
Aetiology of late-life depression

Robert Baldwin

Depressive disorder has no single cause. Arguably, in old age it is a more heterogeneous condition than in earlier adult life, in both clinical presentation and causation. A broad distinction is often made between early- and late-onset depression in later life. The aetiology of these may differ and is currently the subject of new research.

Aetiology is often subdivided into risk factors (vulnerability to depression), precipitating factors and perpetuating factors (features which maintain depression). Perpetuating factors overlap with management issues and will not be discussed in detail. Lastly, there are factors which protect (or 'buffer') against depression.

Risk factors

Genetic susceptibility

In general, the later the onset of a depressive disorder, the less significant the role of genetic factors in its aetiology. Hopkinson (1964) found that the prevalence of depressive disorder among first-degree relatives of individuals with depression whose illness began after the age of 50 was less than half of that of probands with early-onset depression.

Gender and civil status

In cross-sectional studies women, widows and widowers and divorcees have been shown to be at greatest risk (Kivela *et al*, 1988).

Neurotransmitter changes

Normal ageing is associated with decreased brain concentrations of serotonin, dopamine, noradrenaline and their metabolites (Veith & Raskind, 1988), which would be expected to predispose to depression. However, turnover and availability also change with age, so that the picture is not straightforward. A decrease in plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) (suggestive of increased noradrenaline turnover) may be associated with late-life depression (Karege *et al*, 1989) and the 5-hydroxytryptamine (5-HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA) has consistently been shown to increase with age (Karlsson, 1993) suggesting hyperactivity in serotonergic pathways. However, decreased levels of 5-HIAA in cerebrospinal fluid (CSF) may correlate more closely with certain symptoms of depression – notably anxiety and suicidal behaviour – than age of onset. Furthermore, 5-HT₁ and 5-HT₂ binding sites decrease in number with age, whereas they appear to increase in depressive disorders (Sparks, 1989). Changes with ageing in dopaminergic function such as reductions of CSF homovanillic acid (HVA) levels and increased brain, plasma and platelet monoamine oxidase B (MAO-B) activity have all been shown and these could predispose to depression (Veith & Raskind, 1988) – although other evidence suggests that platelet MAO activity may correlate with severity and certain symptoms of depression (e.g. anhedonia) more than age of depression onset (Schneider, 1992). In one study of elderly females with depression, those with depression onset before 55 years had lower platelet MAO activity than those with later onset (Alexopoulos *et al*, 1984). Also, there

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is evidence of decrease in platelet 5-HT uptake sites in elderly patients with depression (Schneider 1992). Lastly, neuropeptides may act as neurotransmitter modulators but there is no convincing evidence that their levels alter significantly with age (Leake & Ferrier, 1993). Table 1 summarises the data. It is clear that some but by no means all age-associated changes are similar to those which occur in depression.

Neuroendocrine changes

At all ages, depression is associated with hyperactivity and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Ageing is associated with increasing cortisol levels and cortisol non-suppression. Schneider (1992) has speculated that normal ageing is associated with enhanced limbic-HPA axis activity, perhaps related to neuronal degeneration in the hippocampus, and that the latter may be exacerbated by raised glucocorticoid secretion, caused either by depression or repeated stressful life events or both (the 'feed-forward cascade'). In support, Krishnan (1991) reported reduced T₁ spin-lattice relaxation times in the hippocampus, as measured by magnetic resonance imaging (MRI), in a group of patients with depression compared with controls. The effect was particularly striking for elderly patients and was suggestive of tissue damage. The TSH (thyroid-stimulating hormone, thyrotropin) response to administered thyroid-releasing hormone is less age-dependent but is not specific for depression and is quite variable in ageing persons (Schneider, 1992).

Table 1. Neurotransmitter changes in depression and ageing: direction of change in key markers

Markers	Ageing	Depression
MHPG (NA)	↑	↓
β-receptors	↓	↑
α ₂ -receptors	↓ or normal	↑
5-HIAA (5-HT)	↑	↓
5-HT ₂ receptors	↓	↑
HVA (DA)	↓	↓
MAO-B	↑	↑
Acetylcholine	↓	?

↑, increased; ↓, decreased; NA, noradrenaline; DA, dopamine; MHPG, 3-methoxy-4-hydroxyphenylglycol; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MAO-B, monoamine oxidase B

The dexamethasone suppression test (Carroll *et al*, 1981) has not proved a reliable aetiological marker of late-onset depression. It cannot reliably differentiate depression from dementia and is influenced by a host of medical conditions and drugs.

