Depression in Late Life: Etiology, Presentation, and Management

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Abstract

Depression in late life is common with a community prevalence of approximately 15%. The figures are higher among hospital inpatients (20–25%) and patients in long-term care (10–40%). It is the most frequent cause of emotional suffering in the elderly and can have a significant impact on a person's physical health and cognitive and social functioning. Suicide among older adults is more often associated with depression than at any other age, and suicide attempts are more likely to be fatal. Depression in late life may refer to either depression with first onset in later life (late-onset depression) or depression that occurs for the first time in younger years and recurs in later life (early-onset depression). The two syndromes differ in terms of etiology, presentation, and natural history. Late-onset depression can be considered to be a geriatric syndrome similar to frailty, falls, or incontinence. Affective symptoms may be less to the fore with motivational-type symptoms and somatic complaints relatively more prominent. The

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_10

physiological and psychological effects of poor physical health and the organic changes of the aging brain are fundamental considerations in this age group. Successful management of depression in late life, regardless of the subtype, requires a flexible and thoughtful multidisciplinary approach. While pharmacotherapy undoubtedly plays a vital role in moderate to severe cases, it must be used cautiously given the increased risk of adverse side effects in the elderly. Physical health, social disconnection, and functional or occupational decline must also be identified and targeted according to the individual needs and abilities of the patient.

Keywords

Late life depression • Comorbidities • Dementia • Cognitive impairment • Social network • Psychological factors • Antidepressant • Prevention

Contents

Introduction

When considering many of the factors associated with later life – personal loss, physical ill health, and cognitive decline – the onset of a depressive syndrome could seem to be almost an inevitability. However, with community prevalence rates of between 8% and 16% for a clinically significant depression (Blazer 2003; Kirby et al. 1997), it is clear that the majority of the older population are not depressed and depression cannot, therefore, be seen as part of the normal aging process. Late life depression is associated with poorer physical and cognitive health, impaired social functioning, increased suicide risk, and higher overall mortality. It is hugely distressing for patients and impacts widely on families and friends.

One of the greatest challenges faced by clinicians when treating patients with late life depression is unpicking the etiological and clinical heterogeneity of the condition. Increasingly, however, we are seeing that the successful management of late life depression requires a multidisciplinary approach that takes advantage of this very heterogeneity. The aim of this chapter is to explore our current understanding of the etiology, presentation, and management of late life depression. By drawing from the rapidly expanding knowledge base in this area, we hope to provide a framework for how late life depression may be formulated and managed in order to improve outcomes and enhance the quality of life of patients.

Definitions

"Depression" refers to a disorder of mood that causes persistent feelings of sadness or loss of interest that impact negatively on a person's quality of life and normal occupational or social functioning. DSM-5 and ICD-10 have classified and defined depressive episodes as summarized in Figs. 1 and 2. In milder forms of depression, where the symptom count falls below the threshold required for a diagnosis of major depression, the terms "minor depression," "subsyndromal depression," or "subthreshold depression" are used interchangeably.

"Depression in late life" refers to a major depressive episode that occurs in later years. The debate as to when "later life" begins, however, is contentious with age thresholds differing significantly between countries, cultures, and health services. Traditionally, an age cutoff of 65 years is used to determine access to specialist geriatric care. However, 65 is no longer considered to be "old" in many developed countries where life expectancy now exceeds 80 years and the general health of the population is better than ever before. Studies which address specific age-related issues, such as physical frailty, increasingly draw from populations of the "old old," a term used more frequently now to describe those aged over 80 or 85 years of age. By and large, however, "late life" is still taken, by convention, to refer to those aged 65 years and older and will be used in that way throughout this chapter unless stated otherwise.

"Depression in late life" encompasses both depression with first onset in younger years that recurs in later life and depression that occurs for the first time in later years. Approximately half of the older depressed population experience their first depressive episode in later life. This will be referred to as late-onset depression (LOD), while depression of earlier life that recurs in later years will be referred to as early-onset depression (EOD).

Etiology

Successful treatment of depression in late life requires an approach that carefully considers all of the potential biological, psychological, and social factors which contribute to the individual's experience of depressive illness and a

A. At least 5 of the following symptoms present during the same 2-week period, representing a change from previous functioning. One of the symptoms must be either depressed mood or loss of interest or pleasure
   - Depressed mood most of the day, nearly every day
   - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
   - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
   - Insomnia or hypersomnia nearly every day
   - Psychomotor agitation or retardation nearly every day
   - Fatigue or loss of energy nearly every day
   - Feelings of worthlessness or excessive or inappropriate guilt nearly every day (which may be delusional)
   - Diminished ability to think or concentrate, or indecisiveness, nearly every day
   - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation or a suicide attempt or specific plan for committing suicide

B. There is significant distress or impairment in social, occupational or other important areas of functioning due to these symptoms
C. The episode is not attributable to the effects of a substance or another medical condition
D. The episode is not better explained by a schizophrenia spectrum or other psychotic disorder
E. There has never been a manic or hypomanic episode

Fig. 1 DSM-5 diagnostic criteria for major depressive disorder (Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*)

multidimensional treatment plan that targets them. Figure 3 illustrates the interplay of these multiple factors in the etiology of depression in late life.

Biological Factors

The pathophysiology of depression in late life can be conceptualized, in part, as a series of dysfunctional physiological processes that lead to disruption of the neural networks responsible for mood. Of the multiple neural networks implicated in the experience, regulation, and expression of mood, cortical and limbic structures appear to be of most significance. The prefrontal cortex, cingulate cortex, amygdala, hippocampus, and hypothalamus are each densely interconnected, and disruption at any level can cause a range of emotional, behavioral, and cognitive disturbances

Symptoms Group A	Symptoms Group B
Depressed Mood	Reduced concentration & attention
Loss of interest & enjoyment	Reduced self-esteem and self-confidence
Reduced energy and activity	Ideas of guilt and unworthiness
	Disturbed sleep
	Diminished appetite

F32.0 Mild Depressive Episode

At least 2 symptoms from Group A and 2 from Group B present to a mild degree for a minimum duration of 2 weeks

F32.1 Moderate Depressive Episode

At least 2 symptoms from Group A and at least 3 from Group B present to a marked degree for a minimum duration of 2 weeks

F32.2 Severe Depressive Episode without Psychotic Symptoms

All 3 symptoms from Group A and at least 4 from Group B should be present, some with severe intensity. Symptoms should be present for at least 2 weeks but an earlier diagnosis may be justified if symptoms are particularly severe or of very rapid onset

F32.3 Severe Depressive Episode with Psychotic Symptoms

A severe depressive episode which meets the criteria for F32.2 and in which delusions, hallucinations or depressive stupor are present

Fig. 2 ICD-10 criteria for depression (Adapted from the International Statistical Classification of Diseases and Related Health Problems 10th Revision)

that produce the clinical depression phenotype. Figure 4 depicts how the biological factors discussed below may interact as potential insults to the fragile neural networks of the aging brain.

Medical Illness

Medical ill health and late life depression are intimately related. Poor physical health is implicated in both the onset and persistence of depression and presages a poorer outcome, while depression adversely affects medical outcomes. It is uncertain whether this relationship is propelled by the illness entity or by the symptom experience though the likelihood is that a combination of both psychological and physiological factors is at play.

