

## DEPRESSION IN LATER-LIFE: AN OVERVIEW OF ASSESSMENT AND MANAGEMENT

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### SUMMARY

The elderly are the fastest growing segment of the global population with the number of people age 60 or older having doubled since 1980 and the number of people age 80 or older expected to increase more than 4-fold (to 395 million) by the year 2050. While depression is overall less common in older people compared to younger people, there are sub-groups of elderly, such as those with significant medical comorbidity, who are at greatly elevated risk for depression. Negative consequences of late-life depression include functional decline and disability, increased use of non-mental health services, increased mortality rates due to cardiovascular causes, increased cancer rates, and substantially greater risk for suicide. Geriatric suicide is a global epidemic, which is worsened in many countries and cultures by socioeconomic disparities and cultural/social upheaval.

Geriatric depression should be carefully assessed and treated. Treatments for geriatric depression include biological modalities such as antidepressant medications and Electroconvulsive therapy (ECT) as well as psychotherapy and psychosocial interventions. When they are prescribed pharmacotherapies for depression, older adults are especially likely to experience adverse drug effects as a result of their multiple chronic diseases, use of multiple concomitant medications, and the pharmacokinetic and pharmacodynamic changes that accompany aging. Antidepressants that minimize side effects are generally preferred in elderly individuals although the expected therapeutic response to drug treatment is generally modest. Psychosocial and psychotherapeutic measures can also be effective in late-life depression. Complexities of assessment and treatment include the risk of missing a bipolar depressive diagnosis, which would contra-indicate the use of antidepressant monotherapy. Given the projected increased proportions and overall numbers of older people with mental disorders there is a need for all clinicians to be familiar with mental health issues in elderly patients.

**Key words:** depression - later life – antidepressants – ECT – psychotherapy - psychosocial interventions

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### INTRODUCTION

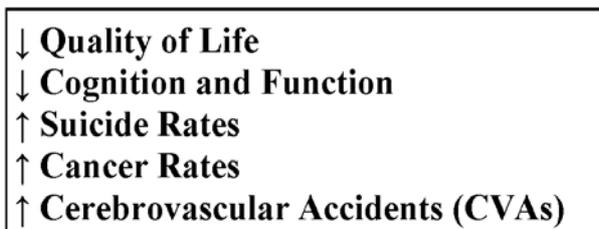
The elderly are the fastest growing segment of the global population with the number of people age 60 or older having doubled since 1980 and the number of people age 80 or older expected to increase more than 4-fold (to 395 million) by the year 2050. The numbers of older people with mental disorders such as depression are thus likely to increase both in absolute numbers and in relative proportion among the population. While depression is overall less common in older people compared to younger people, there are sub-groups of elderly, such as those with significant medical comorbidity, who are at greatly elevated risk for depression. This review on geriatric depression will address the epidemiology and consequences of late-life depression, the assessment and differential diagnosis of depressive symptoms in older people and aging-related changes relevant to medication treatment. The review will also address treatments for late-life depression including biologic methods such as medications and Electroconvulsive therapy (ECT) as well as psychotherapeutic/psychosocial management.

### EPIDEMIOLOGY AND CONSEQUENCE OF LATE-LIFE DEPRESSION

Major depression is not as common in late-life as in younger ages (Judd et al. 2002). Prevalence of late-life

depression varies among different studies and populations. A meta-analysis showed that the pooled prevalence of major depression is 7.2% and depressive disorder 17.1% in the population age 75 and above (Luppa et al. 2012). An American study (Steffens et al. 2009) revealed that prevalence of combined major and minor depression is 11.2% in the population age 71 and above; men and women have similar rates. Studies also found that sub-threshold depression, characterized by somatic complaints, dysthymia, and cognitive manifestations, was even more common in individuals 65 years old and above, potentially leading to an underestimation of depression rates in the elderly (Judd et al. 2002). Bipolar disorder can also cause depression in the elderly. However, prevalence of bipolar disorder in the elderly is 0.1%, much lower than that in younger populations.

