] or sertraline.[37] Nevertheless, elderly patients may tolerate these medications better if they start with half the usual dose and increase that to the minimum effective dose after 1 to 2 weeks (Table 4). The patient should be maintained on the minimum effective dose for 3 to 4 weeks before an increase in dose is considered. If there is no improvement in the patient's condition, then the dose should be gradually increased, guided by its tolerability and efficacy.

Other antidepressants

Trazodone (Desyrel) blocks postsynaptic serotonin (5-HT_2) receptors and weakly inhibits serotonin reuptake.[38] It has a short elimination half-life (3–9 hours)[38] and therefore requires multiple daily doses, which may lead to poor patient compliance. Trazodone has a strong sedating effect that can result in daytime drowsiness, falls and impaired cognitive functioning.[38] It can also cause orthostatic hypotension (with the risk of falls) and ventricular arrhythmias.[38,39] These factors can limit its usefulness as an antidepressant in late life. Low doses (25–50 mg) of trazodone are sometimes combined with nonsedating antidepressants, such as some SSRIs, to treat insomnia associated with depression during the acute phase of treatment.

Nefazodone (Serzone), which is structurally related to trazodone, is a weak inhibitor of serotonin reuptake but a potent 5-HT_2 receptor antagonist.[40] Because of this latter mechanism, it has been hypothesized that anxiolytic effects may occur earlier with nefazodone than with SSRIs and thus nefazodone may be especially useful in treating anxious depression.[41] However, a recent double-blind study comparing nefazodone and paroxetine found that the drugs were equally effective in relieving anxiety symptoms of depression.[42] Nefazodone's short elimination half-life necessitates 2 doses daily.[40] Aging affects the pharmacokinetics of nefazodone, so older patients require half the usual starting dose (50 mg twice daily instead of 100 mg twice daily), slower dose titration and a lower therapeutic dose range (200–400 mg/d) than younger people.[43] The

Table 2: Selected drugs metabolized by cytochrome P-450 isoenzymes 1A2, 2C, 2D6 and 3A4[29,30]

1A2	2C	2D6		3A4	
Antidepressants	**Antidepressants**	**Antiarrhythmics**	**Antipsychotics**	**Antiarrhythmics**	**Calcium-channel blockers**
Amitriptyline	Amitriptyline	Encainide	Clozapine	Lidocaine	Diltiazem
Clomipramine	Citalopram	Flecainide	Haloperidol	Propafenone	Felodipine
Fluvoxamine	Clomipramine	Mexiletine	Perphenazine	Quinidine	Nifedipine
Imipramine	Imipramine	Propafenone	Risperidone	**Antidepressants**	Verapamil
Antipsychotics	Moclobemide	**Antidepressants**	Thioridazine	Amitriptyline	**Opiates**
Clozapine	**Barbiturates**	Amitriptyline	Zuclopenthixol	Clomipramine	Dextromethorphan
Haloperidol	Hexobarbital	Clomipramine	**Beta-blockers**	Imipramine	**Miscellaneous**
Beta-blockers	Mephobarbital	Desipramine	Metoprolol	Nefazodone	Carbamazepine
Propranolol	**Benzodiazepines**	Fluoxetine	Propranolol	Sertraline	Cortisol
Calcium-channel blockers	Diazepam	Imipramine	Timolol	**Antihistamines**	Cyclosporine
	Beta-blockers	Maprotiline	**Opiates**	Astemizole	Dexamethasone
Verapamil	Propranolol	Nortriptyline	Codeine	Terfenadine	Erythromycin
Miscellaneous	**Miscellaneous**	*N*-desmethyl-citalopram	Dextromethorphan	**Benzodiazepines**	Ethinyl estradiol
Acetaminophen	Omeprazole		Ethylmorphine	Alprazolam	Tamoxifen
Caffeine	Phenytoin	Paroxetine	**Miscellaneous**	Midazolam	Vinblastine
Phenacetin	Proguanil	Trazodone	4-hydroxy-amphetamine	Triazolam	
Tacrine	Tolbutamide	Trimipramine			
Theophylline	Warfarin	Venlafaxine	Phenformin		

most common side effects associated with this antidepressant are nausea, drowsiness, dry mouth, dizziness, constipation and asthenia.[44] At higher doses, it may impair cognitive and psychomotor functioning in the elderly.[45] Nefazodone does not cause sexual dysfunction, and it does not appear to have clinically significant cardiovascular effects.[44] It is a potent inhibitor of P-450 3A4. Consequently, it should not be used with terfenadine or astemizole, and caution should be exercised when it is administered with other drugs metabolized by this isoenzyme.[29]