A wide array of illnesses has long been known to be associated with depression (Table 1), and many are screened for routinely as part of the initial work-up process. Disorders which are common in elderly populations such as chronic obstructive

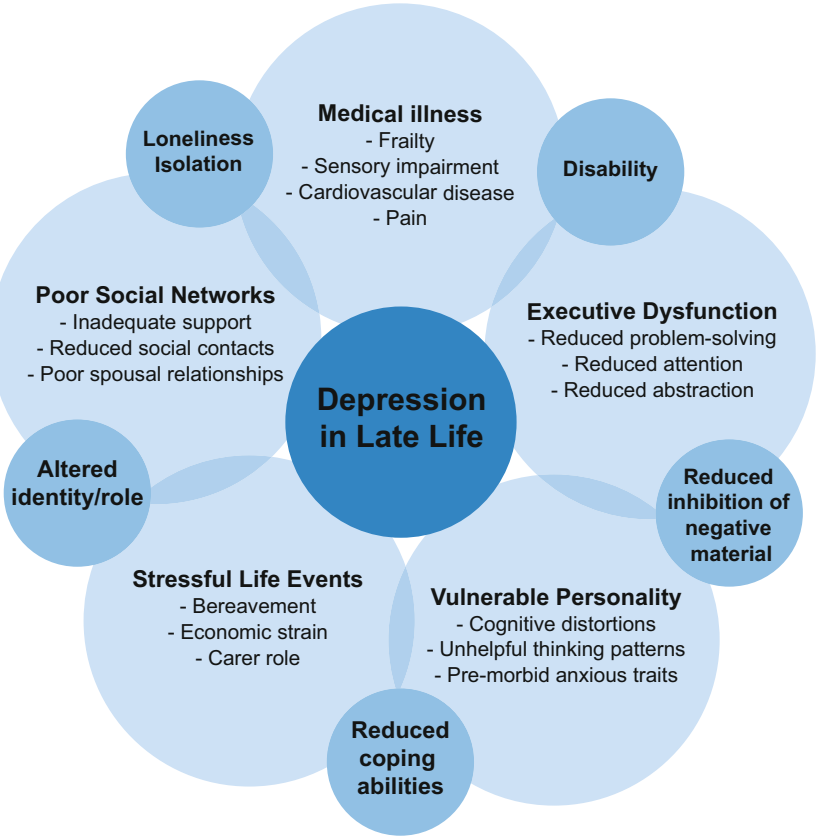

Fig. 3 Biopsychosocial model of depression in late life

pulmonary disease (COPD), osteoporosis, arthritis, type 2 diabetes, chronic pain, and obstructive sleep apnea (OSA) are frequently comorbid with depression. The link between Parkinson's disease and depression is particularly notable with a 2008 systematic review finding major depression among 19% of Parkinson's patients and clinically significant depressive symptoms in another 35% (Reinjders et al. 2008). Depression and stroke are highly comorbid also with pooled data from a systematic review showing a prevalence of 21.7% for major depression in stroke patients (Robinson and Spalletta 2010), while depression was seen to increase stroke risk among a large sample of 85-year-olds in Sweden when followed for 3 years (Liebetrau et al. 2008).

The relationship between cardiovascular disease (CVD) and late life depression has been extensively explored and can serve as a paradigm for the bidirectional association between poor physical and mental health. Large, multicenter studies have conclusively shown that CVD increases the risk of depression over time, while those who are depressed are at higher risk of suffering cardiovascular events. Even after correction for other cardiovascular risk factors, major depression has been

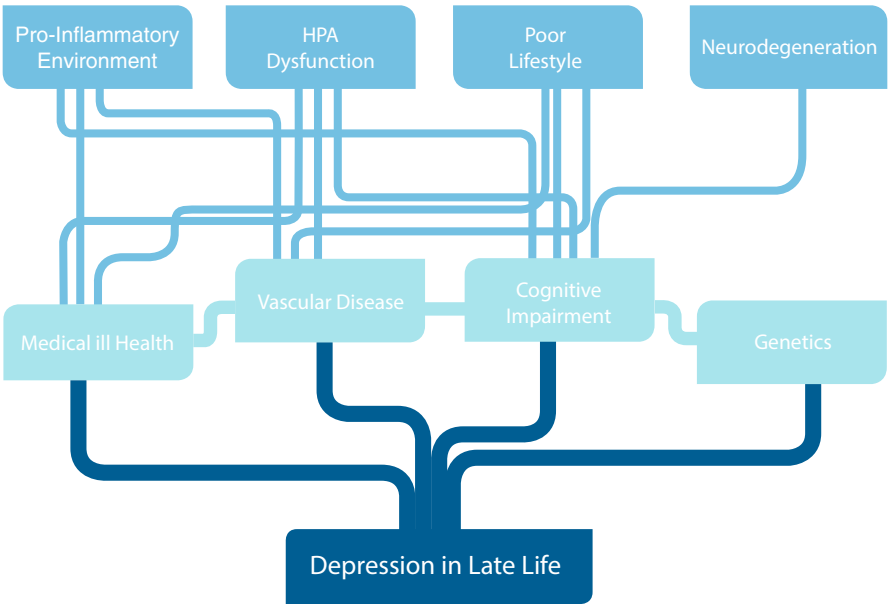

Fig. 4 The interplay of biological factors in the etiology of depression in late life

Table 1 Medical conditions associated with depression

Medical conditions	
Endocrine/metabolic	Hypo-/hyperthyroidism
	Type 2 diabetes
	Pernicious anemia
	Hypercalcemia
	Cushing's disease
	Addison's disease
Malignancy	Pancreas
	Lung
	Breast
	Bowel
Infections	Hepatitis
	HIV
	Mononucleosis
	Brucellosis
Hematological disease	Anemia
	Lymphoma
	Leukemia
Organic brain disease	Cerebrovascular disease/stroke
	Parkinson's disease
	Alzheimer's and vascular dementia

shown to confer an 80% increased risk of CVD on older adults, and outcomes for each disease are worse when comorbid (Choi et al. 2014; Gallagher et al. 2012). A meta-analysis of over 10,000 postinfarction patients (mean age 61 years) which adjusted for cardiac disease severity showed that depression was associated with a 22% increased risk of all-cause mortality (including cardiac mortality) and 13% increased risk for cardiovascular events (Meijer et al. 2013).

An underlying genetic vulnerability common to both conditions would be plausible to explain the degree of reciprocity between depression and cardiovascular disease. Physiological factors such as increased platelet reactivity, reduced heart rate variability, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated inflammatory markers, and activated cytokine and chemokine cascades are common to both, implicating a pro-inflammatory physiological environment as common to their etiology. Psychological stress and poor lifestyle habits contribute to hypertension, vascular damage, and a weakened immune system, and depression is associated with poor maintenance of cardiovascular risk factors at a population level (Choi et al. 2014).

The physiological mechanisms underlying the relationship between depression and medical illness are, therefore, manifold. It is essential, however, to be cognizant, also, of the psychological and social effects that physical illness and disability can have on mental health, particularly in the elderly. These factors will be discussed in further depth at a later point but should be borne in mind when considering the research literature on late life depression and medical illness. The highest rates of depressive symptoms in older people are to be found among those receiving high-level home support, hospital, or institutional care. This could be interpreted purely as a function of the medical burden seen invariably in this cohort of patients. However, it is important to be aware of the wider meaning and impact of the particular illness on the individual patient and to appropriately contextualize the contribution of biology when considering the etiology of depression.

