Depression in older patients with neurologic illness:
Causes, recognition, management

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ABSTRACT

Depression is common in the elderly, particularly in older persons with neurologic illness. Its etiology in this population is incompletely understood and likely to be multifactorial. Identifying depression in elderly patients with neurologic illness can be a challenge, as many of its features resemble symptoms of the underlying neurologic disease or of the aging process itself. Nevertheless, recognition and effective management of depression in this population is vital, since depression is a major source of excess morbidity and since treatment often results in improved quality of life for patients and their caregivers. Assessing for suidicality is a key diagnostic consideration in this population. Antidepressant medications, psychotherapy, and electroconvulsive therapy all can be effective in treating depression in elderly neurologic patients.

KEY POINTS

Elderly persons with neurologic disease have higher rates of depression than the general elderly population.

Depression is associated with increased physical disability in elderly patients with neurologic illness, and resolution of depression appears to be associated with improved physical function in these patients.

Effective diagnosis of depression in this population is eminently possible with alertness to clues in the patient interview and with careful use of screening questions, particularly to assess for persistent depressed mood and lack of interest and pleasure in life.

Sorting out depressive symptoms from those of the underlying neurologic illness can be difficult and is often confounded by neurologic medications, focal symptomatic lesions, and cognitive impairment.

Age should not be a basis for denying treatment for depression in neurologic patients. The elderly respond to antidepressant therapy at about the same rate as younger age groups, and they also may respond to psychotherapy and electroconvulsive therapy.

Primary care physicians can effectively treat many depressed elders with neurologic disease; referral to a specialist is appropriate for patients with suicidal thoughts and those who have not responded to an adequate course of initial depression management.

All my griefs to this are jolly,
Naught so sad as melancholy.
—Robert Burton (1577–1640)

Depressive illness is one of the most common complications of neurologic disease, particularly in the elderly. A key clinical challenge is knowing whether to attribute an older patient's individual symptoms to the underlying neurologic disease or to depressive illness, given the frequent overlap between the two. Despite this overlap, all physicians who treat older patients with neurologic illness should recognize that persistent depressed mood and lack of interest in life cannot be ascribed to severe physical illness alone. Appropriate clinical assessment can help identify and resolve depression in many of these patients, avoiding the disability, diminished survival, and increased medical costs that accompany depression in this population. This article

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presents an overview of depression in elderly neurologic patients, focusing on its clinical features, epidemiology and etiology, diagnostic considerations, and therapeutic approaches.

CLINICAL FEATURES: LOW MOOD AND ANHEDONIA ARE KEY

The term "depression" describes a spectrum of mood disturbances ranging from mild to severe and from transient to persistent. Depressive symptoms are distributed continuously in any population. They are of clinical significance when they interfere with normal activities and persist for at least 2 weeks, in which case a diagnosis of depressive illness or disorder may be made. The diagnosis depends on the recognition of two cardinal symptoms: (1) persistent and pervasive low mood and (2) loss of interest or pleasure in usual activities (anhedonia).

The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV),[1] classifies an illness as a major depressive disorder if, during the same 2-week period, the patient experiences depressed mood or decreased interest or pleasure and at least four of the following symptoms, which represent a change from normal functioning:

- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide, or suicide attempt.

EPIDEMIOLOGY OF DEPRESSION IN THE ELDERLY

Depression is without question one of the most common and important psychiatric problems in the elderly. Data from the National Institute of Mental Health Epidemiologic Catchment Area Study suggest that a substantial fraction of seniors—perhaps as many as 15% of those residing in the community—have major or minor depressive symptoms.[2] While major depression has generally been believed to occur somewhat less frequently in the elderly than in younger persons, this may be due to underreporting.[3] The prevalence of depression is clearly higher in the medically ill[4] and in those relocating to or living in assisted-living facilities and nursing homes.[5]

Depression accompanying neurologic disease

Elderly patients with neurologic disease clearly seem to have higher rates of depression than the general population of seniors, although there is considerable variability in reported prevalence among studies. Commonly cited rates of major depressive disorder in the neurologically impaired elderly vary from 10% to 40%. Patient selection and diagnostic techniques[6] appear to be the major sources of variability. Interestingly, rates and associations appear to be much the same across a wide range of neurologic conditions.

A recent prospective cohort study[7] that assessed 300 consecutive new neurology outpatients using diagnostic interviews and self-report measures found that almost half met the criteria for one or more DSM-IV anxiety or depressive diagnosis. Major depression was the most common condition, occurring in 27% of patients in the overall series. The major depressive disorders tended to persist, and 46 of 54 patients remained depressed at 8-month follow-up. Significantly, a change in categoric diagnosis on interview from depressed to not depressed was accompanied by a mean drop of 10 points on the Hospital Anxiety and Depression Scale, suggesting real (categorical) change in mental state rather than subtle shifts along a continuum.

