

Depression is linked to dementia in older adults

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Dr Vyara Valkanova BSc (Hons) MD
Honorary Clinical Research Fellow and Specialist Trainee in Psychiatry,
Department of Psychiatry, University of Oxford,
and Oxford Health NHS Foundation Trust,
Warneford Hospital, Oxford, UK

Professor Klaus P. Ebmeier MA MD
Professor of Old Age Psychiatry and Honorary Consultant Psychiatrist,
Department of Psychiatry, University of Oxford,
and Oxford Health NHS Foundation Trust,
Warneford Hospital, Oxford, UK

Dr Charlotte L. Allan MD MRCPsych
Consultant Old Age Psychiatrist, Centre for the Health of the Elderly,
Northumberland,
Tyne and Wear NHS Foundation Trust,
Newcastle, UK

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AUTHORS

Dr Vyara Valkanova

BSc (Hons) MD
Honorary Clinical
Research Fellow and
Specialist Trainee in
Psychiatry, Department
of Psychiatry, University
of Oxford, and Oxford
Health NHS Foundation
Trust, Warneford
Hospital, Oxford, UK

Professor Klaus P. Ebmeier

MA MD
Professor of Old Age
Psychiatry and Honorary
Consultant Psychiatrist,
Department of
Psychiatry, University
of Oxford, and Oxford
Health NHS Foundation
Trust, Warneford
Hospital, Oxford, UK

Dr Charlotte L. Allan

MD MRCPsych
Consultant Old Age
Psychiatrist, Centre for
the Health of the Elderly,
Northumberland,
Tyne and Wear NHS
Foundation Trust,
Newcastle, UK



What are the common mechanisms?

Which depressed patients are most at risk of dementia?

Which patients should be referred?



DEPRESSION AND DEMENTIA ARE COMMON IN OLDER PEOPLE, AND FREQUENTLY OCCUR TOGETHER.

Large-scale community surveys in the United States using structured interviews based on DSM-IV-TR found that the 12-month point prevalence of major depressive disorder in community-living adults aged 65 and older is 3.0-4.3%.¹ Depression affects up to 20% of patients with Alzheimer's disease and up to 45% of patients with vascular dementia.²

The comorbidity of depression and dementia is more than that simply expected by chance, implying that they are related.³ Their interrelationship, however, is not well understood. Depression can be an independent risk factor, a prodromal symptom or a consequence of dementia.³

Current research suggests that timing

of depression may be important in defining the nature of the association. Depression with onset in early life (before the age of 60) has been linked to a two-fold increase in dementia risk.⁴ Recent meta-analyses, which included other types of dementia confirm these findings.^{5,6}

Rather than a risk factor, depression with onset in later life is more likely to be either prodromal to dementia⁷ or a condition that unmasks pre-existing cognitive impairment by compromising cognitive reserve and thus shortening the latent period between the development of dementia-related pathology and the onset of clinical symptoms.⁸

Brommelhof and colleagues reported that a depression diagnosis within ten years of dementia onset was associated with a four-fold increase in the likelihood of having dementia, while depression

onset occurring more than ten years prior to dementia onset was not, providing support for this hypothesis.⁹ Methodological limitations of the studies and the long preclinical phase of dementia make disentangling the temporal relationship challenging.¹

Depression can be seen as a psychological response to receiving a diagnosis of dementia. Studies that found high rates of anxiety and depression, particularly early in the course of dementia support this explanation.¹¹

COMMON NEUROBIOLOGICAL MECHANISMS

Multiple interacting neurobiological mechanisms are likely to underlie the relationship between depression and dementia.

Vascular disease has been linked to both depression and cognitive

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impairment.¹² The vascular depression hypothesis postulates that cerebrovascular disease may 'predispose, precipitate, or perpetuate' depression in late life.¹³ Vascular damage to frontostriatal brain regions is particularly relevant, as they are linked to both mood regulation and executive function.⁸ Vascular damage is the main pathophysiological mechanism in vascular dementia. However, it plays a role in other dementias, including Alzheimer's disease, and the prevalence of mixed pathologies is high.⁸

A large body of evidence suggests

'A large body of evidence suggests there are common molecular pathways between depression and cognitive impairment'

that there are common molecular pathways between depression and cognitive impairment. Chronic low-grade inflammation characterised by increased pro-inflammatory markers and activated microglia, HPA (hypothalamic-pituitary-adrenal) axis abnormalities resulting in elevated cortisol and deficits of circulating neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) have been demonstrated both in depression and Alzheimer's disease.¹⁴ They act via multiple mechanisms, including altering serotonin metabolism, reducing synaptic plasticity and hippocampal neurogenesis, interfering with beta-amyloid metabolism, and increasing vulnerability to toxins.^{14,15} Therefore, accelerated neurodegeneration, weakened neuroprotection and impaired neurogenesis are implicated in both depression and dementia.