Vascular Risk

The strong association between vascular risk factors, white matter lesions (WMLs), and depression led to the development of the vascular depression hypothesis which proposes that cerebrovascular disease can predispose, precipitate, or perpetuate a distinct clinical phenotype of depression in late life (Alexopoulos et al. 1997). It is thought that damage to the vasculature supplying cortico-striato-pallido-thalamic pathways disrupts the neural circuitry responsible for the regulation of mood. Fronto-striatal dysfunction may impair executive cognitive processes also, and the common co-occurrence of depressive symptoms and executive dysfunction in older adults, particularly those experiencing depression for the first time in later life, gave rise to the so-called depression-executive dysfunction syndrome. Neuroimaging findings bolster these propositions by demonstrating that white matter change is associated with incident depression in later life, higher scores on depression scales, and lower remission rates with treatment (Firbank et al. 2012; Gunning-Dixon et al. 2010). Opinions diverge on whether WML location or volume is of greater clinical import in the pathogenesis of these syndromes.

The vascular depression hypothesis implies a unidirectional relationship between vascular risk factors and depression, but this is likely an overly simplistic view. For example, WMLs are seen in an array of nonvascular conditions such as multiple sclerosis and hydrocephalus. In addition, not everyone with significant white matter disease burden is depressed. There must, therefore, be other factors mediating the relationship between cerebrovascular disease and depression.

The threshold hypothesis provides a useful model to conceptualize this. It proposes that after crossing an initial vulnerability threshold, vascular or other processes, e.g., inflammatory or endocrine, may serve as one of the multitude of factors that increase susceptibility to depression through disruption of affective and cognitive neural circuits (Taylor et al. 2013).

Cognitive Impairment

The dementia prodrome hypothesis is based on the findings of longitudinal studies that demonstrate an increased risk of progression to cognitive impairment among those with late-onset depression (Baldwin et al. 2006). It is thought in these cases that the emergence of depressive symptoms may be the first manifestation of the neurodegenerative processes responsible for the later effects on cognition. Consistent with this is the finding that depression in earlier or midlife does not seem to confer the same level of risk, though it is additive for a person who suffers both early and late life episodes (Barnes et al. 2012). Progression to both Alzheimer's dementia and vascular dementia is increased when compared to the nondepressed population, and the severity of depressive symptoms is linked to a greater risk of cognitive decline. Emerging data suggests that the risk of later dementia may be predicted by the particular course that depressive symptoms take over time. A recent study that followed over 3,000 depressed but dementia-free patients aged over 55 for 11 years monitored the trajectories of depressive symptoms and assessed for incident Alzheimer's dementia. Those whose depressive symptoms followed a course of persistently increasing severity over time had a significantly higher risk of transitioning to dementia compared with those whose symptoms followed a trajectory of lower severity as measured on the Center for Epidemiologic Studies Depression Scale (CES-D) (Mirza et al. 2016).

Given the link between depression and Alzheimer's disease, amyloid plaque deposition is coming under increasing scrutiny as potentially contributory to the etiology of certain types of depression. A postmortem examination of the brains of patients with cognitive impairment and major depression showed that Alzheimer's pathology predominated (Sweet et al. 2004). Another study using amyloid PET imaging to investigate amyloid deposition in patients with remitted major depression showed that half of the patients who met the criteria for MCI had amyloid patterns in the range of Alzheimer's patients (Butters et al. 2008). These are small studies, however, which are still a long way from establishing a causal link.

Cerebrovascular, neuroendocrine, and inflammatory processes are also implicated in the link between depression in late life and later dementia. For example, the hippocampus, which is integral to both mood regulation and memory

functioning, has been identified as an area which is particularly vulnerable to the effects of elevated circulating glucocorticoids and ischemia.

These factors – poor vascular health, amyloid deposition, and a chronic pro-inflammatory environment – are not mutually exclusive, and a threshold model can be useful in this context, also, to conceptualize the accumulation of various neuropathological insults which may account for the link between late life depression and dementia.

Genetics

A family history of depression is significantly less likely in late-onset depression than in depression of earlier onset (Gallagher et al. 2010). Studies are inconsistent as to the contribution of genetics to the overall variance of depression, but the interplay of genes with the environment and protective factors in later life is an active area of research nonetheless.

Brain-derived neurotrophic factor (BDNF) plays a key role in synaptic regulation and plasticity and is coded for by the BDNF gene on chromosome 11. The met66 allele of the BDNF gene may be associated with an increased risk of late life depression, a higher burden of WMLs, and, interestingly, higher rates of remission with treatment. Animal models suggest that BDNF expression is associated with stress and higher remission rates are hypothesized to be due, in part, to the effects of antidepressants on a dysregulated HPA axis (Dwivedi 2013).

The serotonin transporter is an important site of action for many antidepressants, and polymorphisms in the promoter region of the serotonin transporter gene (5HTTLPR) are thought to be relevant to both the pathogenesis and treatment of late life depression. There is evidence to suggest that carriers of the S/S genotype who have experienced childhood trauma bear an increased vulnerability to depression in adulthood – and by extension into later life. The HPA axis is once again implicated in this gene-stress association. The S/S genotype is also thought to confer lower treatment response rates with the L/L allele linked to better treatment outcomes (Naismith et al. 2012).

The role of the APO E gene – and the E4 allele in particular – is well established in the pathogenesis of Alzheimer's disease and is now coming to attention as potentially important in late life depression. A recent study of a sample of 800 patients aged over 70 without either depression or dementia at study entry showed that the APO E4 allele was associated with incident depression when the sample was followed for 5 years. The association remained even after those who became depressed and later developed dementia were removed from the analysis (Skoog et al. 2015). Studies looking at whether the E4 allele is associated with early- versus late-onset depression have produced inconsistent results.

Psychological Factors

By and large, the psychological factors which are implicated in the development of depression in later life are similar to those relevant to earlier onset illness. A person's personality traits and cognitive characteristics are central to their response to adversity,

be that in a protective capacity or a more maladaptive pattern. The stress-vulnerability model proposes that depression arises when environmental stressors and a negative or highly stressful experience impact on a vulnerable personality (Goldberg and Huxley 1992). The nature of these triggering events may differ in late-onset depression from those commonly associated with depression in earlier life. Physical ill health, loneliness, and bereavement are in general more pertinent in late-onset depression.

Personality Factors

Neuroticism confers a well-established vulnerability to depressive symptoms and major depression. Longitudinal studies have shown that neuroticism predicts the recurrence of depression in later life and the severity of symptoms (Steunenberg et al. 2010; Koorevaar et al. 2013).

Cluster C personality disorders seem to predominate among the older depressed with avoidant and dependent personalities particularly prevalent and associated with a poorer treatment response.

There is also a strong association between low scores on measures of personal mastery and risk of depression. Low mastery is associated with negative affect, anxiety, and depression with higher mastery protective against negative life events. The risk of recurrence of depression in patients aged over 55 years at study outset was increased threefold among those who scored poorly on measures of mastery when followed for 6 years (Steunenberg et al. 2010).

Cognitive Style

The cognitive model of depression proposes that cognitive distortions may be a cause of depression. Catastrophization and overgeneralization are more likely to be associated with depressive symptoms than more positive thinking processes such as positive reappraisal. Cognitive styles that lead to difficulties inhibiting the processing of negative material are associated with greater rumination among the depressed, and executive dysfunction, which is closely aligned with late life depression, may be a mediator in this relationship (Von Hippel et al. 2008). Depressed elderly patients have been shown to feel a greater negative impact of life events in the preceding year than dysthymic or euthymic controls (Devanand et al. 2002). However, depression itself can give rise to negative thinking patterns, and the direction of the relationship between cognitive style and depression remains an ongoing source of debate. Nonetheless, it is widely accepted that there is a cohort of people across all age groups, who are caught in a cycle of unhelpful cognitive processes, with an overemphasis on negative material, who are particularly vulnerable to the onset of a depressive episode.