Depression and physical symptoms

This same study[7] compared patients with and without emotional disorders, finding that those with emotional disorders reported more physical symptoms, poorer physical function, and more bodily pain. This finding of an association between depression and increased physical disability is in keeping with reports on individual disorders such as stroke,[8,9] Parkinson disease (PD),[10] epilepsy,[11–13] and multiple sclerosis.[14] This relationship is reported consistently and tends to hold whether subjective or objective disability ratings are used. This, of course, does not indicate the direction of causality.

While it is likely that the prevalence of depressive illness is affected by the severity of the neurologic disease,[15] there are two persuasive reasons for believing that depression is an independent risk factor for physical disability in patients with neurologic illness. First, there is strong evidence that, at least after a stroke, depression is an independent risk factor for increased mortality.[16,17] Second, most (but not all) cohort studies and randomized controlled trials have shown that resolution of depression through natural remission or treatment results in an improvement in physical function.[18–20]

Depression and cognitive disorders

The high frequency of depression in patients with cognitive disorders is also notable. At least 20% of patients with Alzheimer disease (AD) may meet cri-

teria for major depression, and an additional 30% may have minor depression.[21] A recent study found the combined prevalence of major and minor depression to be 36% in a cohort of patients with mild cognitive impairment and also revealed a faster pace of cognitive deterioration over 3 years in these depressed patients compared with their nondepressed counterparts.[22]

ETIOLOGY OF DEPRESSION IN NEUROLOGIC ILLNESS

Anxiety, sadness, and somatic discomfort are part of the normal psychological response to life stresses, including medical illness. Clinical depression is a final common pathway resulting from the interaction of biologic, psychological, and social factors. The likelihood of this outcome depends on such factors as genetic and family predisposition for depression, the clinical course of the concurrent medical illness, the nature of the treatment, functional disability, the effectiveness of the patient's coping strategies, and the availability of social and other support.

Other important factors in the expression of depression in older patients with neurologic illness include anatomic and physiologic changes in the brain and sensory systems associated with aging itself. Anatomically, global reductions in focal brain volume have been established,[23,24] as has an increased frequency of several kinds of white matter abnormalities easily seen on MRI.[25] Physiologically, reductions in measures of neuronal function (eg, cerebral glucose metabolism[26]) occur, as do declines in various markers of some relevant neurotransmitters.[27,28] These brain volume and metabolic reductions have been linked convincingly to age-related cognitive impairment, which can affect symptom expression in some forms of depression, and both these changes and the alterations in neurotransmitters may affect the maintenance of mood and/or predispose to or modulate depression as well.[27]

Of particular interest in depression associated with neurologic disease is whether the risk for depression is directly affected by damage to specific brain pathways. Common neurologic diseases, such as PD, multiple sclerosis, and Huntington disease, can present initially with depressive illness. Further, depression and anosognosia can coexist. This would suggest that depression is an integral part of brain disease and is not solely a reaction to chronic illness. Unfortunately, the identification of common pathways for depression and neurologic diseases has so far proved elusive.

Cognitive disorders and depression

The etiology of depression in the cognitive disorders remains incompletely elucidated and is probably multifactorial.[29] Psychological reaction to the diagnosis may play a role in mild cognitive impairment or early dementia, but with established dementia, neuropathologic factors probably become significant. For example, in AD, reduced cell counts[30] and markers of neurotransmitter production[31] in brain regions critical for regulating mood (eg, the locus ceruleus) may reflect neurodegeneration-related damage to these areas. Moreover, the global brain atrophy and volume reduction in specific cortical and subcortical regions reported in late-life depression with intact cognition[32] is found at least as strikingly in Alzheimer-type dementia, so additivity of these findings is probable. In particular, hypercortisolemia-associated hippocampal atrophy, which has been recognized in late-life depression,[33] may add to the well-recognized hippocampal atrophy of AD. Further, white matter lesions, seen with increased frequency on magnetic resonance imaging (MRI) in late-life depression,[34] have also been proposed to be more common in patients with dementia, so additivity may be at work as well. The impact of these lesions on mood is thought to be mediated by circuitry-disruption effects,[35] and the effects of atrophy and white matter lesions are certainly complementary.[36]

Stroke and depression

Much interest has centered on stroke, but it has been difficult to obtain useful estimates of the incidence, correlates, and consequences of poststroke depression.[37] The reason may be the difficulty of identifying patients with affective illnesses as distinct groupings within the population of neurologically impaired patients (see "Diagnosing Depression in the Elderly with Neurologic Disease" below). Studies have also been limited by variable methodologies, small sample sizes, and lack of suitable controls.