Venlafaxine inhibits the reuptake of both serotonin and noradrenaline.[9] Its pharmacodynamics resemble tertiary amine TCAs such as amitriptyline and imipramine, but it lacks their unwanted affinity for cholinergic, histaminergic and α_1-adrenergic receptors. The most common side effects of venlafaxine are nausea (which usually resolves rapidly), somnolence, dry mouth, dizziness, nervousness, constipation, sexual dysfunction, sweating, asthenia and anorexia.[9] Blood pressure monitoring is recommended before and during venlafaxine treatment because a small number of patients experience modest dose-dependent elevations of blood pressure.[9] Venlafaxine is only a weak inhibitor of P-450 2D6 and is less likely than paroxetine or fluoxetine to interact with drugs metabolized by this isoenzyme.[29] Unlike SSRIs, venlafaxine does not have a flat dose-response curve, and higher doses are associated with better responses.[9] The effective dose of venlafaxine has not been established in elderly people. The drug has a wide dose range (75–375 mg/d), but clinical experience has shown that many older patients need at least 150 mg/d to respond to treatment. A starting dose of 37.5 mg/d is recommended to avoid nausea. Because of its short half-life, venlafaxine should be administered twice daily.[9]

Duration of treatment

Treatment with antidepressant medication is commonly divided into acute, continuation and maintenance phases. The goal of the acute phase is the remittence of the acute or index episode of depression. Continuation treatment is designed to prevent a relapse of the index episode. Maintenance therapy aims to prevent future episodes of depression once there has been a complete recovery from the index episode.

There is considerable evidence that response to antidepressant medication depends not only on dose but also on length of treatment.[8] Response may occur later in elderly patients than in younger patients and requires at least 6–12 weeks of treatment.[8,46] It has been well established that when treatment with antidepressant medication is continued for at least 4 months after remission of depressive symptoms, the rate of relapse is approximately 20%, as compared with 50% among patients treated with placebo.[47,48] Thus, any patient who responds to antidepressant medication should continue taking the drug for at least 4–8 months. Maintenance therapy thereafter should be considered for any patient with a history of 1 or more episodes of major depression (especially if these occurred within the last 5 years) or who is otherwise at high risk of recurrence.[49] One risk factor for recurrence is having the first onset of depression occur after the age of 60.[5] Therefore, some psychiatrists recommend that *all* elderly patients with major depression continue taking antidepressant medication for at least 2 years after the remission of symptoms.[50,51] Life-long treatment should be considered for elderly patients who have had 3 or more episodes in their life. Reducing the dose of the antidepressant appears to increase the risk of relapse and recurrence, and there is now a consensus that patients should be maintained on the dose to which they responded.[49] Up to 75% of elderly patients who remit from an episode of depression and are maintained on full-dose antidepressant treatment remain free of relapse and recurrence when followed for 2 years.[50,51] Patients who are stabilized on medication should be followed on a regular basis (e.g., every 3 months) to monitor efficacy, side effects and compliance. Patients who do not have regularly scheduled appointments are more likely to be noncompliant. Without planned follow-up, relapses and recurrences of depression often go undetected,[52] and the longer the episode is left untreated the worse the prognosis.[53] To maximize compliance, patients and their families need ongoing education about the chronic and recurrent nature of untreated depression and the need for long-term treatment.

Treatment of nonresponders

The goal of the acute phase of treatment is to achieve

Table 3: Inhibitory effect of selective serotonin reuptake inhibitors (SSRIs) on P-450 isoenzymes*

	Isoenzyme†			
SSRI	1A2	2C	2D6	3A4
Fluoxetine/norfluoxetine	+	++	+++	++
Fluvoxamine	+++	++	+	++
Paroxetine	+	+	+++	+
Sertraline	+	++	++	++

*Based on currently available in vitro and in vivo data.[29,31,32]
†Potency of inhibition: + = mild; ++ = moderate; +++ = strong. A rating of ++ or higher is usually necessary for the inhibition to have clinical significance.