Geriatric depression leads to severe consequences such as functional decline and increased disability, increased use of non-mental health services, increased risk of cancer, increased mortality rate related to cardio- and cerebro-vascular diseases, and suicide (Figure 1) (Beekman et al. 1997, Frasure-Smith et al. 1993, House et al. 2001, Penninx et al. 1999, Penninx et al. 1998). The elderly are particularly vulnerable to cognitive impairments when depressed, affecting all cognitive domains including visuospatial ability, episodic memory, executive functions, and language ability (Butters et al. 2004, Elderkin-Thompson et al. 2003, Kramer-Ginsberg et al. 1999). In a study involving 140 subjects,



**Figure 1.** Health risks associated with late-life depression

more than half of depressed elderly patients performed below the 10th percentile of control subjects (Butters et al. 2004). The impairments were mediated mostly by slowed information processing speed. In the U.S. Cardiovascular Health Cognition Study involving 2220 subjects who had high cognitive function at baseline, depression was associated with increased risk of later developing mild cognitive impairment (MCI), independent of underlying vascular disease (Barnes et al. 2006). In this same study (Barnes et al. 2006) 19.7% of those with moderate or high depressive symptoms developed MCI after 6 years of follow-up in comparison to 10.0% in those with no depression. In addition, a meta-analysis showed that a history of depression may confer risk for later developing Alzheimer's disease (odds ratio of 2.0 for case-control and of 1.9 for cohort studies) (Ownby et al. 2006). Another meta-analysis (Diniz et al. 2013) revealed that late-life depression is associated with a significant risk of all-cause dementia, Alzheimer's disease, and vascular dementia. It is thought that depression can be both a risk factor for and a prodromal symptom of dementia.

Specific pathways that might lead to brain pathology as it relates to dementia that follows depression are unclear. In a postmortem study (Sweet et al. 2004) that involved 10 subjects with late-onset major depression with 7 of them later developing dementia, Alzheimer's pathology was present in 6/10 subjects, Lewy body pathology in 5/10 subjects, and stroke in 4/10 subjects. Some patients had overlapping pathologies. Imaging technologies such as MRI scans have been utilized to study brain size in late-life depression. Interestingly, reduced volumes of brain structures such as hippocampus, basal ganglia especially caudate and putamen, and prefrontal cortex, as well as deficits in the white matter have been reported (Bell-McGinty et al. 2002, Bora et al. 2012, Butters et al. 2009, Sheline et al. 2003, Sheline et al. 1999, Wen et al. 2014). In addition, a lower hippocampal volume has been found to correlate with a longer duration of depression. A lower caudate volume also correlates with a higher severity of depression. The mechanism by which late-life depression leads to cognitive impairments is still not completely understood. It has been proposed that depression contributes to hippocampal atrophy via elevated glucocorticoid levels, and to cardio- and cerebro-vascular diseases via a poor general health (Butters et al. 2008).

Depression is the most frequent mental disorder preceding suicide. Older adults over 65 years of age have the highest suicide rate of any age group while those over 85 years of age have a suicide rate two times of national average. Over half of older adults who committed suicide had a visit with their physician in the prior month. It is to be remembered that physical illness is a frequent stressor in older adults, significantly contributing to suicide risk.

## ASSESSMENT AND DIFFERENTIAL DIAGNOSIS INCLUDING BIPOLAR DISORDER

Geriatric depression can be a complex entity often with multiple causes and complex symptom formation that can be quite misleading in the course of developing a diagnostic formulation. The geropsychiatric evaluation requires a methodical approach that examines the medical, neurocognitive and psychological presentation of the patient. The differential diagnosis involves primary psychiatric disorders, medical and neurological disorders. Primary psychiatric disorders need to be differentiated among three entities: mood, anxiety and primary psychotic disorders.

