Depression in late life

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Despite its prevalence and seriousness, depression in late life remains underappreciated as a source of disability and suffering for older people and their families. Despite a solid and substantial body of research, recognition of depression remains problematic and is often attributed to normal developmental changes in aging. Treatment efficacy data notwithstanding, the adequacy and appropriateness of treatment is highly variable. This paper contains a broad overview of new research developments in depression in late life and the disabilities associated with it. Serving as an introduction to the specific papers that follow in this issue of Dialogues in Clinical Neuroscience, *this article scans the knowledge base in basic, clinical, and health services research, identifying the highlights of current work in the area and proposing areas of needed expansion of research efforts.*

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Three factors combine to make depression in late life a primary concern in worldwide public health. First, the global population is growing older, gaining nearly 30 years of life expectancy in this century.[1] Second, our appreciation of the disabling consequences of depression has been underscored by the landmark report of the World Health Organization on the "global burden of disease."[2] Third, the tools of contemporary neuroscience have significantly enhanced our understanding of the pathophysiologic and etiologic mechanisms of depression.[3-7]

Depression in older people is a significant public health problem.[8] It is the cause of unnecessary suffering for those whose illness is unrecognized or inadequately treated, and it burdens families and institutions providing care for the elderly. Because of the stereotypic notion that older people are necessarily beset by many physical illnesses and social and economic problems, clinicians, family members, and older people themselves often conclude that depression is a normal condition of late life. Clinically, the symptom of depressed mood may be less commonly reported than a variety of somatic complaints, sleep and appetite change, and general loss of interest.[9] These factors combine to make diagnosis and treatment of depression highly variable and problematic.[10]

This paper, and the other papers in this issue, will demonstrate that depression in older people is widespread and serious, and that the comorbidity of depression with other illnesses is particularly significant. Moreover, we will show that depression can be diagnosed in the older patient and that it can be differentiated from normal aging. Importantly, a variety of treatments have been demonstrated to be safe and efficacious in the elderly, and long-term treatment might be indicated.

Onset and course of depression

Depression in late life is a very heterogeneous condition. Onset may be early in life with the course recurrent from a first episode earlier in adulthood, or the onset of the first episode may be late in life. In general, compared

with patients of the same age with recurrent depression, those patients with the first onset of depression in late life are likely to have a less satisfactory response to treatment and a more chronic course.

There are significant brain changes in depression: frontal and temporal lobe atrophy,[11,12] periventricular and subcortical deep white matter hyperintensities,[13] and significantly decreased metabolism in a variety of brain regions (dorsolateral prefrontal cortex, inferior frontal cortex, basal ganglia).[14] Many of these changes are associated with normal aging as well. Late-onset depression often is associated with a variety of brain abnormalities, such as ventriculomegaly and white matter hyperintensities, and with cognitive impairments. Recent research has uncovered important sources of clinical and biological heterogeneity within late-life–onset depression, and subgroups with distinctive patterns of clinical presentations, course, mechanisms, and outcomes have been identified.[15-17]

The association between depression and cognitive impairment has been well established, though the direction of causality has been disputed, as has the methodology of assessment.[18,19] There does seem to be general agreement, however, that late-life depression with cognitive impairment that is reversed by antidepressant treatment is, more often than not, a predictor of the development of an irreversible dementia such as Alzheimer's disease or vascular dementia.[20]

Converging findings implicate vascular disease in the pathogenesis of one particular subgroup. Geriatric depression is often comorbid with vascular disorders and is accompanied by lesions in the basal ganglia and prefrontal areas of the brain. The clinical profile of depression in patients with vascular disease is often characterized by motor retardation, lack of insight, and impairment of executive functions. This clinical presentation suggests that dysfunction of frontal brain systems is a possible contributing factor to depression in late life.[21-24] It also suggests that treatment for cerebrovascular disease may have preventive implications for late-life–onset depression. The article by Alexopoulos and colleagues in this issue of *Dialogues in Clinical Neuroscience* addresses this specific topic.