Desmond and colleagues[38] attempted to correct some of these deficiencies in a prospective study of depression in 421 elderly stroke patients (mean age, 71.5 ± 8.0 years) and 249 age-matched, stroke-free control subjects. The investigators diagnosed depression in 11.2% of their stroke patients 3 months after stroke compared with 5.2% of the control subjects in the same time frame (odds ratio, 2.52; 95% confidence interval, 1.33 to 4.80). Depression in the stroke patients was significantly correlated with greater severity of stroke, particularly in vascular territories supplying limbic structures, and with dementia and

female sex. The frequency of somatic symptoms, rather than depressed mood, discriminated between patients with and without stroke and between stroke patients with and without dementia. The researchers concluded that clinicians should perhaps rely more on somatic than nonsomatic symptoms to diagnose depression in this population.

Robinson and colleagues[39] developed an impressive animal model of poststroke depression using experimentally produced lesions in the cortex of rats. They hypothesized that lesions in the left frontal lobe are associated with an increased rate of depressive illness, particularly soon after stroke. There are several objections to this view, however, and a recent meta-analysis did not support this localization hypothesis.[40] It seems unlikely that further descriptive studies in humans will yield meaningful insights, as depression after stroke is probably too common and almost certainly too multifactorial for this mode of research to be helpful. Among those who remain interested in this hypothesis, attention is shifting to the role of the limbic system in the development of poststroke depression.[41,42]

A condition termed "vascular depression" has been hypothesized to explain some geriatric depression.[35] This concept emerged from research identifying an increased frequency of white matter pathology on the brain MRIs of some depressed elderly patients,[43] particularly those whose first episodes occurred at an advanced age (ie, > 85 years).[44] Such pathology can range from subtle to definite cerebrovascular disease and can occur in individuals with or without a history of stroke. Such lesions have been reported to be especially prominent in the frontal lobes, and specifically in regions thought to be components of neural circuitry subserving mood and affect. It is through disruption of such circuits that cerebrovascular disease might cause depression.

RECOGNITION AND SCREEENING

In spite of its enormous clinical and public health importance, depressive illness is substantially underdiagnosed and undertreated,[45] particularly when it coexists with physical illness. Depression is often a cause of great distress for patients who have mistakenly assumed that symptoms such as weakness or fatigue are caused by an underlying medical condition.

Attributing symptoms to medical illness is especially common in the elderly, in whom a tendency toward somatic orientation and de-emphasis of cognitive/affective symptoms is recognized.[3] Clinician bias (ie, "ageism") may also promote underrecognition of depression in the elderly with neurologic illness.

It is vital that all clinicians know how to diagnose and manage depressive illness effectively. Doing so is eminently possible with alertness to clues in the interview, especially the patient's manner, and with the use of screening questions for those at risk. Clinicians should particularly screen patients for the two cardinal symptoms of major depression: low mood and lack of pleasure.

Self-report screening instruments, such as the Beck Depression Inventory and the Hospital Anxiety and Depression Scale, cannot replace systematic clinical assessment, but they are useful in drawing attention to depression and other emotional disturbances in clinical settings in which mood is not routinely assessed. Physicians should recognize that persistent depressed mood and lack of interest and pleasure in life cannot be accounted for by severe physical illness alone. The usual response to illness and successful treatment is impressive resilience.

One screening tool developed specifically for use with elderly patients and commonly used both in geriatric research and in clinical practice is the Geriatric Depression Scale (Table 1).[46]

When there is doubt about the diagnosis of depression, clinicians may resort to an empirical trial of treatment. The wider availability of safer medications and psychological therapy makes treatment a more attractive option than in the past.

DIAGNOSING DEPRESSION IN THE ELDERLY WITH NEUROLOGIC DISEASE

Depression in elderly patients with neurologic illness manifests as a mixture of phenomena that may be associated with the neurologic condition and with the aging process itself (including biologic, psychological, and social aspects) as well as with depression. Among neurologic conditions, cerebrovascular disease and the dementias are arguably the most common in the elderly. Depression is especially challenging to assess and manage in elderly patients with these conditions.

Sorting out the source of symptoms

In patients with neurologic disease, a key difficulty is knowing whether to attribute individual symptoms to a depressive illness or to the neurologic disease.[47,48] Several common symptoms of depression are prominent in many neurologic conditions; examples include fatigue (particularly frequent in multiple sclerosis[49,50]), loss of appetite, and diminished concentration. Further, epidemiologic research shows a unimodal distribution of mood symptoms in neurologic