Recent studies of the corticotropin-releasing hormone (CRH) have shown that CRH mRNA levels in the paraventricular nucleus of elderly patients with depression are higher than the levels in patients with Alzheimer's disease (also elevated), and very much higher than in normal controls (Raadsheer *et al*, 1995). This has led to speculation that hyperactivation of paraventricular CRH neurons may contribute to the aetiology of late-life depression.

Structural change

Volumetric change

Generalised atrophic changes in late-life depression are suggested by prominence of cerebral sulci and increased ventricular size. Some studies have reported focal volume reductions in the frontal lobes (Coffey *et al*, 1993) and the caudate nucleus (Krishnan *et al*, 1992).

It is unclear whether such changes predispose to depression or whether depression causes atrophy. Possible mechanisms include hypercortisolism, malnutrition or weight loss. Electroconvulsive therapy (ECT) is also associated with cerebral atrophy (Coffey *et al*, 1991) but it is not thought that ECT itself is responsible for this (Devanand *et al*, 1994).

White matter and other lesions

High-intensity signals (hyperintensities) in the white matter, visualised using MRI, are very common in late-life depression; so too are subcortical changes involving the basal ganglia and caudate (summarised in Baldwin, 1993) (see Fig. 1). Silent stroke is also common (Fujikawa *et al*, 1993).

The vascular depression hypothesis

This is based on a number of premises (discussed in more detail by Alexopoulos *et al*, 1997) (see Box 1). First, patients with vascular disease have a high rate of depression. Second, diseases affecting blood vessels, such as stroke, hypertension and diabetes, are associated with frequent white matter hyperintensities (WMH). Third, neurological diseases affecting the subcortex are associated with a high rate of depression. Fourth, late-onset depression may be associated with higher rates of vascular disease and vascular risk factors compared with early-onset

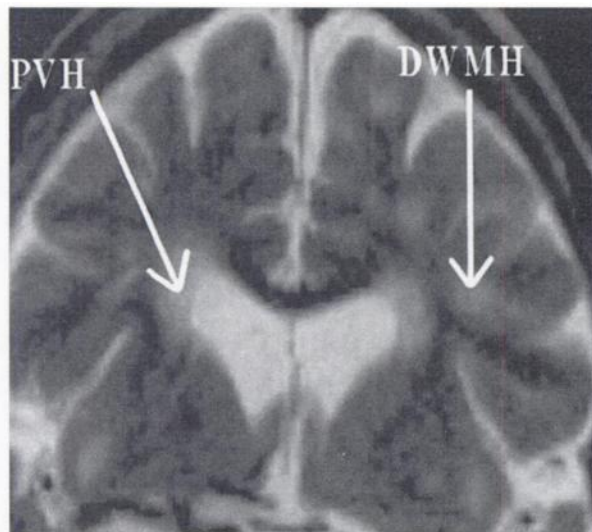
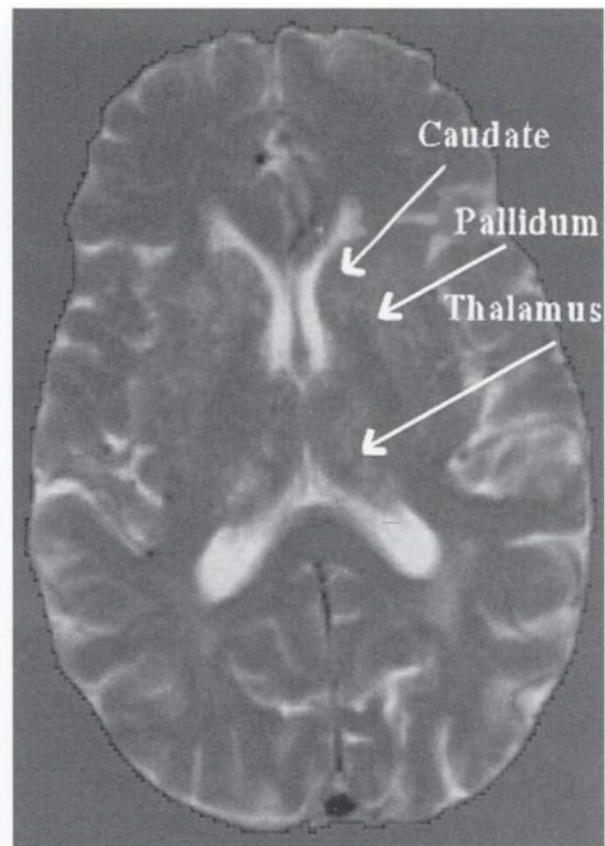