Social Factors

Stressful Life Events

Each of the 36 participants in a 2011 study of the meaning of depressed mood to older adults attributed the onset of their depression to a precipitating life event

despite demonstrating an awareness of the importance of biological mechanisms to the etiology of a depressive episode (Gustavson 2011). This underlines the salience given to life stressors, on a personal level, in crafting an interpretation of one's experience of depression.

Debate exists around whether depression is more likely to arise in the context of the cumulative effect of a number of stressors or in response to a sudden, severe negative event such as a bereavement or relationship breakdown. It has been proposed that exposure to specific negative experiences earlier in life, for example, childhood abuse, increases the vulnerability to depression in later life due to changes in the biology of stress management which confer vulnerability to depression onset in response to a triggering event. "Allostatic load" has been proposed as a measure of dysregulation of multiple physiological systems including the HPA axis. It has been shown to increase in response to the buildup of stress across the life cycle and is associated with impaired physical and mental health and functional decline in older adults (Karlamangla et al. 2002).

The relationship between chronic strain and depression is clearly illustrated in studies of caregivers which consistently show that they are particularly vulnerable to depression. An assessment of 100 informal carers of community-dwelling patients of a geriatric psychiatry service revealed a prevalence of depression of 21%. Higher scores were associated with more problem behaviors or functional disability in those they were caring for (Molyneux et al. 2008).

Socioeconomic adversity is an established source of chronic stress with longitudinal studies showing an inverse relationship between social gradient and the prevalence and persistence of depression (McCrory et al. 2013; Mojtabai and Olfson 2004).

Retirement brings about very significant life changes with effects on daily occupation, personal relationships, and identity. The literature on the impact of retirement on mental health is inconsistent, reflecting the complexities associated with such a significant transition. It is likely that certain additional factors will increase the risk of depression postretirement as seen in a group of older Irish adults where involuntary or forced retirement or retirement due to ill health was associated with a negative and statistically significant effect on mental health (Mosca and Barrett 2016).

Bereavement is one of the life events that are experienced with increased frequency in later years. It is argued that the elderly may be more prepared for significant loss than younger adults for whom bereavement may be more unexpected and difficult to accept. Nonetheless, for many older people, grief represents a significant challenge to their psychological resources and coping abilities. A large meta-analysis of people aged over 50 showed that bereavement had the greatest effect size of all the factors studied, more than tripling the risk for the onset of depression (Cole and Dendukuri 2003). Death of a spouse or partner is particularly linked to depression with loneliness appearing to underlie the excess risk (Golden et al. 2009).

Social Support

Social network size and composition, frequency of social contacts, and instrumental/emotional support were some of the parameters found to be associated with

depression in a study of community-dwelling elderly in Hong Kong. Satisfaction with social support was found to be the most important predictor of depression severity with both inadequate and excessive support linked to late life depression (Chi and Chou 2001; Nolen-Hoeksema and Ahrens 2002). This may reflect varying personal attitudes on concepts such as personal independence, social role, and identity as well as differences in individual psychological makeup. Unsurprisingly, spousal relationships play a key role in moderating psychological well-being with poor quality of partner interactions associated with depression, anxiety, and suicidal ideation in older adults (Ivan Santini et al. 2015).

The role of loneliness in the etiology of late life depression cannot be underestimated, though it is often overlooked. Social loneliness and emotional loneliness are thought to represent two distinct manifestations of the experience of loneliness with emotional loneliness, which occurs due to the loss of an intimate bond, being perhaps more important in older populations whose close relationships are thinning out due to aging and death (Luanaigh and Lawlor 2008). Thirty-five percent of older adults were identified as lonely in a 2009 community-based study, with highest rates among women, the widowed, and the physically disabled. There was a clear relationship to depression with a population attributable risk of 61% (Golden et al. 2009). Loneliness is associated with more severe depression, lower remission rates, and an increased risk of suicide in the elderly (Holvast et al. 2015; Waern et al. 2003).

Presentation

Depression in late life is a heterogeneous condition that encompasses late-onset depression and early-onset, recurrent depression, and the presentation varies accordingly. See Table 2. Patients with late-onset depression present as less clearly affectively disturbed, more preoccupied somatically, and more agitated. Amotivation, anhedonia, and hopelessness are commonly endorsed. Cognitive impairment is more pronounced and less likely to resolve. Patients with late-onset depression tend to be physically frailer with a high burden of chronic and disabling illnesses. A past history or family history of depression is less likely in late-onset depression, possibly implying a stronger genetic influence in early-onset illness.

A lack of clarity in the literature on whether depression in late life is in fact a phenomenologically distinct condition may be explained, in part, by the fact that most studies do not specifically distinguish between late- and early-onset illness. Studies which categorize patients according to age of onset of the first depressive episode are, unfortunately, relatively few in number.

Studies also differ in their participant populations, age cutoffs, diagnostic tools, and methods of classification. Overlap of somatic symptoms common to both depression and age-related physical illnesses (pain, fatigue, sleep disturbance) may lead to under- or overdiagnosis of depression resulting in a phenomenological depiction of an "impure" cohort. Diagnostic accuracy may also be limited by sociocultural differences between generations which affect the perception and

Table 2 Characteristics of early-onset/recurrent depression and late-onset depression

	Early Onset/Recurrent Depression	Late Onset Depression
Biological Factors		
Past Psychiatric History	Common	Less common
Family History	Likely	Less likely
Medical History	Closer to population norms for age	Multiple co-morbidities
		Chronic, disabling conditions
		Physically frail
Neurocognitive Factors		
Neuropathology	Closer to population norms for age	Increased white matter lesions
		Cerebrovascular disease
		Possibly increased amyloid deposition
		Hippocampal atrophy
Cognitive Impairment	Relatively milder attentional and executive deficits	Marked attentional and executive deficits
		Slowed psychomotor processing speed
	Temporal association with depression onset	
	Insight into deficits may be present	Less insight
	More likely to resolve	May not fully resolve
		Association with later dementia
Presentation		
Symptom profile	Prominent affective symptoms	Affective symptoms may be less prominent

(*continued*)

Table 2 (continued)

	Early Onset/Recurrent Depression	Late Onset Depression
	Feelings of worthlessness and guilt may be relatively more prevalent	Agitation, sleep disturbance, anhedonia may be relatively more prevalent
	Less somatic preoccupation	Somatic preoccupation and somatic delusional themes common
	Anxiety highly co-morbid - work, finances, interpersonal relationships common themes	Anxiety highly co-morbid - family, physical health, disability common themes. May increase risk of cognitive decline.
	Clear precipitants may be less obvious	Poor health, grief, loneliness, changing role common precipitants
Suicide	Recurrent suicidal behaviour and para suicide seen more commonly	Suicidal behaviour less common
		High level of intent
		Methods of high lethality used
		More likely to succeed

expression of depression. Additionally, many studies fail to account for what are proposed to be age-specific subtypes of depression, such as vascular depression or non-dysphoric depression, which, as a result of organic changes of the aging brain, are thought to be neurobiologically distinct from early-onset depression.

The vascular depression phenotype is typified by significant psychomotor retardation with less agitation and guilt and poorer insight than depression without vascular risk factors. MRI-defined vascular depression groups are older at age of the first onset, endorse more apathy and anhedonia, and are less likely to have a family history of depression (Krishnan et al. 2004). Executive cognitive impairment is prominent ("depression-executive dysfunction syndrome") with impaired

planning, organization, sequencing, problem-solving, and set-shifting as well as reduced speed of information processing. Contrary to the long-held assumption that cognitive deficits resolve as depressive symptoms remit, studies are demonstrating that some degree of cognitive dysfunction tends to persist even after successful treatment of the mood symptoms.