During the initial evaluation a neurocognitive exam should be conducted. Checking for clouding of sensorium, waxing or waning features and acute neurocognitive decline from a clinically established baseline can rule out delirium. Advanced dementia can be confused with delirium and requires careful evaluation of neurological, medical and mental status changes from baseline to differentiate. Cognitive and vegetative features of dementia often overlap with those of depression and also need to be differentiated. Neuropsychological impairments can be found in geriatric depression further complicating evaluation (Bhalla et al. 2006, Boone 1995, Butters et al. 2004, Elderkin-Thompson et al. 2003, Kramer-Ginsberg et al. 1999, Palmer et al. 1996, Sheline et al. 2006). Fortunately, cognitive impairments are to at least some extent more reversible in depression than they are in dementia.

Geriatric depression presents with a constellation of mood, somatic and cognitive symptoms that are characteristic of geriatric compared to adult depression. Mood features include weariness, hopelessness, anger, anxiety and thoughts of death. Somatic features include increased pain with overlapping somatic features, side effects of medications and comorbid disease. Cognitive features include loss of selective attention, working memory and retrieval, new learning, processing speed and diminished executive function (Devanand et al. 1994, Gallo et al. 1997, Geiselman et al. 2000, Lavretsky et al. 2002, Lezak 1994, Mazure et al. 2002).

Bipolar disorder can present with depressive features and can go undetected. Bipolar disorder diagnosis can be challenging since many of the classic features may not be evidenced or apparent from the history

or the current clinical presentation. Significant comorbid anxiety (Keller 2006) and chronic insomnia are important clues that should indicate the need for further diagnostic evaluation to determine whether the clinical historical and recent presentation may reflect a bipolar versus a unipolar depressive disorder.

Psychotic disorders including schizophrenia can also present with overlapping features with depression that complicate diagnosis. Depressive features can be a frequent finding in older persons with schizophrenia (Meesters et al. 2014). Negative symptoms of schizophrenia including withdrawal, loss of motivation, loss of energy and blunted affect can be confused or overlap with vegetative features of depression. A careful history and neuropsychiatric evaluation can help distinguish between primary psychotic vs. mood disorders.

Contributing factors are essential to assess in the diagnostic evaluation of late-life depression. Life stresses can influence the emergence of late-life health effects. Stressors can include medical illness, changes in social support structure or dependence, employment status including retirement, financial difficulties and significant losses on multiple levels.

Essential elements of the late-life depression evaluation include a complete physical examination, neurological examination, laboratory tests, electrocardiograph (EKG), head CT or magnetic resonance imaging (MRI). MRI structural studies support the notion that loss of brain volume and white matter integrity are associated with poorer treatment outcomes (Aizenstein et al. 2014). Functional MRI studies have indicated that lower task based activity in the prefrontal cortex and limbic areas have been associated with poorer outcomes (Aizenstein et al. 2014). Further diagnostic evaluation may include neuropsychological assessment, other imaging modalities, electroencephalogram (EEG) and driving assessment.

## **AGING RELATED CHANGES RELEVANT TO MEDICATION TREATMENT**

When considering pharmacological treatment of late-life depression, age-related pharmacokinetic and pharmacodynamics need to be appreciated (Berra et al. 2007, Wollmer et al. 2009). In the elderly, brain neurochemistry is modified by multiple factors that include stress, toxic factors, deficiencies in essential nutrients, neuroendocrine disturbances, autoimmune effects, genetic effects, trauma, vascular disorders and neurodegenerative disease. Further, in normal aging there are morphological changes occurring secondary to decreased brain volume and number of neurons, changes in glia and loss of both dendrites and synapses. In the aging brain there are white matter changes and the deposition of senile plaques and tangles.

Factors affecting the individual variation in clearance of drugs include age, gender, diet, illnesses

(Pollock 2005), environmental effects, smoking, alcohol consumption, other concomitant drug effects and heredity (Spina et al. 2002). Elimination half-life tends to be prolonged and steady state plasma concentrations tend to be increased in elderly patients. However, inter-individual differences account for the greatest part of the variance in the pharmacokinetic parameters compared to direct age effects.