TABLE 1
Geriatric Depression Scale—mood scale, short form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? Yes/**No**
2. Have you dropped many of your activities and interests? **Yes**/No
3. Do you feel that your life is empty? **Yes**/No
4. Do you often get bored? **Yes**/No
5. Are you in good spirits most of the time? Yes/**No**
6. Are you afraid that something bad is going to happen to you? **Yes**/No
7. Do you feel happy most of the time? Yes/**No**
8. Do you often feel helpless? **Yes**/No
9. Do you prefer to stay at home, rather than going out and doing new things? **Yes**/No
10. Do you feel you have more problems with memory than most? **Yes**/No
11. Do you think it is wonderful to be alive now? Yes/**No**
12. Do you feel pretty worthless the way you are now? **Yes**/No
13. Do you feel full of energy? Yes/**No**
14. Do you feel that your situation is hopeless? **Yes**/No
15. Do you think that most people are better off than you are? **Yes**/No

Answers in **bold** indicate depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score greater than 5 suggests depression and warrants a follow-up interview. Scores greater than 10 almost always indicate depression.

Adapted from reference 46.

disease.[38] Such a continuous distribution throughout the population with neurologic disease, with variation in degree but not in kind, makes identifying distinct subgroups of neurologic patients with and without depression problematic.

Gainotti and colleagues[47] attempted to see if different clusters of symptoms in stroke patients identified different "types" of depression, but they found little evidence to support such a theory.

The problem of classification is especially pronounced in patients with PD. Many depressive symptoms overlap with the core features of PD—motor retardation, attention deficit, sleep disturbance, hypophonia, impotence, weight loss, fatigue, preoccupation with health, and reduced facial expression. This complicates interpretation of diagnostic criteria and standardized rating scales. Anhedonia and sustained sadness, particularly when out of proportion to motor signs, are important diagnostic features of depressive illness in patients with PD.[51]

One approach to this diagnostic challenge is to focus on symptoms other than somatic ones. Instruments such as the Hospital Anxiety and Depression Scale[52] have been designed to do this. But even this is not a complete solution, as the neurobehavioral consequences of cerebral lesions, such as aphasia, indifference, denial, cognitive impairment, and dissociation of subjective from displayed emotion, can all interfere with the diagnosis. There is therefore a risk of tautology if this approach is used.

In addition to major depression (and its most severe form, psychotic depression), elderly patients with neurologic illness frequently suffer from adjustment disorders. This stems from the high rate of negative life events among these patients, who are more likely than their younger counterparts to have comorbidities, face financial difficulties, and suffer the loss of loved ones.

A poorly understood but probably important variable in the expression of geriatric depression in this population is the past history of depression, particularly in patients with late-life onset of neurologic disease. While there is no distinctly geriatric presentation of depression, specific syndromes have been described in this population that might modulate the expression of coexistent neurologic conditions. Among them are "late-onset" geriatric depression (ie, depression in the very old, usually meaning ≥ 85 years), vascular depression, and at least two syndromes (discussed below) associated with cognitive impairment.[53] Late-onset geriatric depression is characterized by a higher incidence of both cognitive and sensory impairment than depression in the younger elderly. Vascular depression highlights a putative contribution of cerebrovascular disease to the expression of depression, even in individuals without a clear history of stroke.[35] The concept of vascular depression as a clinical entity is still investigational and requires further definition, but it is likely to have significant therapeutic and etiologic implications.

Another diagnostic obstacle is the frequent misattribution of the source of symptoms by patients themselves. Patients (and their caregivers) often erroneously attribute depressive symptoms to their neurologic disease and thus unwittingly mislead their physician. For this reason, a high index of suspicion is necessary when confronted with any of the following symptoms: headache, insomnia, reported memory loss, joint or back pain, chest pain, weight loss, nausea/vomiting/constipation, disrupted menses, fatigue/tiredness, and malaise. Changing how questions are oriented at examination, as reflected in

Table 2, can be helpful in overcoming this problem.

Neurologic medications can cloud the picture

Treatments for the neurologic illness can also complicate the clinical picture. For example, mood changes can accompany the symptom fluctuations ("on-off" phenomena) that often occur in patients with PD who have been treated with levodopa over a long period. Some of these patients fulfill criteria for major depressive disorder during the "off" phase but not during the "on" phase.[54,55] Cyclic mood changes (bipolarity) in association with on-off phenomena have also been described.[56]

As another example, beta-interferon therapy has been reported to cause depression (and fatigue) in 40% of patients with multiple sclerosis.[57] However, depression is highly prevalent in patients with untreated multiple sclerosis, and some studies have found no increase in depression following beta-interferon therapy.[58,59] In one prospective study, the rate of depression actually fell with beta-interferon treatment.[60]