It has long been recognized that elderly people may minimize feelings of sadness – possibly a reflection of a generation raised in an era when emotional or mental difficulties were not openly discussed and were viewed as evidence of personal weakness. Non-dysphoric depression characterizes those elderly patients who deny sadness but endorse hopelessness, anhedonia, and a lack of interest in personal care. Though lacking a core diagnostic feature of operationalized depression (sadness), the syndrome was associated with increased psychological distress, disability, and mortality in a 13-year interval follow-up study (Gallo et al. 1997). A 2010 study of 787 elderly primary care patients demonstrated that those with vegetative symptoms of depression without mood disturbance showed poorer cognitive and functional performance, highlighting a need for vigilance for depression in the absence of clear-cut mood changes (Paradiso et al. 2010).

The link between late life depression and dementia was explored previously. However, the nature of a dementing illness can make the diagnosis of a superimposed or comorbid depression quite challenging due to the overlap of certain symptoms (apathy, sleep disturbance) and impaired recognition and expression of an emotionally disturbed state. Olin et al. have proposed criteria to assist in the diagnosis of depression of Alzheimer's disease. Three or more features of major depression are required, excluding poor concentration, but including more non-somatic symptoms such as irritability and withdrawal (Olin et al. 2002). Depression in the context of dementia can present as increased behavioral disturbance, wandering, and an impairment of ADLs out of keeping with the degree of cognitive impairment.

Because these less "typical" presentations do not necessarily cleave strictly to the core DSM and ICD criteria for a depressive disorder, it is likely that they are under-recognized and undertreated. They may be dismissed as an "understandable" and therefore "normal" reaction to age-related life events. Overlooking a depression, however, will exclude people from access to treatment, leading to prolonged suffering both for patients and their families and increasing the risk of other adverse outcomes such as functional decline, deterioration in physical and cognitive health, and suicide.

Anxiety

Anxiety is highly comorbid with depression and contributes substantially to levels of distress and functional disability. A large study ($n = 14{,}200$) assessing older adults in seven European countries demonstrated that clinically significant anxiety symptoms were present in 87% of those with case-level depression and 67% of those with

subthreshold depression. Anxiety symptoms were associated with increased severity of depressive symptoms and higher functional disability (Braam et al. 2014). In a sample of community-living elderly, comorbid anxiety was found at case level in 17.3% of those who were depressed with sub-case level anxiety found in a further 59.9% (Kirby et al. 1997). While anxiety is highly comorbid in both early- and late-onset depression, the themes are thought to differ (see Table 2). Late life depression is more persistent and difficult to treat when combined with anxiety. Somatic symptom expression is more frequent, and there is a significantly higher risk of suicide. Organic depression, in particular, is thought to be associated with more anxiety, and anxiety may also increase the risk of cognitive decline among older adults with treated depression.

Pseudodementia

The term "pseudodementia" refers to a clinical picture characterized by a reversible dementia syndrome arising due to depression. Organic causes such as vitamin B12 deficiency and hypothyroidism must be ruled out prior to this diagnosis being made. In general, patients are said to be aware of and distressed by their memory impairment and can often date the onset of their problems in contrast to the more insidious onset of a neurodegenerative dementia. Assessment of cognitive function often leads to frequent "I don't know" answers which also differs from those with dementia who try their best but are simply unable to answer accurately. A history which clearly identifies the onset of a mood disturbance as preceding the cognitive symptoms can point toward the diagnosis. In certain respects, however, the term "pseudodementia" is now seen to be slightly outmoded, as we now know that cognitive deficits in the context of depression may not, in fact, be fully reversible and may presage the later onset of a true dementia syndrome. It serves well, however, to identify people who bear monitoring for cognitive decline over time once the initial depression has been treated.

Suicidality

Suicide among older adults is more likely to be associated with depression than suicide at any other age. Suicidal behavior and repeated acts of self-harm are uncommon among older adults, who are also less likely than younger age groups to verbally express suicidal ideation. They are, however, the age cohort most likely to use an immediately lethal means of self-harm and the most likely to complete suicide. More than any other age group, therefore, a suicide attempt in an older adult needs to be recognized as a grave event signaling a severe depression requiring immediate and aggressive treatment. Elderly people attempting suicide are more likely to be widowed, live alone, have a poorer perception of their health status, experience poor sleep quality, lack a confidant, and experience stressful life events

(Conwell et al. 2002). Neurotic personality styles and executive dysfunction are also associated with suicide in later life. Comorbid anxiety increases the risk of suicide in older adults as do comorbid alcohol or substance misuse, each of which is an important therapeutic target when identifying and treating elderly suicidal patients.

Management

A detailed history and collateral information are key to identifying elderly people who may be at risk for or are struggling with depression. Successful management requires a holistic approach. While pharmacotherapy can play a vital role in moderate to severe cases of depression, it must be used with caution in this group who are particularly vulnerable to adverse side effects and the risks of polypharmacy. Physical health, social disconnection, and functional/occupational decline are vital therapeutic targets which demand multimodal treatment plans tailored to the individual needs and abilities of the patient.

Pharmacotherapy

Placebo-controlled studies and meta-analyses support the efficacy of antidepressants in late life depression. However, the benefits are modest with high placebo response rates and smaller treatment effects relative to placebo in patients over 65 compared to younger populations (Cleare et al. 2015). The rate of an adequate response to first-line medication is approximately 50% in the elderly. Medications appear to have greater value in the treatment of moderate to severe cases, and older patients may require longer treatment trials than considered sufficient in younger groups. It is vital to be cognizant also of the potential for reduced tolerability of medications in older people due to age-related physiological changes that affect pharmacokinetics and pharmacodynamics. With that in mind, guidelines are consistent in their advice to initiate treatment at lower doses than used in younger patient groups and to be aware of comorbid medical conditions and co-prescribed medications that may affect drug efficacy and metabolism (NICE 2009; APA 2010).

Treatment Strategies

Accurately elucidating presenting symptoms, previous treatments, medical comorbidities, and patient preference in a comprehensive history should guide decisions around pharmacotherapy. Monotherapy with a safe and effective agent is the ideal, but in cases where the clinical response is suboptimal or absent, consensus opinion suggests a number of possible strategies. See Table 3.

Antidepressant Classes

Table 4 summarizes the effects of the various antidepressant classes in the elderly. Selective serotonin reuptake inhibitors (SSRIs) are generally considered to be the first-line agents in the treatment of moderate to severe late life depression. They are

Table 3 Pharmacologic strategies in suboptimal response or treatment failure

Strategy	Example
Optimization	Dose increase
	Longer treatment course
Substitution	SSRI to another SSRI
	SSRI to a different antidepressant class
Augmentation	Lithium
	Atypical antipsychotic (data for mid-age groups only)
Combination	SSRI and mirtazapine
	Mirtazapine + venlafaxine