Table 4: Usual starting dose, minimum effective dose and maximum dose of SSRIs in elderly patients

SSRI	Usual starting dose, mg/d	Minimum effective dose, mg/d	Maximum dose, mg/d
Fluoxetine	10	20	60
Fluvoxamine	25–50	100	300
Paroxetine	10	20	40
Sertraline	25–50	50	200

complete remission of depressive symptoms. As already noted, the first step is to ensure that the patient has received an optimum dose of antidepressant for a sufficient length of time. However, 30% of elderly patients do not respond to an initial adequate trial of antidepressant medication and require additional or alternative treatment.[8,53] Patients who respond partially to treatment, or not at all, can be managed in 1 of 2 ways: augmentation or substitution. Augmentation refers to the addition of another medication to the antidepressant. The adjunctive agent may be a second antidepressant (e.g., adding a TCA to an SSRI) or a medication that is not primarily an antidepressant (e.g., lithium, triiodothyronine, methylphenidate, buspirone or valproate). The advantage of augmentation is that it does not require discontinuation of the original antidepressant, and therefore patients who partially responded to treatment are not put at risk of returning to their baseline severity of depression. Also, response may be faster with augmentation than with a new trial of antidepressant medication. The disadvantage of augmentation, especially in elderly people, is that the combination of medications increases the risk of side effects and of drug–drug interactions. There have been no controlled trials of augmentation in elderly people, and therefore the effectiveness of this approach in treating geriatric depression has not yet been established.[54] Augmentation tends to be confined to psychiatric practice, and interested readers should refer to other articles[54,55] for further details.

The second strategy, substitution, involves changing from one treatment to another. In primary practice, this usually means switching from one antidepressant medication to another. However, switching from an antidepressant to electroconvulsive therapy, which is a safe and effective treatment in the elderly,[56] should be considered. There are virtually no data on antidepressant substitution in refractory depression that occurs in late life. Rifat and I recently reported that elderly patients who failed to respond to 6 weeks of nortriptyline therapy followed by 2 weeks of lithium augmentation had a 50% response rate to a 6-week trial of phenelzine.[53] This rate of response is comparable to that reported among younger patients refractory to tricyclic antidepressants.[55] All other data on antidepressant substitution has to be extrapolated from research involving patients of mixed ages. As a general rule, switching to another antidepressant within the same class, for example from one TCA to another, is less effective than switching to one from another class.[55] A possible exception to this rule is the patient who fails to respond to an SSRI as first-line treatment. Two recent open and uncontrolled studies reported response rates of 50% and 63% among younger adult outpatients who failed to respond to one SSRI and were then treated with another.[57,58] These findings must be considered tentative but suggest that it may be reasonable to consider a second SSRI trial before switching to another class of antidepressant. Uncontrolled data suggest that venlafaxine may be particularly useful in patients who have not responded to other antidepressants.[9] When switching antidepressants in elderly patients, it is advisable to withdraw the first agent gradually (e.g., over 1–2 weeks) before introducing the new drug. However, even with this gradual crossover the patient needs to be carefully monitored for the possible effects of drug–drug interaction. A drug-free period of 2 weeks is required when switching from a first-generation MAOI to another antidepressant and 6 weeks when switching from fluoxetine to a first-generation MAOI.

When to refer

An elderly depressed person should be referred to a geriatric psychiatrist when: (a) the diagnosis is uncertain, (b) the primary care physician is uncertain about treatment selection, (c) the patient is severely ill (e.g., is suicidal or homicidal, or refuses to eat or drink), (d) the patient has delusions or hallucinations, (e) the patient needs evaluation for electroconvulsive therapy, (f) the patient has not responded to an adequate trial of antidepressant medication, (g) antidepressant side effects or drug interactions limit effective therapy, (h) the patient or caregivers are noncompliant with treatment, or (i) when on maintenance treatment the patient experiences an exacerbation of depression or other worsening of mental state.[59]

Conclusion

The pharmacologic treatment of depression in elderly people is both challenging and rewarding. The challenges include changes in pharmacokinetics and pharmacodynamics related to age, an increased risk of drug interactions and the complicating effects of concomitant medical conditions. Nevertheless, more than 80% of elderly depressed people will eventually respond to vigorous treatment.[53] Furthermore, when effective treatment is maintained, the vast majority of those who respond to treatment will remain well when followed up on a regular basis.[50,51]

Despite major advances in our knowledge about the management of depression in late life, there are still many issues that remain unresolved and require further study. For example, there is a dearth of data on the use of the newer antidepressants in elderly patients. We are only starting to explore the treatment of depression in special populations, such as very old patients or patients with significant medical or neurological comorbidity. Fifty percent or more of older people with major depression are not receiving treatment. We need to improve the detection of depression and ensure that people who are identified receive adequate treatment.

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