Comorbidity and disability

Depression coexisting with physical illness has been shown to increase levels of functional disability, increase the use of health care resources, reduce the effectiveness of rehabilitation in older patients with stroke, Parkinson's disease, heart disease, pulmonary disease, and fractures, and increase risk of death.[25,26] Depression has been shown to exert a strong and independent effect on functional disability. That effect is independent of diagnosis or overall medical burden. Functional disability itself predicts the development of depression and, conversely, depressive symptomatology is a risk factor for the onset or progression of disability.[27-30] Studies have shown that treatment for depression is safe and effective in patients with complex patterns of comorbidity, and suggest that treatment for depression can reduce excessive levels of disability and result in improved levels of functioning.[31]

Studies of the psychosocial and medical correlates of late-life depression have also suggested possible mechanisms for the development of depression in older persons. There is substantial ongoing research on the central nervous system effects of the cytokines, particularly interleukin-1β, in cortisol production, inflammation, and immune system activation. It is hypothesized that these mechanisms may be involved in the physiological and behavioral responses to illness and the genesis of depression.[25] The article by Katz in this issue of *Dialogues in Clinical Neuroscience* specifically examines this topic.

Subsyndromal depression in the elderly

Evidence is mounting to support the notion that clinically significant depression is a spectrum disorder rather than a categorical disease entity. While recent studies report a 1% to 2% prevalence of major depression and a 2% prevalence of dysthymia among community-dwelling elderly, much higher rates (13% to 27%) are observed in this age group for subsyndromal depressions.[32,33] Subsyndromal depressions are levels of depressive symptoms (referred to as subsyndromal, subclinical, or symptomatic depression) that are associated with increased risk of major depression, physical disability, medical illness, and high use of health services but that do not meet the *Diagnostic and Statistical Manual of Mental Disorders* 4 edition (DSM-IV) criteria for major depression or dysthymia.[34] In medically ill elderly and nursing home residents, the prevalence of such symptom levels may be as high as 50%.[35] The course of subsyndromal depressions is variable, but in the con-

text of severe physical disability, from stroke, for example, the depressive symptomatology can be persistent over extended periods of time.[36,37] Ongoing research is actively pursuing questions of treatment response in subsyndromal depressions and whether interventions can have more generalized benefits on functional disability, quality of life, and needs for health care.[37]

Gender and hormonal issues

One of the most striking and consistent findings in psychiatric epidemiology is that women have higher rates of all types of depression than men. Increases in depression have been observed among women during natural or surgical menopause and in response to antiestrogen therapy for breast cancer. Though still under debate, symptoms attributed to menopause-related changes in mid-life women include: depressed mood; decreased self-confidence; difficulty making decisions; anxiety; insomnia and fatigue; problems in memory and concentration; and decreased libido.[38] Hormone replacement therapy has been associated with improvements in mood and quality of life, but the data are still very preliminary.

Despite claims in the popular media, there is no evidence supporting the antidepressant effects of the androgens testosterone and dehydroepiandosterone (DHEA) in either men or women.[39] The data on hormonal factors in the development and treatment of depression remain preliminary, with some suggestive leads for further study.[40] A more detailed understanding of these interactions,[41] and prospective clinical trials, will be needed to determine whether manipulation of estrogen and other sex steroids has a significant role in the treatment of depression in late life.

Treatment issues

The goals of treatment are to achieve remission of symptoms, prevent relapse and recurrence, and improve the quality of life and functional capacity.

Pharmacotherapy

In general, the older tricyclic antidepressants (TCAs) and the newer selective serotonin reuptake inhibitors (SSRIs) have comparable efficacy in elderly patients.

The newer drugs of mixed action have not been extensively studied in the elderly. The SSRIs are coming to be seen as preferable largely because of ease of use, less dosage adjustment, different side effect profiles including a reduced anticholinergic and cardiovascular burden, and greater acceptance.[42,43] The article by Schneider in this issue of *Dialogues in Clinical Neuroscience* specifically addresses this topic. It is uncertain whether this conclusion applies to clinically important subgroups such as those patients with chronic and very severe levels of major depression, or to very old patients.