Table 4 Medication classes and effects in the elderly

	Advantages in elderly	Disadvantages in elderly
SSRIs	Effective	Hyponatremia
	Clinician confidence	Falls
	Better tolerated than SNRIs or TCAs	GI bleeding
		Serotonin syndrome
	Sertraline safe in cardiac disease (mixed-age data only)	Prolongation of QTc with citalopram and escitalopram
SNRIs	Efficacy comparable to SSRIs	Falls
		Postural hypotension
		Hyponatremia
TCAs	Efficacy comparable to SSRIs	Anticholinergic effects
		Postural hypotension
	Can be helpful in sleep disturbance	Sedation
	Useful in comorbid neuropathic pain	Weight gain
	Side effect profile varies within class	Cardiotoxicity
Mirtazapine	Anxiolytic effects	Sedation
	Helpful in sleep disturbance and anorexia	Falls
		Weight gain
	May be useful in hyponatremia	
Bupropion	Limited evidence supports efficacy	Possibly improves energy and motivation
Lithium	Effective as augmentation strategy	Renal impairment over time
	Reduces suicide risk	
	Possibly neuroprotective	Optimal plasma ranges less clear
		Increased vulnerability to neurotoxicity
Antipsychotics	Effective as adjunctive treatment (data in mixed-age samples only)	Metabolic side effects
		Increased cerebrovascular risk and mortality in dementia
	Useful in sleep disturbance	
	Anxiolytic effects	Movement disorders
	Effects seen within days	Akathisia

effective, with a 2008 meta-analysis of randomized, placebo-controlled trials in older people demonstrating a higher likelihood of response for SSRIs when compared to placebo (OR = 1.36, 95% CI 1.19–1.56). Response rates were significantly higher in trials of longer duration (10–12 weeks vs. 6–8 weeks). Discontinuation rates and adverse effects were also higher in the treatment groups with pooled mean adverse event dropout rates of 12% for those in the treatment arms compared to 7% of those receiving placebo (Nelson et al. 2008). A 2014 literature review quotes response rates of 30–60% for SSRIs versus 20–40% for placebo with remission rates of 32–44% for SSRIs compared to 19–26% for placebo (Taylor 2014). Although studies comparing SSRIs and tricyclic antidepressants (TCAs) demonstrate largely equivalent efficacy, SSRIs are associated with a lower risk of adverse effects and are therefore considered preferable as first-line agents.

Common adverse effects associated with SSRIs include headache, sleep disturbance, sexual dysfunction, and gastrointestinal (GI) upset. These are usually mild and resolve within 14 days of treatment or dose increase. More serious adverse effects that are particularly associated with older populations include serotonin syndrome, hyponatremia, falls, and GI bleeding. Diuretics, aspirin, and NSAIDS, commonly prescribed for older people, increase vulnerability to these adverse effects. The period of highest risk for side effects is within the first 28 days of treatment. Citalopram and escitalopram have been implicated in prolongation of the QTc interval at higher doses, and limiting maximum treatment doses to 20 mg and 10 mg, respectively, is now advised in the elderly. Evidence from mixed-age samples supports the safety of sertraline in cardiac patients with depression though there is no data on this specifically in the elderly. SSRIs are considered relatively safe in overdose with the possible exception of citalopram and escitalopram due to QTc prolongation. SSRIs have the potential to cause significant drug-drug interactions via inhibition of the hepatic cytochrome-P450 isoforms.

Serotonin-noradrenaline reuptake inhibitors (SNRIs) are a common second choice when a patient fails to respond to an SSRI. There is no clear difference in efficacy between the two classes, but adverse events may be more common with SNRIs. In particular, postural hypotension, with its attendant risks of falls and cerebrovascular compromise, is a cause for concern in older populations, where physical frailty, autonomic fragility, and polypharmacy are commonplace.

TCAs are as efficacious as SSRIs and may be prescribed either as monotherapy or augmentation if SSRIs and SNRIs are ineffective. Anticholinergic effects, postural hypotension, sedation, and weight gain are particularly associated with the use of TCAs in the elderly though the side effect profile of the individual drugs within the class can vary considerably. They are considered dangerous in overdose due to cardiotoxicity but can be helpful in the management of sleep disturbance or comorbid neuropathic pain. Secondary amines, e.g., nortriptyline, are generally better tolerated with less anticholinergic effects and less sedation. Lofepramine, a tertiary amine, is considered to be less cardiotoxic and is preferred in cardiac disease where treatment with a TCA is unavoidable.

Mirtazapine and bupropion are considered reasonable alternatives. Data with respect to their use in the elderly specifically is limited but points to their being effective in the

relief of depressive symptoms (Hewett et al. 2010; Roose et al. 2003). Bupropion may also improve energy and motivation and reduce functional limitations. Mirtazapine has anxiolytic, appetite stimulant, and sedative properties that can be useful where anxiety, anorexia, or sleep disturbance are features, though falls, sedation, and weight gain are important considerations also. Cases of hyponatremia have been attributed to mirtazapine though the impact on sodium levels appears to be less than that of SSRIs, and, as such, mirtazapine may be a reasonable alternative in these situations.

Lithium augmentation of unipolar major depression in younger depressives is established as effective and well tolerated. Its use in older adults arises from this experience, but studies addressing its efficacy and safety in this age group are scarce. A review of extant studies in older people indicates that lithium augmentation of either SSRIs or TCAs improves response rates in older partial or nonresponders to monotherapy (Maust et al. 2013); however, there are no randomized controlled trials to definitively determine its efficacy. Lithium has additional advantages beyond its antidepressant properties: it reduces suicide risk and could be neuroprotective.

However, up to 50% of older adults on lithium may experience side effects, most commonly tremor, polyuria, dizziness, and renal impairment over time. Optimal plasma ranges are unclear as the correlation between serum level and CNS bioavailability is less reliable in older adults. A 2009 study demonstrated that in patients aged over 50 years, brain lithium levels were associated with impairments on tests of executive functioning, a relationship that was not seen in the younger participants. However, the association was not present for serum lithium levels and suggests that serum measurements, alone, may be insufficient to determine early signs of lithium neurotoxicity in older adults (Forester et al. 2009). Age-related deterioration in renal function, polypharmacy, and medical comorbidity render older adults particularly vulnerable to lithium toxicity.

Discontinuation of lithium augmentation is associated with a substantial risk of relapse. In a naturalistic study of older adults attending a lithium clinic, over 50% relapsed following discontinuation of lithium therapy with a mean time to relapse of 7.8 months. Those that were on lithium for longer and had had more hospitalizations were at significantly higher risk of relapse. In the majority of cases, remission following relapse was achieved upon reinstitution of lithium treatment (Fahy and Lawlor 2001).

Antipsychotics

The role of antipsychotics in the management of psychotic depression is well established with combined antidepressant and antipsychotic treatment more effective than the use of either agent alone. However, second-generation antipsychotics are increasingly being used in mixed-age samples as adjunctive therapy in the treatment of nonpsychotic depression. A therapeutic response is sometimes seen within days of initiation, thought perhaps to be due to their anxiolytic and sedative properties which can provide rapid relief from distress and help to regulate sleep patterns. A 2011 pooled subpopulation analysis that assessed the efficacy and safety of adjunctive aripiprazole in mid-age adults (aged 50–67) showed higher remission rates versus placebo (32.5% vs. 17.1%) though discontinuation rates due to adverse effects were

also higher in the treatment group (5.2% vs. 2%) with akathisia the most common adverse effect experienced (Steffens et al. 2011). There is no data on its efficacy in the elderly specifically. Optimum dosing remains to be determined, though it is felt that lower doses than typically used in primary psychotic illnesses are effective in this context. The long-term effects of antipsychotic augmentation are also unclear with justifiable concern about the metabolic side effects, in particular. Consensus opinion, therefore, advises withdrawal of the antipsychotic when possible after 4–6 months of treatment (Alexopoulos et al. 2001).

Duration of Treatment

The elderly are particularly vulnerable to the risks of relapse and recurrence. Balancing the possibility of relapse with the particular hazards of long-term pharmacotherapy in an older population becomes a question, therefore, of significant import. The 2001 Expert Consensus Guideline, compiled from the collated opinions of 50 experts in late life depression, recommends treating a first episode of major unipolar depression for at least 1 year. One to 3 years of treatment is advised in the case of two episodes. For those experiencing a third episode, treatment is likely to be necessary for longer than 3 years (Alexopoulos et al. 2001). As mentioned previously, gradually tapering antipsychotics after 4–6 months of dual antidepressant-antipsychotic treatment is advisable in the case of psychotic depression or adjunctive treatment.