Focal symptomatic lesions add further complexity

Specific cerebral lesions can further complicate the clinical picture in patients with neurologic disease. This topic has been comprehensively reviewed by Bogousslavsky and Cummings.[61] Of specific note, aphasia requires that the physician draw inferences about mental state from behavior and nonverbal communication. Intense emotional frustration accompanying expressive aphasia may be secondary to problems in social interaction,[62] and patients who have recovered from receptive aphasia have reported thinking that their examiner was being deliberately incomprehensible.[63] Anosognosia may coexist with depression,[64] suggesting that separate neural systems exist for different aspects of emotion[65] and that depression after stroke cannot be explained solely as a psychological reaction to disability.[66] By contrast, affective dysprosodia is the impairment of the production and comprehension of those language components that communicate inner emotional states in speech.[67] These include stresses, pauses, cadence, accent, melody, and intonation. Its presence is not associated with an actual deficit in the ability to experience emotions but rather in the ability to communicate emotions or recognize them in the speech of others.[67] Affective dysprosodia is particularly associated with right-sided lesions. Depressed patients with dysprosodia appear depressed and say they are depressed but do not "sound" depressed. In contrast, patients with anosognosia appear and sound depressed but may deny that is how they feel.

TABLE 2
Questions to ask when evaluating for depression in a patient with neurologic disease

Depression
Have your symptoms got you down at all?
Do you ever get the feeling that you can't be bothered to do things?
Is there anything you look forward to (or does your illness stop you)?
Has this illness affected your confidence?
Do things ever get so bad you think about death?
Anxiety/panic
Do you ever worry about your symptoms?
When you're worrying like this, is it sometimes hard to stop yourself?
Do you ever have attacks where you have a lot of symptoms all at once? What happened? Was it frightening?
Did you do anything differently because of these attacks?

Perhaps the hardest distinction to make is between depression and apathy. Patients with apathy show little spontaneous action or speech and have delayed, short, or slow responses—or no responses whatsoever.[68] Apathy is frequently associated with hypophonia, perseveration, grasp reflex, compulsive motor manipulations, cognitive and functional impairment, and older age. Hypoactivity of the frontal and anterior temporal regions has been observed in patients with apathy.[69]

Special challenges with cognitive disorders

The nexus of cognitive impairment and depression in neurologic disease merits specific discussion because it affects the elderly disproportionately. Cognitive impairment is a common symptom in late-life depression. Depression can also coexist with and complicate cognitive disorders. Cognitive impairment in the elderly ranges from mild age-related memory disturbance through an increasingly recognized transitional state, termed mild cognitive impairment,[70] to frank dementia.

Dementia in the elderly is most often caused by neurodegenerative disorders, particularly AD, but it can also have frontotemporal origins or be attributable to PD. Non-neurodegenerative conditions, such as cerebrovascular disease and systemic illnesses (eg, hypothyroidism), are also common etiologies. Regardless of cause, some of the "depression-like" symptoms mentioned above that result from neurologic diseases and specifically focal lesions occur with reg-

TABLE 3
Clinical features suggesting Alzheimer disease (AD) or depression

Clinical feature	AD	Depression
Severity of depressive symptoms	Relatively mild or atypical	Relatively severe (ie, level of major depression)
Subjective complaints of cognitive impairment	Less likely	More likely
Onset and progression of depressive symptoms and cognitive deficits	Gradual	Rapid
Performance on tasks assessing effort	Appropriate	Prominent deficit
Breadth of cognitive deficits (eg, language, gnostic, and practice deficits)	Broad	Narrow

ularity in the cognitive disorders.[71] These include apathy, insomnia, weight loss, and crying spells as well as unique problems such as lack of awareness of the level of cognitive deficit. Most geriatric cognitive disorders are progressive, and communication skills routinely diminish with progression. All of these phenomena can mimic depression and confound its diagnosis.

Two discrete syndromes in which cognitive impairment and depression are admixed have been recognized in the elderly—depression with reversible dementia (historically called "pseudodementia") and depression complicating dementia.

Depression with reversible dementia is important because it is common in the elderly and has been increasingly recognized as a risk factor for subsequent irreversible dementia, even in the case of complete recovery from the depressive episode; up to 40% of such patients will be diagnosed with dementia in the following 3 years.[72]

Depression complicating dementia has been studied mainly in relation to AD. It is important because it is a major source of additional morbidity—ie, alleviating depression in patients with dementia can improve functional status even if the course of the underlying cognitive disorder cannot be changed. This makes it critical that clinicians understand how depression may be manifested in patients with dementia so that depressive symptoms are recognized as such and not simply attributed to dementia. Similarly, it is important to learn how to distinguish between dementia-associated cognitive symptoms and those due to major depression (Table 3).[73] The recent proposal of diagnostic criteria for depression in AD[21] may facilitate advances in diagnosis and treatment.