Side effects

As in younger adults, the elderly tend to tolerate the SSRIs better than TCAs. This is based on fewer anticholinergic effects, little or no adverse effects on cognition at recommended doses, and minimal cardiovascular effects. Common complaints linked to SSRIs include nausea, diarrhea, insomnia, headache, agitation, and anxiety. Side effects of SSRIs that may be relatively more common or more problematic in older patients include SSRI-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH), extrapyramidal symptoms, and bradycardia.[26] Based on available data, it is not possible to determine whether the elderly are more sensitive to these more frequent side effects than younger populations. It should be noted that SSRIs are metabolized in the liver and inhibit the drug-metabolizing enzyme cytochrome P450, the route through which many other medications commonly taken by older people are metabolized. Such drugs include β-blockers, class Ic antiarrhythmics, and benzodiazepines. The combination of drugs may result in clinically significant alterations in drug concentration levels or in complex drug interactions.[44-46]

Psychotherapy

Research has clearly demonstrated the efficacy of standardized approaches to treatment, such as cognitive-behavioral therapy, interpersonal therapy, and problem-solving therapy, both alone and in combination with pharmacotherapy.[47] No single standardized approach to psychosocial treatment has a consistent advantage.[48-50] Psychotherapy is a powerful component of long-term treatment strategies where the contribution of therapy alone has been shown to provide sub-

stantial benefit in prolonging periods of good health free from depression.[47] Psychotherapy also has particular utility in older patients who cannot or will not tolerate medication, or who are dealing with obviously stressful situations, interpersonal difficulties, or low degrees of social support.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) remains an important, safe, and efficacious approach to the acute treatment of depression in older patients.[51,52] ECT is particularly useful in older patients whose medical condition is so fragile that they cannot tolerate pharmacotherapy, or in patients who are so acutely suicidal that a rapid response is required. ECT is also commonly used with patients who have not responded to pharmacotherapy and for patients with psychotic depression. Relapse rates following ECT are very high, however.[53] Important research is now investigating the longer-term efficacy of continuation pharmacotherapy and continuation ECT to address the problem of relapse.

Long-term treatment

Evidence has also continued to accumulate on the necessity for long-term treatment in late-life depression. Indeed, older patients with recurrent depression may need antidepressant treatment indefinitely to remain well. Moreover, long-term treatment should be of the same type and same intensity as that which was successful in the initial, acute phase. This is in contrast to much prevailing practice; longitudinal data demonstrate that the intensity of antidepressant treatment typically decreases prematurely, prior to 8 weeks of recovery.[54] The appropriate intensity for maintenance regimens using psychotherapy only has not been systematically studied. Treatment response and long-term outcome for older patients are generally similar to those observed in mid-life adults, but the temporal course may be somewhat slower in the elderly and the risk of relapse somewhat greater.[55] These differences are especially pronounced in patients over the age of 70.[56] The article by Schneider in this issue of *Dialogues in Clinical Neuroscience* is devoted to issues in treatment.

Health care service and resource use

In mixed age samples, major depression leads to excessive utilization of medical services and greater health care costs. In nursing homes and among high utilizers of medical services, patients with depression incur significant increases in direct costs for medical care.[57-60] Longitudinal data demonstrate that depressive symptomatology in elderly primary care patients is associated with increased physician visits, medication use, emergency room visits, and outpatient charges.[61,62] Among medical inpatients, major depression has been associated with increased utilization of health care resources, including longer hospital stays and greater mortality, for example, in those undergoing elective coronary artery bypass grafting.[63-65] After discharge, depression accounts for a substantial increase in ambulatory health care use.[66]

The general health care sector is by far the principal source of treatment for older persons with depression. Recently analyzed data from the 1987 National Medical Expenditure Survey show that over 55% of older persons using mental health care received this care from general physicians. In contrast, less than 3% of individuals over age 65 report having received outpatient treatment from mental health professionals, a proportion lower than that for any other adult age group.[67]

The scope and responsibility of primary care providers are being expanded and redefined in many health care systems. Primary care providers are charged with greater responsibility for diagnosis, treatment, and long-term management in all areas of health care, including care of older patients with mental disorders. That being the case, older people may derive substantial benefit from increased sensitivity to identification of depression on the part of their primary care physicians. Interventions directed toward improvement, recognition, and treatment, however, have not necessarily translated into added benefit when compared to practice as usual in the primary care setting.[68-70]

Suicide and late-life depression

Suicide rates increase with age in most countries of the world, and men outnumber women suicide completers by a substantial amount. Recent studies of completed suicide have reinforced the close association with major

depressive illness, especially in the elderly.[71,72] With increased age, the relative importance of the contribution of depression to suicide risk is magnified. The typical clinical profile of the older suicide completer is late-onset, nonpsychotic, unipolar depression of moderate severity uncomplicated by substance abuse or personality disorder.