DIAGNOSING DEPRESSION

NICE recommends that clinicians ask patients whether they have had depressed mood or loss of interest in

activities in the past month (see table 1, below) when they suspect that a patient may be depressed.

Following a positive response for either question a detailed assessment of the severity and duration of symptoms and functioning should follow, see table 1, below left. NICE recommends that clinicians consider using a validated instrument to inform and evaluate treatment.¹⁶

There are many tools available, including the Patient Health Questionnaire 9 (PHQ-9)¹⁷ and the Geriatric Depression Scale-15 (GDS-15).¹⁸ The GDS-15 may be better suited to older adults, as it is less focused on somatic symptoms. A recent systematic review found limited evidence of the effectiveness of assessing depression severity in adults using structured measures such as the PHQ-9.¹⁹ However, a meta-analysis of ten studies that used the GDS-15 concluded that the GDS-15 has added value in primary care.²⁰ Further research is needed to clarify this question.

In complex cases, a referral to mental health services can be considered, see table 2, below left.

'A major barrier to recognising depression is the attribution of symptoms to old age, physical illness and psychosocial stressors, such as bereavement or social isolation'

The diagnosis of depression in older adults can be challenging. There is greater variety in presentation; cognitive and somatic symptoms are usually predominant and cognitive or anxiety symptoms may mask the core feature of low mood.

A recent meta-analysis suggested that late life depression has a partly different phenomenology compared with early life depression.²¹ Compared with younger people, older adults with major depression show more agitation, somatic, general and gastrointestinal symptoms and hypochondriasis, but less guilt and loss of sexual interest.²¹

Medical conditions are common in

Table 1

Diagnosis of depression (from NICE CG90, based on the criteria in DSM-IV)¹⁶

Key symptoms	Associated symptoms
At least one of these, most days, most of the time for at least two weeks: ● Persistent sadness or low mood ● Marked loss of interest or pleasure in doing things	If either of the two key symptoms are present, ask about: ● Disturbed sleep (decreased or increased compared with usual) ● Decreased or increased appetite and/or weight ● Fatigue or loss of energy ● Agitation or slowing of movements ● * <i>Poor concentration</i> or indecisiveness ● * <i>Feelings of worthlessness</i> or excessive or inappropriate guilt ● * <i>Suicidal thoughts or acts</i>
*Symptoms particularly relevant in people with a chronic physical health problem	

Table 2

Criteria for referral to mental health services (from NICE CG90)¹⁶

Routine referral	Urgent referral
● Inadequate response to two or more interventions ● Recurrent episode within a year of the last one ● History suggestive of bipolar disorder ● The patient or relatives request referral ● More persistent suicidal thoughts ● Self-neglect	● Actively suicidal ideas or plans ● Psychotic symptoms ● Severe agitation accompanying severe symptoms ● Severe self-neglect

Table 3

Differential diagnosis of depression and dementia (modified from www.helpguide.org/articles/depression/depression-in-older-adults-and-the-elderly.htm)

Dementia (especially Alzheimer's disease)	Major depression
Gradual mental decline	Rapid mental decline
Presented by relatives or professionals	Self-referred
Lack of insight (does not notice memory problems or does not seem to care: 'I remember the things I want to remember')	Notices or worries about memory problems ('I think I am losing my mind')
Can be confused and disoriented in time and place	Usually oriented in time and place
Impairment of episodic memory ● Impaired free recall ● Impaired total recall (cueing does not improve recall due to inability to store new information) ● Flat learning curve despite repeated exposure	Impaired concentration, results in impaired encoding ● Recall improves with repeated exposure ● Normal recall, if encoding is controlled
Writing, speaking and motor skills can be impaired	Language and motor performance are typically slowed

this population and sleep problems, fatigue and low energy associated with them can mimic depressive symptoms. A major barrier to recognising depression, however, is the attribution of symptoms to old age, physical illness and psychosocial stressors, such as bereavement or social isolation. A lack of knowledge about depression and the stigma associated with mental illness may also be contributing factors.²²

The differential diagnosis is complex and the distinction between depression and early dementia may be particularly difficult. Obtaining a detailed history from patients and their relatives as well as longitudinal follow-up are important. Cognitive testing can be very helpful, see table 3, above.