Adverse drug reactions increase with age (Norman 1993, Spina et al. 2002). In the cardiovascular system there is decreased albumin with corresponding increased free drug percentage in plasma. There is decreased renal clearance due to decreased glomerular filtration rate. Lean muscle mass is decreased with increased adipose tissue resulting in increased volume of distribution (VOD) for fat soluble drugs and decreased VOD for water soluble drugs. Liver tissue and blood flow are diminished with age and CYP450 activity is also diminished resulting in decreased hepatic clearance. Additionally in the elderly there is increased sensitivity to side effects secondary to relatively high rates of medical burden and polypharmacy. Medication non-adherence secondary to cognitive limitations may make clinical assessment of therapeutic effects and determination of drug dosing challenging as well.

## **ANTIDEPRESSANT TREATMENT OF LATE-LIFE DEPRESSION**

Antidepressant agents form one of the modalities for treatment of late-life depression although only a minority of depressed patients (30-40%) are taking these medications. Some patients may respond better to combining pharmacotherapy with psychotherapy, ECT or other modalities. Choice of antidepressant in the geriatric population necessitates a complex consideration of the efficacy, potential benefit and indications balanced against the side effects and risks. Benefit, risk and alternatives should be discussed with the patient to the extent that they are competent to make or participate in this treatment decision. When a patient is impaired in making an appropriate decision it is important to attempt to involve the patient's most significant support system (family or others) to help make an informed decision about use of antidepressants.

Generally, newer antidepressants have fewer drug-to-drug interactions and improved safety. SSRI treatment in the elderly has increased while at the same time tricyclic antidepressant treatment has declined (Dolder et al. 2010, Nelson et al. 2008). Meta-analyses of antidepressant treatment studies indicate that antidepressants probably have at least modest superiority over placebo in the treatment of late-life depression. Interestingly, cognitive comorbid conditions of mild cognitive impairment or dementia do not appear to impact short-term pharmacotherapy response variability in patients whose depression responded to open trial antidepressant treatment when delivered in a very

supportive environment (Koenig et al. 2014). Placebo-controlled randomized trials found overall antidepressant response rates in late-life depression to be 35 - 69% compared 19 -47% with placebo. For every two patients who responded to treatment there was one patient who discontinued secondary to adverse effects (Nelson et al. 2008). In addition, patients who had greater than ten years of illness and greater depression severity overall had better response. Patients who had illness for greater than ten years and whose score on the Hamilton Depression Rating Scale (HAMD) was greater than 21 had the most robust response to treatment. Antidepressant versus placebo response was mild in other patients. Elderly patients with depression and dementia did experience improvement in behavioral symptoms (Nelson et al. 2013).

Tricyclic antidepressants have significant anticholinergic effects, hypotension, sedation and cardiac dysrhythmias. The anticholinergic effects will exacerbate hypocholinergic states found in delirium and dementia resulting in further cognitive compromise, confusion and increased behavioral disturbances. Desipramine has applications in adjunctive and neuropathic pain in addition to depression, dysthymia and anxiety. Nortriptyline has efficacy for depression but side effects pose a challenge for tolerability. When attempting to treat with a tricyclic antidepressant agent lower therapeutic levels are targeted dose ranges in the frail elderly.

The selective serotonin reuptake inhibitors (SSRIs) can benefit depression, dysthymia and anxiety. They are associated with gastrointestinal increased motility, nausea, vomiting and insomnia. Trazodone is associated with sedation as well as falls and hypotension. SSRI agents can be associated with hyponatremia.

Other antidepressant options include agents that affect combinations of neurotransmitter action and include bupropion, mirtazapine, venlafaxine, and duloxetine.

Bupropion acts primarily through norepinephrine and probably dopamine to create its antidepressant effect (Foley et al. 2006). Bupropion is associated with risk of irritability, insomnia and seizures especially in emaciated patients. It generally is not associated with sexual side effects and cardio-toxic effects are low.

Duloxetine, a norepinephrine serotonin agent (Bochsler et al. 2011), appears to have safety and efficacy in late-life depression comparable to that in adult depression (Del Casale et al. 2012). Duloxetine is effective in depression and pain as are other serotonin noradrenaline agents such as venlafaxine and milnacipran (Mika et al. 2013). Duloxetine may be associated with nausea and insomnia. Dosing precautions are needed in renal or hepatic compromise. Venlafaxine can be associated with hypertension at higher doses, insomnia and nausea. These agents can be associated with hyponatremia (SIADH) and osteoporosis.