Electroconvulsive Therapy (ECT)

ECT is the most effective option in the management of acute depression, and it is the treatment of choice for psychotic depression. It can be of particular utility in the management of late life depression where physical frailty, sensitivity to side effects, or the organic changes of the aging brain may limit aggressive treatment with antidepressants or the achievement of a complete therapeutic response. Additionally, as discussed previously, suicidal ideation in old age indicates immediate and particular risk, and in this context the rapid therapeutic response induced by ECT can be particularly welcome.

ECT has been shown to be more effective than antidepressants in the elderly with remission rates of 50–85% quoted in a 2013 review of the literature. Remission rates are even higher in psychotic depression, approaching 90%. There is evidence to suggest that older people may respond better to ECT than their younger counterparts, though this is inconsistent (Ramos-Garcia and González-Salazar 2013).

ECT is safe and well tolerated in the elderly. Mortality rates for ECT across all age groups are very low (1:80,000), and safety appears to be independent of age. Respiratory and cardiovascular disease and issues to do with anesthesia appear to confer increased risk, underscoring the need to carefully assess patients for suitability, regardless of age.

The cognitive effects of ECT, however, are of particular relevance to the elderly where impairment of cognition may be comorbid with, compounded by, or directly attributable to the depressive episode. However, the relationship between mood,

cognition, and ECT in late life depression has yet to be fully teased apart by the literature. From mixed-age studies, we know that anterograde amnesia for the period immediately preceding treatment generally resolves within days. Retrograde amnesia for personal or autobiographical events has also been described, though proponents of ECT would argue that studies investigating this phenomenon fail to control for the normal loss of autobiographical memory with time as well as persisting depressive symptoms. Controversy exists as to whether the elderly are particularly vulnerable to these effects though it does appear that they are more susceptible to a prolonged postictal confusion. By contrast, the cognitive impairment associated with the so-called depressive pseudodementia syndrome is likely to improve with successful treatment with ECT. This is supported by studies that show that within 2 weeks of ECT, certain cognitive domains such as processing speed, working memory, and some aspects of executive functioning will improve beyond the pre-ECT baseline (Semkovska and McLoughlin 2010). However, where there is a concern about a preexisting, organic cognitive impairment or a prior history of an adverse cognitive outcome with ECT, variations in ECT technique can attenuate the incidence and severity of cognitive side effects. Increasing the time between treatment sessions or using unilateral rather than bilateral electrode placement has been shown to reduce the risk of cognitive side effects, though treatment response may be less rapid. An important recent study addressed this issue by establishing that high-dose unilateral ECT (6 × seizure threshold) was non-inferior to moderate-dose bitemporal ECT (1.5 × seizure threshold) in terms of response and remission or 6-month relapse status with less adverse cognitive side effects noted with the high-dose unilateral treatment (Semkovska et al. 2016).

Although ECT is extremely effective in the acute treatment of depression, relapse rates approach 80% within 6 months without continued active treatment. Individual patient factors will determine the preferred mode of continued therapy. At a minimum, patients will require antidepressant therapy. However, for those who cannot tolerate medication or who fail to maintain remission on antidepressants alone, maintenance ECT is a valid option. 2012 and 2013 reviews suggest that relapse and readmission rates are substantially lower for older patients receiving maintenance ECT versus antidepressants without evidence of serious or persistent adverse effects even when patients with comorbid cardiac or neurological conditions are treated (Ramos-Garcia and González-Salazar 2013; Van Schaik et al. 2012).

Psychological Interventions

A range of psychological treatments have been empirically determined to be effective in the treatment of late life depression. Common to many of these therapies is a behavioral component that addresses the problems of activity limitation, amotivation, or social disengagement – issues of particular relevance in depressed older people. Additionally, many of these treatments are “manualized” and

educational, rather than reflective, an approach which may be of more utility among certain groups of older people who, for sociocultural reasons, may find the exploration of emotional and psychological issues to be particularly challenging. Psychological interventions may be the first-line treatment in cases of mild to moderate depression. Patient factors such as the ability to commit to weekly therapy sessions and engage in a therapeutic relationship as well as the local availability of services will determine whether a psychological approach is likely to be feasible and of benefit.

Cognitive behavioral therapy (CBT) is based on the premise that reframing dysfunctional and unhelpful thoughts will lead to changes in behavior which increase social engagement and pleasure. It is effective in older people during acute depressive episodes and has benefits in the prevention of relapse, also. Best outcomes, however, are seen when CBT is combined with antidepressant treatment.

Interpersonal therapy (IPT) is another manualized treatment that targets four components that are proposed to precipitate and maintain depression: grief, role transitions, interpersonal deficits, and interpersonal disputes. The therapist guides an assessment of these areas and helps the patient to redirect the associated negative emotions in more positive ways. IPT has been specifically adapted for use in older people and has been shown to be effective, in combination with antidepressant treatment, in the treatment of depression and prevention of relapse.

The benefits of CBT and IPT are less clear among patients with cognitive impairment, a group that are also less responsive to antidepressant therapy. By contrast, problem-solving therapy (PST) effectively treats depression in older patients with executive dysfunction by training them to develop skills to cope with stressful life problems. The structured and practical approach of this treatment modality seems to be particularly helpful in the context of executive impairment with a reduction in disability when compared to supportive therapy and continued benefits following the completion of treatment (Alexopoulos et al. 2011).

Psychodynamic psychotherapy, reminiscence therapy, and mindfulness-based cognitive therapy are among some of the many other psychological treatments which have potential in the management of depression in late life. As yet, there is a lack of definitive evidence as to their efficacy in late life depression. However, they are likely to be beneficial for groups of patients who have been carefully selected according to their individual needs and abilities. This is an area where further high-quality research is required to guide best practice and treatment decisions.

Though psychotherapy may be employed as monotherapy in mild to moderate depression, combined treatment using psychotherapy and antidepressants appears to be most effective to induce and preserve recovery in moderate to severe cases. Patient-specific factors, as well as personal preference and the availability of resources, will guide decisions around the optimum treatment strategy for a particular individual.

It is difficult to empirically quantify the importance of interventions which target physical health, social disengagement, environmental disadvantage, and sensory impairment in late life depression. It is likely, however, that these strategies are often of the greatest value for older depressed people. Loneliness, loss of role, physical disability,

and executive impairment are very amenable to practical interventions designed to improve how the individual interacts with the environment and other people. Central to this multidisciplinary care model is the imperative to enable the individual to continue to enjoy a life of personal meaning and fulfillment while growing older.

Hard-to-Treat Subgroups

White matter hyperintensities on MRI and cognitive impairment are associated with increased disability, poorer response to antidepressants, and higher risk of relapse and recurrence (Alexopoulos et al. 2002). Executive dysfunction can impact negatively on engagement and compliance. Longitudinal studies show that depression in Alzheimer's dementia will tend to remit over time, but depressive symptoms in the context of vascular dementia can prove refractory to treatment. Comorbid alcohol or substance misuse and personality disorders also presage poorer outcomes (Koorevaar et al. 2013). Comorbid anxiety predicts a more severe illness course and is an independent risk factor for suicide. Up to one third of patients will experience a depressive episode in the 5 years following a stroke. Damage to the neural pathways important for the regulation of mood and residual functional disability contribute to the difficulty of achieving remission in this group.