Tragically, the depression in these older people was rarely recognized or treated. The failure to recognize and treat depression was not due to restricted access to care. A majority of these depressed suicide victims had seen a health care provider in the last month of life, 39% in the last week, and 20% on the day of suicide.[73] The article by Bruce and Pearson in this issue of *Dialogues in Clinical Neuroscience* examines this topic.

Future directions

Practice-relevant intervention studies

The rich and valuable literature on treatment of depression in late life has not been as informative for practice as it might be. In particular, we do not know why treatments rarely work as well in practice as they do in clinical trials, whether treatment enhances functioning, whether early treatment predicts a more favorable response, how can we keep people well once they have been made well, or the approaches that should be used for the treatment-resistant patient.

These issues are raised within the context of what has been called a public health model of treatment.[74] We cannot yet address these as well as we would like, however, largely because the direction and culture of treatment research has been determined by a more narrowly defined regulatory model[75] geared to the approval and registration of pharmacologic agents. This regulatory model has been the dominant force shaping treatment research.

In general, the rigid exclusions of most regulatory-oriented clinical trials have significantly distorted the conclusions of these studies. Age itself is the most common concern, with most studies being restricted, to all intents and purposes, to the "young-old" population of patients in their sixties. Few older patients have ever been studied[76] despite the clear impact of advanced age on pharmacokinetics, dynamics, and drug metabolism[46] and on treatment response.[56] Geriatric treatment

research protocols have simply taken mid-life adult protocols and substituted a different age-range while keeping the remainder of the study unchanged with respect to eligibility, dosing, duration of treatment, and instrumentation.

Studies that are informed by a public health model are often called "effectiveness studies." Public health studies bring research into the world of actual practice with time-pressured clinicians taking care of large numbers of patients with uncertain clinical presentations, complex comorbidities, varying degrees of interference, and with ideal levels of compliance. The exclusive focus on symptomatology is expanded to include outcomes related to issues of function, disability, morbidity, mortality, resource use, and quality of life. The classic public health trial is used to assess the expected outcome under usual circumstances of practice.

In contrast to the elegantly crafted efficacy trial, a public health trial must be bigger in size, simpler in design, broader in terms of inclusions, and narrower in terms of exclusions, and more representative with respect to settings of care. These settings will not be limited to academic health centers or tertiary care institutions, but will include primary care, community settings, and long-term care institutions. Unlike efficacy trials where specially trained clinicians carry out state-of-the-art assessment and treatment, public health trials are carried out in settings of usual practice where there is a broad and variable range of clinician expertise and experience with the disorder under study. Outcome measures will necessarily extend beyond symptomatology to include function, disability, morbidity, mortality, health care and other resource use, family burden, institutionalization, and quality of life.

Development of preventive interventions

Given the breadth and depth of the knowledge base regarding depression in late life, a clear opportunity is now presented to mount an initiative directed toward prevention. Prevention has many aspects. An intervention may be based on models of pathophysiology or etiology to prevent onset of the illness. Vascular depression presents one such opportunity, as does the research on bereavement[77-79] and a variety of comorbidities, such as vision or hearing loss and other illnesses. In the context of treatment, preventive interventions may well be

directed at relapse, recurrence, or excessive levels of functional disability.

Safety and consumer protection

As part of a public health mission, we must also attend to issues of safety and consumer protection. For example, the widespread use of over-the-counter, unregulated treatments needs to be carefully examined for possible benefit and for potential harm. Use of complementary and alternative approaches is very high and growing.[80,81] Even in patients volunteering for participation in clinical drug trials, use of herbal medications is substantial; in a series of 150 such subjects,[82] 56% reported having used herbs in the last month. It is therefore incumbent upon us to evaluate these treatments including natural products such as St John's Wort or kava, psychophysiologic approaches such as eye movement desensitization reprocessing (EMDR), and somatic approaches such as acupuncture, if for no other reason than that our patients are using these in large, uncontrolled, natural experiments.