Mirtazapine is a unique agent acting as a noradrenergic and specific serotonergic (NaSSA) antidepressant which may be preferred in certain geriatric patients over an SSRI (Holland et al. 2013). Mirtazapine is sedating and can be associated with hypotension. Mirtazapine also has anxiolytic effects (An et al. 2013).

In summary, selecting a particular antidepressant in late-life depression requires weighing effectiveness against potential drug interactions and sensitivity to adverse side effects.

## PSYCHOTHERAPIES FOR DEPRESSION

Given the limitations of antidepressants such as a moderate effect, drug-drug interactions, and increased vulnerability of older adults to side effects, psychotherapy can serve as a good alternative. Therapies for late-life depression include cognitive behavioral therapy (CBT), interpersonal therapy, brief psychodynamic therapy, problem-solving therapy and reminiscence therapy. According to two recent meta-analyses (Francis et al. 2013, Huang et al. 2014), these psychotherapies are effective although study interpretation must be tempered by methodological limitations. Supportive therapy has been proposed to best control for non-specific factors in therapy such as attention, education, reassurance, and monitoring symptoms (Huang et al. 2014). In 5 trials that used supportive therapy as a control, mean effect size was 0.39 (Huang et al. 2014). This is meaningful, considering the moderate effect size of antidepressants at 0.14 (Nelson et al. 2008). There is little evidence to show that one type of psychotherapy is better than another (Francis et al. 2013). Practically, a combination of an antidepressant and psychotherapy, though not well studied, is often utilized to treat late-life depression.

## BIPOLAR DEPRESSION TREATMENT

There are a variety of medications that are used to treat bipolar disorder including medications that have U.S. FDA approval. FDA-approved drugs for bipolar disorder can be broadly categorized as medications for the management of acute mania, for bipolar depression and for maintenance or long-term treatment of bipolar disorder (Ketter 2010). FDA-approved drugs include the classic mood stabilizers such as lithium and anticonvulsants such as divalproex as well as antipsychotic drugs such as olanzapine, quetiapine and lurasidone. The number of FDA-approved treatments for bipolar depression are extremely limited (olanzapine-fluoxetine combination, quetiapine and lurasidone). There are also no FDA-approved treatments specific to geriatric bipolar disorder and a paucity of published evidence to inform treatment approaches to older adults with bipolar disorder. As discussed in the discussion of unipolar depression, older adults with bipolar depression are

prone to medication adverse effects. For example, lithium, with a narrow therapeutic window, may be associated with weight gain, GI disturbances, cognitive slowing, neurotoxic effects with minor overdose, thyroid toxicity and diabetes insipidus (Baldessarini 2002). Titrating drug dosing and close monitoring of side effects is needed to optimize both drug tolerability and therapeutic response. Illustrating the need to closely monitor clinical status and not just serum lithium levels, a cross-sectional evaluation of 26 patients with bipolar disorder (10 over age 50) assessed levels of lithium in brain and serum using Magnetic Resonance Spectroscopy (MRS) (Forester et al. 2009). In this study, serum and brain levels correlated in the group as a whole, but not for older patients. In older pts higher brain lithium was associated with frontal lobe dysfunction and higher depression ratings (Forester et al. 2009). General recommendations for the treatment of older adults with bipolar depression include avoiding in most cases the use of antidepressant monotherapy, monitoring drug interactions and medical comorbidity as well as communicating with other providers who may not be aware of BD or may prescribe drugs that can destabilize BD such as duloxetine (Cymbalta) for pain.

## CONCLUSIONS

Given the projected increased proportions and overall numbers of older people with mental disorders there is a need for all clinicians to be familiar with mental health issues in elderly patients. Assessing and treating late-life depression is complicated mostly by medical comorbidity and reduced tolerance of standard medication treatments. There is a need for more research in this area given demographic trends globally and the need to most efficiently use healthcare resources.

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