In addition to these syndromes, depression also occurs in individuals with mild cognitive impairment. This is important because it may predict progression to AD, especially if the depression is resistant to antidepressant therapy.[22]

Assessing risk of suicide

When depression is a consideration, assessing the risk of suicide is imperative. A recent prospective study[74] found that 1 in 11 patients (26/300) examined consecutively in general neurology clinics had given serious thought to committing suicide in the prior 2 weeks. Major depression had been diagnosed in almost all of these patients (23/26). While one might assume that suicidal ideation would be more likely in patients with progressive, debilitating neurologic conditions, this was not the case. Of the 26 patients with suicidal ideation, 12 had somatoform symptoms, and most of the remainder had nonprogressive conditions. Of note, the elderly have the highest suicide rate of any segment of society.[75] At least in the United States, the highest rate of all is for elderly men who live alone.[75]

Physicians are often reluctant to inquire about suicidal ideation, in part out of fear of putting ideas in a patient's head. This is unlikely, and, in our experience, patients are often relieved when their doctor prompts them to discuss such thoughts.

The use of a set of progressively more direct questions is recommended, for example:

- Have your symptoms ever got you down?
- Do you ever wonder if you have the strength to go on?
- Does it ever get so bad that you wonder if life is worth living?
- Have you ever thought about ending it all?

Clearly, suicidal ideation exists on a continuum, and not all vague thoughts of an existential nature are a cause for alarm. Table 4 presents criteria for estimating risk, although they are rules of thumb and should not be viewed as prescriptive.

When in doubt, be pragmatic

When the diagnosis of depression in the setting of neurologic disease is uncertain, we suggest that clinicians take a pragmatic approach and make a provisional diagnosis, especially if symptoms of low mood or anhedonia are present and are accompanied by some somatic symptoms (eg, insomnia, anorexia) and lack of engagement with the environment (eg, poor participation in physiotherapy).

MANAGEMENT: GENERAL CONSIDERATIONS

The main aims of the treatment of depression in this population are to improve mood and quality of life, reduce the risk of medical complications, improve compliance with and outcome of physical treatment, and facilitate the appropriate use of health care resources. The development of a treatment plan depends upon a systematic assessment that, whenever possible, should involve partners or other key family members as well as the patient.

Besides major depression, adjustment disorders are also frequent in elderly patients with neurologic illness and occur in relation to significant life events, including health care developments. When mild or brief, these conditions can usually be managed by general health care staff without recourse to specialists. Education, advice, and reassurance are of value. For these reasons, it is important for general health care staff to be familiar with the properties and use of the common antidepressant drugs and the value of brief psychological treatments, such as cognitive behavioral therapy, interpersonal therapy, and problem-solving.

Patients with more enduring or severe symptoms of depression usually require specific forms of treatment, most commonly an antidepressant. Generalists should also be able to assess suicidal thinking and risk. In patients with such ideation or who have not responded to initial depression management, referral to a specialist is the next step.

Expert opinion holds that age should not be a basis for denying treatment.[4] Improvement in the quality of life of the elderly patient and of affected family and caregivers is a worthy goal and may also have wider benefits, such as reduced use of health care services.

TABLE 4
Criteria for estimating suicide risk

Low-risk patient
Suicidal ideation but no fixed plans or attempts
Physically healthy
Supportive environment
No significant premorbid history
Management: Can be kept under clinic review; no specific action required, though referral to a psychiatrist or psychotherapist can be considered
Medium-risk patient
Low-lethality suicide attempt (note: it is the patient's perception of lethality that must be assessed)
Frequent thoughts of suicide
Previous suicide attempts
Persistent depressive symptoms
Serious medical illness
Inadequate social support
Past psychiatric history
Management: Refer to psychiatrist to be seen same week
High-risk patient
Definite plan for suicide (when? where? how?)
Major severe depressive disorder
High-lethality suicide attempt or multiple attempts
Advanced medical disease
Social isolation
Past psychiatric history
Management: Must be referred to psychiatry on an emergency basis

PHARMACOLOGIC THERAPY

Antidepressant medication has been shown to be effective in treating major depression, even if the mood disturbance is deemed to be "exogenous," ie, caused by events or circumstances in the patient's life. There have been relatively few trials of antidepressant therapy in the medically unwell, but the available evidence is in keeping with the treatment of depression generally. The elderly respond at about the same rate as younger age groups,[47] although the time to response may be longer.[48]

Antidepressant options

One of the most commonly asked questions is which antidepressant should be used, as the range of available drugs, and the claims made about them, can be bewildering. There are four main classes of antidepressants:

- Tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Monoamine oxidase inhibitors
- Others (eg, serotonin-norepinephrine reuptake inhibitors [SNRIs] and other agents such as mirtazapine and bupropion).

Data from the Cochrane Collaboration[76] and other systematic reviews[77] show that the difference in overall tolerability among the different medications is minimal in healthy adults. In general, patients are slightly less likely to drop out of trials because of unacceptable side effects when taking an SSRI but are slightly less likely to drop out because of treatment inefficacy when taking a TCA.