The specific challenges of these patient subgroups demand a flexible and multimodal treatment approach aimed at reducing disability, optimizing quality of life, and minimizing risk. Successful management often requires a longer-term treatment plan with an emphasis on psychological and behavioral interventions. For example, psychosocial therapies with an emphasis on reducing disability and social isolation are effective, in conjunction with pharmacotherapy, for both the treatment and prevention of poststroke depression. Interventions that provide psychoeducation and support to family members have also been shown to be of benefit to the patients themselves. Similarly, engaging carers of dementia patients in structured treatment programs which focus on their personal skills, communication, and coping abilities improves outcomes for the patients.

New Treatments

Ketamine, a NMDA receptor antagonist, with effects on the glutamatergic neurotransmitter system, has been the source of considerable interest as a potential novel antidepressant agent. Used at sub-anesthetic doses for analgesia in certain settings, it has been shown to induce a rapid antidepressant response. Data on its use in the elderly is limited. Case reports suggest that the dramatic improvements seen in younger groups may be replicated in older patients. It appears to be well tolerated, even among the physically frail and those who were unsuitable for ECT because of medical contraindications. Cardiovascular side effects appear to be transient and generally do not require medical attention (George et al. 2016; Horr et al. 2014). Maximal therapeutic effect is seen within hours to days but longer follow-up data is

lacking. The clinical utility of ketamine, however, remains questionable. Therapeutic response is transient, it is administered intravenously, and there are concerns about its potential as a substance of abuse. It remains of interest in research settings, however, as a means of learning more about the role of the glutamatergic system in depressive disorders.

The role of anti-glucocorticoid drugs (e.g., ketoconazole, dehydroepiandrosterone), vasoactive agents (e.g., nimodipine), and stimulants (e.g., methylphenidate) in the pharmacological management of depression is unclear. Data specific to their use in the elderly is minimal. Maust summarizes the very limited data available on the use of methylphenidate to accelerate response to antidepressants in older adults. While improvement of depressive symptoms was seen within 2 weeks in two trials, numbers were small, and a subsequent comparison to placebo led to high dropout rates in the treatment group because of intolerable side effects (Maust et al. 2013).

Repetitive transcranial magnetic stimulation (rTMS) is a newer treatment for depression that uses a rapidly changing magnetic field to induce electrical currents in the brain. The electromagnetic field is generated by a coil held over the scalp. The treatment does not require anesthesia and there are no apparent cognitive side effects. Sessions are held five times per week over 4–6 weeks. While rTMS has been shown to be effective compared to placebo in the treatment of depression, it is inferior to ECT, particularly in severe illness. This is mirrored in the literature for rTMS in late life depression. Response rates for rTMS vary between 20% and 50% for non-psychotic depression in the elderly, but it is not as effective in psychotic depression with ECT far superior in terms of outcomes. Cognitive functioning does not appear to be adversely affected in the elderly, however, and although there have been no studies specifically designed to examine safety in this group, it appears well tolerated (Galvez et al. 2015).

Transcranial direct-current stimulation (tDCS) and vagus nerve stimulation (VNS) are other brain stimulation techniques that aim to produce brain changes by means of electrical currents. There are a small number of individual case reports that indicate favorable results for tDCS in the elderly, but there are no RCTs to date looking at its efficacy in older age groups. Neither are there any studies looking at the efficacy of VNS in the geriatric population. NICE does not currently recommend any of these three techniques for clinical use.

Physical exercise is effective in reducing depressive symptoms among the elderly depressed (Sjösten and Kivelä 2006). It is cheap, has advantages for physical and cognitive health, and can be a means of social engagement and integration. Studies exploring the benefits of exercise in depression have been criticized for poor quality methodology. Patients who are sufficiently motivated to engage in a structured exercise program likely represent a highly selected cohort who is unrepresentative of the general older depressed population. Despite these methodological flaws, however, with its manifold advantages on physical and general well-being, physical exercise should be considered an important therapeutic intervention that may offer multiple treatment benefits for specific patient groups.

Prevention of Depression in Late Life

Successful treatment of depression in late life is difficult. Preventing the onset of illness in the first place is, naturally, preferable as a means of averting emotional suffering as well as illness-related morbidity and mortality. Primary prevention must take a biopsychosocial approach that encompasses the physical, cognitive, psychological, and social aspects of late life depression. Public education has the potential to reduce stigma, improve awareness, and increase understanding of depression, anxiety, and addiction. Community initiatives designed to promote and maintain older peoples' resilience to adversity may offset the more severe mental health consequences of bereavement, physical illness, and loss. Community social groups and outreach programs can reduce the risks associated with loneliness and isolation. However, these interventions should be implemented in midlife so that support networks are well established and adaptive coping mechanisms entrenched prior to the onset of older age.

Secondary prevention should focus on identifying and intervening in at-risk groups. Subsyndromal depressive symptoms are associated with a 40% risk of depression with a number needed to treat of 5.8 (Schoevers et al. 2006), supporting the treatment of subsyndromal states. Stroke patients who receive preventative antidepressant medication are less likely to become depressed than those who receive placebo (Whyte et al. 2006). Intervening in poor physical health, chronic pain, and sensory impairment further reduces incident depression. Carers of ill or disabled people are very vulnerable to depression, but programs that enhance their caring skills and coping strategies as well as support groups are effective in reducing their risk of becoming depressed. As at all stages across the life cycle, managing alcohol and substance dependency is a challenging but essential component of preventative mental health care.

Tertiary prevention strategies identify cases of late life depression and treat them at an early stage to reduce the risk of illness-related morbidity, chronicity, and mortality.

Course and Prognosis

The prognosis of late life depression is poor. Early-onset depression is associated with more depressive episodes across the life-span, but the comparatively better response to medications in this group lends to a more characteristic relapsing-remitting course. Late-onset depression is associated with a chronic course, longer duration of illness, high risk of relapse, increased mortality, and increased risk of later dementia. A longitudinal study of 127 depressed older patients living in the community showed that at 3 years, 30% had died, 35% had persistent or relapsed depression, 25% had another mental illness, and only 10% had maintained a complete recovery (Denihan et al. 2000). In this older, physically frailer group, medical comorbidity is a risk factor for poor medication response and tolerability.

Cognitive impairment predicts a poor prognosis, and the depression-executive dysfunction syndrome is associated with particularly poor outcomes: poor response to treatment, long-term persistence of symptoms, disability, and higher rates of relapse and recurrence (Sheline et al. 2010; Alexopoulos et al. 2002). Complete resolution of cognitive deficits is rare, particularly in late-onset depression. Comorbid neurological disorders, anxiety, substance misuse, and personality disorders also predict poorer outcomes.

Conclusion

Depression in late life is an etiologically heterogeneous condition that leads to significant suffering, functional disability, and social disruption. It is associated with increased morbidity and mortality and may be a harbinger of neurocognitive decline. It is common, though under-recognized. The physiological and biochemical effects of the aging brain as well as physical illness and age-related psychosocial changes distinguish late-onset depression from early-onset, recurrent depression. Late-onset depression may present quite differently with less affective disturbance and more somatic preoccupation and executive dysfunction. Depression in later life is amenable to treatment, but successful management requires a comprehensive, integrated, and biopsychosocial approach that links patients and families to medical services, community resources, and social supports. Our knowledge of the etiology, presentation, and management of late life depression has expanded exponentially in very recent decades. As the populations of developed nations continue to age, we can expect the demand due to depression on geriatric and psychogeriatric services to increase also. An evidence-based care pathway for depression that considers every point along the illness trajectory, from population-level prevention to individual intervention, is a necessity if we are to meet this demand and provide the best care for our patients and their families.

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