The neuropsychological test used should be sensitive, as the cognitive changes are subtle, and should assess all cognitive domains. Considering the limited time GPs have, a referral to secondary care mental health services to clarify the diagnosis may be required. Alternatively, training a practice nurse to administer the Montreal Cognitive Assessment (MoCA) may be possible.^{12,23}

Finally, the role of physical ill health and prescribed medication should be considered, as many medical conditions and medications are associated with a risk or worsening of depression.¹⁶ The former include: neurological

conditions (e.g. Parkinson's disease, multiple sclerosis and stroke), sleep disorders, endocrine disorders, diabetes, chronic obstructive pulmonary disease and chronic physical ill health when associated with disability, loss of autonomy or pain. Medications that can increase the risk of depression include: corticosteroids, antihypertensives (e.g. beta blockers, reserpine, calcium channel blockers), statins, cancer treatments (interferon-alpha; chemotherapeutic agents) and central nervous system depressants (opioids, barbiturates, benzodiazepines).

RISK FACTORS FOR DEMENTIA IN DEPRESSED PATIENTS

Depression and dementia are both common, have shared risk factors and can have overlapping clinical presentations (e.g. reduction in working memory, poor sleep, reduced social function).¹⁰ There is an association between late life depression and risk of dementia, but a causal association is still debated, and some studies of late life depression find no increased risk of dementia.^{3,5,10} What seems to be more important is the duration and severity of depressive symptoms. Older patients with a pattern of high and increasingly severe depressive symptoms are at higher risk for dementia.²⁴

Chiefly, the presence of vascular risk

factors in those with depression increases the risk of developing all types of dementia.^{3,25,26} Diabetes and depression were independently associated with an increased risk of dementia, and there is a synergistic effect, when both are present.²⁷

'Older patients with a pattern of high and increasingly severe depressive symptoms are at higher risk for dementia'

It is unclear whether shared vascular risk factors themselves cause structural and functional brain changes that increase the risk of depression and dementia, or whether increased vascular risk factors for depression start a pathway that leads to an elevated risk of dementia. Research to date favours a bidirectional relationship, especially as vascular risk factors may lead to the development of other organic brain changes including hippocampal atrophy, increased deposition of amyloid-beta plaques, and inflammatory changes.^{2,3,10}

In summary, older people with depression are at elevated risk of developing dementia and this risk is increased if they have had symptoms for a long time, if their symptoms are severe, where there are multiple (vascular) comorbidities, and where there are structural brain changes including hippocampal atrophy and white matter abnormalities. Clinically, neuroimaging and cognitive screening is helpful to identify individuals at higher risk of dementia.

MANAGEMENT OF OLDER DEPRESSED PATIENTS

Management of older depressed patients should follow the same principles as for younger adults.¹⁶ For those with moderate to severe depression first-line treatment with an SSRI, such as sertraline or escitalopram, has the best evidence in terms of efficacy and tolerability.²⁹ In older adults, antidepressants should be prescribed at the lowest possible dose and titration should be slow. Careful monitoring should take place and clinicians should be mindful of side effects, particularly hyponatraemia and the potential for increased bleeding, if there are medical comorbidities or polypharmacy. As an »

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key points

SELECTED BY

Dr Phillip Bland

GP with an interest in mental health, Dalton-in-Furness, UK

Depression and dementia are both common conditions in older people, and they frequently occur together. Late life depression affects about 3.0-4.5% of adults aged 65 and older. Depression occurs in up to 20% of patients with Alzheimer's disease and up to 45% of patients with vascular dementia.

Depression can be an independent risk factor, a prodromal symptom or a consequence of dementia. Rather than a risk factor, depression with onset in later life is more likely to be either prodromal to dementia or a condition that unmasks pre-existing cognitive impairment by compromising cognitive reserve. Depression can be a psychological response to receiving a diagnosis of dementia.