Prescribing advice for nonspecialists

Rather than continuously experiment with a range of drugs, it is advisable to stick to prescribing one drug from each class to become familiar with its dosing regimens, actions, interactions, and side effects. Nonspecialists should also be aware that there are certain situations in which one class of drug or one drug within a class may be more advisable than another (eg, for elderly patients, individuals with certain comorbidities, and patients taking certain other medications). Specifically, the SSRIs fluoxetine and paroxetine significantly inhibit cytochrome P-450 2D6, which makes them problematic in patients taking certain antiarrhythmics, some beta-blockers (eg, propranolol), and verapamil. Similarly, TCAs are dangerous in the setting of a recent myocardial infarction or a cardiac conduction defect. Because of their anticholinergic properties, TCAs are also less favorable in the elderly (and especially those with dementia) than SSRIs and SNRIs. If TCAs are used in the elderly, secondary amines such as nortriptyline and desipramine are preferable. The SSRIs sertraline and citalopram have been the most widely investigated newer medications in the elderly, and mirtazapine is also often used in this population.

Ensure adequate dose, duration, and compliance

The debate about different agents has obscured a potentially more important issue: medication dosage and compliance. Antidepressants are often prescribed in inadequate doses and more often than not for too short a time.[78] This problem is compounded by the finding that only 30% to 60% of patients comply with prescribed regimens.[78] A recent study of neurology outpatients[79] found that many believed that antidepressants were addictive and could permanently damage the brain.

If patients are to be successfully treated with antidepressants, their physicians need to demonstrate that they understand their problems, have considered individual issues, and are recommending the best treatment available. Before commencing drug therapy, patients should be told about the drug's side effects and be reassured that side effects are often worst during the first 2 weeks of treatment and then diminish. Patients also must be advised that they are unlikely to feel benefits from treatment in the first 4 weeks. They should be given follow-up appointments or be otherwise closely monitored during this period to encourage compliance.

After initial pharmacologic treatment has led to response and, ideally, symptom remission, subsequent treatment can be divided into two phases. First, 4 to 6 months of continuous treatment at full dose are needed to consolidate improvement and prevent early relapse. Second, consideration should be given to preventive maintenance, to reduce the risks of depression recurrence. Maintenance treatment is usually indicated if the patient has had two or more episodes of depression within the past 5 years. Psychological treatment (see below) may also help to prevent recurrence and can be used in combination with drug therapy.

Treatment considerations in stroke

It is generally recommended that treatment for depression in stroke survivors should be started early, to maximize functional outcome, but few randomized clinical trials have evaluated this recommendation. Most studies have reported improved outcomes with regard to mood, but findings have been contradictory in measures of function.[18,19,80–83]

Both SSRIs and TCAs have been found effective for depression in stroke patients, but SSRIs are probably preferable because they have fewer adverse effects, particularly if cognitive or cardiac function is compromised. However, this greater tolerability must be balanced against the finding that the TCA nortriptyline was more effective than the SSRI fluoxetine in the only trial that compared these agents.[80] What is clear is that all stroke patients taking antidepressants should be closely monitored for both treatment effectiveness and adverse effects. Psychological treatment—particularly cognitive behavioral therapy—may also be of value, but it has received only limited evaluation to date.[84,85] One small study suggested that cognitive behavioral therapy is adequate for only a minority of depressed stroke patients and provides some benefit for others, while nearly half of such patients do not benefit at all.[86]

Treatment considerations in multiple sclerosis

The few randomized controlled trials of antidepressant therapy in patients with multiple sclerosis suggest only modest efficacy,[87] as for depression associated with neurologic illness in general.[88]

Treatment considerations in Parkinson disease

Current evidence is insufficient to support definitive recommendations for the treatment of depression in PD.[89] While SSRIs are popular, there have been case reports of exacerbation of motor symptoms with fluoxetine, citalopram, and paroxetine.[90–94] In recent small-scale trials, TCAs have shown better motor outcomes, but medications with marked anticholinergic effects, such as amitriptyline, should be used with

caution because of their effects on cognition and autonomic function.[89] Newer drugs, such as mirtazapine, may offer a compromise. The nonergot dopamine agonist pramipexole, which is indicated for treatment of PD itself, has been found to improve both mood and motivation in PD patients.[95] Case report data suggest that both electroconvulsive therapy and transcranial magnetic stimulation can be used to treat depression in PD, although the latter is associated with short-lived effects and seizures.[89,96]

Treatment considerations in epilepsy

Most experts advocate the use of SSRIs as first-line therapy for depression in patients with epilepsy because of these drugs' limited propensity to lower the seizure threshold. Further consideration needs to be given, however, to possible drug interactions with anticonvulsant medications (paroxetine may have the most favorable profile in this regard). This consideration must be balanced, in turn, against treatment efficacy, since depression is an independent risk factor for unprovoked seizures.[97] Thus, TCAs sometimes produce improved mood and correspondingly improved seizure control, even after allowing for theoretical reduction in seizure threshold.