Dissemination

A final priority must be dissemination. Our patients are not helped by treatments that are available in only in scientific journals. A recent example highlights the problem. Lehman and Steinwachs[83] report that fewer than half the patients with schizophrenia in the United States received a level of care that was consistent with the current state of the art. This is an important finding that cannot be ignored. As a field we must take on the challenge of translating our research into practice and placing the most powerful clinical tools in the hands of patients, their families, and the clinicians that take care of them. The Geriatric Psychiatry Alliance initiatives on depression[84] represent an important and potentially valuable approach to this problem.

Conclusions

There has been significant progress in our understanding of the nature, clinical course, and treatment of depression in late life. Important findings have emerged in a number of areas directly affecting clinical care and have, in turn, stimulated further research. These findings include: the association of late-onset depression with brain abnormalities and vascular disease; the mutual reinforcement of depression and functional disability; the clinical importance of subsyndromal states; the possible role of sex steroids; the clinical utility of new antidepressant treatments, including the SSRIs and standardized psychotherapies; the need for long-term treatment; the importance of depression in the general health care system; and the clear relationship between depression and suicide. New opportunities have emerged for research in a more public-health–oriented model, in prevention, and in dissemination.

Depression remains a central concern to older people, their families, and the clinicians who take care of them. Even when it appears to be an understandable response to illness, the onset of depression should be viewed as a sentinel event that increases the risk for subsequent declines in health status and functional ability. Early recognition, diagnosis, and initiation of treatment of depression in older persons present opportunities for improvements in quality of life, the prevention of suffering or premature death, and the maintenance of optimal levels of function and independence for older people. ❑

Depresion en sujetos de edad avanzada

A pesar de su alta prevalencia y de su gravedad, la depresión en los estadios avanzados de la vida continúa siendo menospreciada. Ella causa incapacidad sufrimiento en los sujetos de edad avanzada y en su entorno familiar. Aunque hay sólidos y sustanciales datos que provienen de la investigación, el reconocimiento de la depresión continúa siendo un problema y se la considera todavía como una adaptación normal al envejecimiento. Aunque existen datos sobre la eficacia de su tratamiento, la adecuación y especificidad de éste es altamente variable. Este artículo entrega una visión general de los últimos desarrollos de la investigación en el campo de la depresión en estadios avanzados de la vida y de las incapacidades que ella conlleva. Este artículo sirve de introducción a los termas específicos de este número de Dialogues in Clinical Neuroscience *y revisa los aspectos más importantes de la investigación básica y clínica, como también la atención que ofrecen los servicios de salud. Se identifican los aspectos más relevantes del trabajo actual en esta área y se proponen las vías necesarias para extender los esfuerzos en futuras investigaciones*

La dépression du sujet âgé

En dépit de sa fréquence et de sa gravité, la dépression du sujet âgé reste sous-estimée en tant que source d'incapacité et de souffrance, autant pour le sujet concerné que pour son entourage. Malgré des données solides et substantielles fournies par la recherche, la reconnaissance de la dépression demeure problématique, au point qu'elle est souvent attribuée aux conséquences physiologiques du vieillissement. Malgré l'efficacité démontrée du traitement, l'adéquation et l'opportunité de celui-ci sont des plus variables. Cet article donne une large vue d'ensemble sur les nouvelles voies de recherche qui gravitent autour de la dépression du sujet âgé, mais aussi sur les handicaps qui lui sont associés. Il sert d'introduction aux articles plus spécifiques qui suivent dans ce numéro de Dialogues in Clinical Neuroscience, *en examinant les connaissances de base dans des domaines de recherche aussi divers que les sciences fondamentales, la clinique et les services de santé. Il souligne aussi les phénomènes les plus marquants dans les travaux en cours et propose des voies qui devraient bénéficier d'efforts de recherche soutenus.*

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