The diagnosis of depression in older adults can be challenging. There is greater variety in presentation, cognitive and somatic symptoms are usually predominant and cognitive or anxiety symptoms may mask the core feature of low mood. Medical conditions are common in this population and sleep problems, fatigue and low energy associated with them can mimic depressive symptoms.

The distinction between depression and early dementia may be particularly difficult. Detailed histories from patients and their relatives as well as longitudinal follow-up are important. Cognitive testing can be very helpful. It is preferable to use a neuropsychological test that is sensitive to subtle cognitive changes and assesses all cognitive domains such as the Montreal Cognitive Assessment.

Older people with depression are at elevated risk of developing dementia and this risk is increased if they have had symptoms for a long time, if their symptoms are severe, where there are multiple (vascular) comorbidities, and where there are structural brain changes including hippocampal atrophy and white matter abnormalities.

In older adults antidepressants should be prescribed at the lowest possible dose and titration should be slow. Careful monitoring should take place and clinicians should be mindful of side effects, particularly hyponatraemia and the potential for increased bleeding, if there are medical comorbidities or polypharmacy. When treating older adults, particularly those with cognitive impairment, medication with a high cholinergic burden such as certain tricyclic antidepressants, e.g. amitriptyline, should be avoided.

alternative, first-line therapy may include atypical antidepressants such as mirtazapine which may better target problematic symptoms such as anxiety, anorexia and insomnia.^{30,31}

When treating older adults, particularly those with cognitive impairment, medication with a high cholinergic burden such as certain tricyclic antidepressants, e.g. amitriptyline, should be avoided.

'Medication with a high cholinergic burden such as certain tricyclic antidepressants, e.g. amitriptyline, should be avoided'

It is important to review other medication that may also worsen cognition (e.g. oxybutynin) and stop it where possible. Vascular risk factors (especially diabetes, hypertension and hypercholesterolaemia) should be treated and patients should be given lifestyle advice on diet and exercise.

Treatment of depression in people with dementia can take longer and be more challenging.³² Augmentation with a second antidepressant or another class of drug may be needed and clinicians should be mindful of the increased potential for side effects, if combination therapy is used. Augmentation with antipsychotic medication can be helpful,³³ but there is an increased risk of cardiovascular disease (stroke and myocardial infarction) in those with dementia, so these should be used at low doses, and should be avoided if there are significant vascular risk factors. Use of antipsychotic augmentation strategies with a more favourable metabolic side-effect profile (e.g. aripiprazole) may be preferable.³⁴ Other options for augmentation include mood stabilisers (e.g. lithium) and psychotherapy.^{35,36}

MONITORING AND FOLLOW-UP

Older people should be reviewed two weeks after making a change to medication, or more frequently with higher depression severity (e.g. concerns over lack of self-care, or suicidal ideation). Follow-up should focus on review of mood, but should also consider cognitive changes. Antidepressant medication should be

continued for at least two years sometimes longer after resolution of symptoms to reduce the risk of relapse.³⁷

Cognition is best reassessed once depressive symptoms have remitted; with effective treatment for depressive disorder cognition may improve and may return to normal once depressive symptoms have been treated. Clinicians should be mindful of an increased risk of developing dementia, particularly in people with recurrent, or increasingly severe symptoms. For those with continuing or recurrent symptoms, cognition should be reviewed on a regular basis (e.g. annually).

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Useful information

Alzheimer's Society

www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=139

Helpguide.org

www.helpguide.org/articles/depression/depression-in-older-adults-and-the-elderly.htm

HeretoHelp

www.heretohelp.bc.ca/factsheet/senior-s-and-depression-the%20difference-between-depression-and-dementia

Mayo Clinic

www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048362

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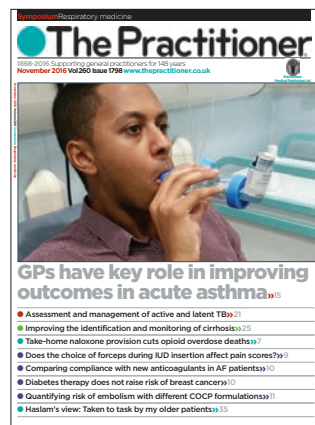
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