Treatment considerations in cognitive disorders

The value of pharmacotherapy for depression in patients with cognitive disorders has been explored over the years, with early studies of TCAs showing some equivocal results.[98] Such findings, together with recognition of the TCAs' adverse effects in elderly demented patients, led to a focus on the SSRIs and other newer agents. In an important recent study,[99] the SSRI sertraline was found to be superior to placebo in treating depression in patients with AD.

OTHER TREATMENT MODALITIES

Electroconvulsive therapy

Electroconvulsive therapy (ECT) remains the gold standard for severe depression in adults generally,[100] and its safety and efficacy have been increasingly recognized in the elderly.[101] The use of ECT in depressed patients with neurologic impairment is not new, but its value has not been systematically evaluated in controlled studies of adequate size and design. In PD, for example, small and mostly retrospective studies over many decades have reported benefit in mood and behavior, along with motor improvement of varying degrees and durations.[102] One large recent study of this kind confirmed benefit in 25 patients with PD, a few of whom might have had drug-induced parkinsonism.[103] Similar data exist for poststroke depression,[104] although patient numbers are smaller and the benefit may not be long-lasting. A high rate of response to ECT has been reported in elderly patients with depression who had substantial white matter lesions.[105] ECT has been examined to a limited extent as a treatment for depression in patients with dementia. A retrospective case study of ECT in 31 such patients reported significant improvements in mood and even improvement in cognition.[106]

Treatment-emergent delirium and memory impairment (usually short-lived) have been noted in reports of ECT in patients with various neurologic disorders, as in other populations. While such problems may constrain the use of this therapy, they should not preclude its consideration in medically appropriate patients with refractory depression.

Psychological treatment

Psychological treatment can range from discussion and problem-solving to more specialized cognitive or dynamic behavioral psychotherapies. In many cases, short-term treatment by those who are not mental health specialists can be effective in both primary and secondary care. Such interventions may include education and reassurance about the common reactions to the threats and losses associated with illness, as well as empathic listening to the patient's views, uncertainties, and beliefs about the illness. Education and advice about the medical condition and associated depression may prevent needless worry, reduce feelings of helplessness, and diminish irrational fears. Therapeutic approaches that support or promote active coping strategies are an important aspect of treatment in physically ill patients.

Cognitive behavioral principles may be used by nonspecialists to correct cognitive distortions related to the illness and to support behavioral strategies that contribute to the patient's sense of mastery and well-being. Training in briefer forms of treatment using cognitive behavioral principles for general health care staff may be a worthwhile investment.

Cognitive behavioral therapy, interpersonal therapy, and problem-solving have all been shown to be effective for treating depression,[107–109] although their efficacy has seldom been tested in physically ill populations. Although time-consuming compared with drug treatment, psychological treatment may reduce relapse rates and may be cost-effective in the long run. Some patients may require preliminary pharmacologic treatment to enable them to fully benefit from psychological treatment.

Contrary to perceptions among the public and health care providers, psychotherapy is often effective in treating depression in the elderly. Both interpersonal therapy and cognitive behavioral therapy have demonstrated efficacy comparable to that of antidepressants in this population, and the combination of both was most effective.[108,109]

Psychotherapy in the cognitively impaired should not be dismissed out of hand. Individuals with mild cognitive impairment can certainly benefit from it, and novel forms of supportive psychotherapy are being explored in the demented. Examples include facilitated reminiscing and techniques emphasizing nonverbal communication (eg, therapeutic touch, pet therapy, and music). Aggressive reorientation to reality is generally viewed as inadvisable.

CONCLUSIONS

In elderly patients with neurologic disease, depression often manifests as a mixture of phenomena associated with the neurologic condition or with aging itself in addition to the depressive illness. Effective diagnosis of depression is possible with alertness to clues in the interview and the use of screening questions for those at risk. Generalist physicians can and should assess for suicidal thinking and risk. When the diagnosis of depression in the setting of neurologic disease is uncertain, clinicians do well to take a pragmatic approach and make a provisional diagnosis, especially if low mood or anhedonia is evident and accompanied by somatic symptoms and lack of engagement with the environment.

The objectives of treating depression in this population are to improve mood and quality of life, reduce the risk of medical complications, improve compliance with and outcome of physical treatment, and facilitate appropriate use of health care resources. In many cases, depressed elderly neurologic patients can be effectively treated by generalist clinicians with antidepressant medications and/or psychological therapy. Referral to a specialist is indicated for patients with suicidal ideation or those who have not responded to an initial course of therapy.

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