Fig. 1. A T_2 -weighted magnetic resonance imaging scan illustrates some of the changes which may be important in the aetiology of late-life depression. Abnormal signals appear white (high signal intensity). In a coronal section (*above*), periventricular hyperintensities (PVH) around the lateral ventricles and in the deep white matter (DWMH) can be seen. In a transverse section (*right*), subcortical grey matter lesions are apparent and involve the caudate, pallidum and thalamus (from top to bottom). These changes may disrupt the striato-pallidal pathway which may be critical in mood regulation (courtesy of Steven Simpson, The Fortson Clinic, Dorset)



depression in late life and with higher rates of WMH (Baldwin & Tomenson, 1995).

In 'vascular depression', damage to end-arteries supplying subcortical striato-pallido-thalamo-cortical pathways disrupts neurotransmitter circuitry involved in mood regulation and may thus cause or predispose to depression.

However, the significance of WMH is controversial. Although more common in elderly people with depression, WMH is not confined to older people or to depression itself (Baldwin, 1993) and may occur in a wide variety of non-vascular disorders such as hydrocephalus, multiple sclerosis, Alzheimer's disease and in normal ageing. A study of late-life depression (Lyness *et al*, 1998) failed to demonstrate any relationship between cerebrovascular disease risk factors and depression severity or symptomatology. In another study (Kumar *et al*, 1997a), brain volume measures were associated with general measures of physical ill health rather than specifically cardiovascular disease or cardiovascular risk factors. So, it cannot be assumed uncritically that visualised brain changes are caused by end-artery disease.

Whether 'vascular' or not in aetiology, there is evidence implicating WMH and subcortical pathology in late-life depression with: subtypes of late-life depression such as psychotic depression (O'Brien *et al*, 1997) and 'minor' depression (Kumar *et al*, 1997b); the presence of particular symptoms

Box 1. Vascular depression hypothesis

Premises

- Vascular disorders are associated with depression
- Hyperintensities on MRI associated with vascular disorder
- Subcortical disease is associated with depression
- Late-onset depression associated with greater vascular disease and vascular risk
- Late-onset depression associated with more deep white matter abnormality than early-onset depression in later life

Proposed features

- Mainly late-onset
- Reduced depressive ideation
- Reduced insight
- More overall morbidity
- Apathy and retardation
- More cognitive impairment (particularly executive dysfunction)
- Poorer recovery

(reduced depressive ideation and increased psychomotor retardation (Alexopoulos *et al*, 1997); more overall physical morbidity (Kumar *et al*, 1997a); and a poorer outcome with antidepressant treatment (Simpson *et al*, 1998).

The vascular hypothesis, although unproven, is an important aetiological concept as it lends itself to hypothesis-driven research which can be supported by modern neuroimaging techniques. It also has important implications for the treatment of depression. These include whether agents to reduce the risk of end-artery occlusion, such as aspirin, may be of use, as well as rehabilitative strategies designed to counter brain-based apathy and lack of motivation.

Dynamic changes

There is a general reduction in cerebral perfusion mainly to the frontal cortex (Sackheim *et al*, 1990). However, it is not known to what extent these changes are state or trait.

Depression and dementia

Neuronal loss is greater in the locus coeruleus of patients with dementia who are depressed compared with those without depression (Forstl *et al*, 1992). This suggests a distinct pathological substrate for depression in these patients. Depressed patients without dementia but with cognitive impairment have reduced flow to the left anterior medial prefrontal gyrus and increased flow to the cerebellar vermis (Bench *et al*, 1992), supporting a neurobiological basis for 'depressive pseudodementia', which most often arises in the context of later-life depression.

Personality

Research has emphasised the presence of obsessional traits, 'avoidant' and 'dependent' types of personality and a difficulty in forming close confiding relationships as possible aetiological factors in late-life depression (Murphy, 1982).

Bergmann (1978) has adapted attachment theory to the aetiology of late-life depression. He suggests that satisfactory attachment behaviour in early life is a necessary prerequisite to later adaptive coping, rather than non-adaptive anxiety, in the face of the very real threats and losses which accompany old age.

Physical health and disability

Both hospital (Murphy, 1982) and community (Prince *et al*, 1998) series reveal a close association between

the onset of depression and physical ill health. Physical impairment may provoke a depressive disorder, which may in turn increase the degree of disability associated with the original physical impairment (Prince *et al*, 1998).

There are several mechanisms whereby physical disorder may lead to depression. The dementias, stroke and Parkinson's disease are all associated with depression. Specific brain-based aetiologies have been proposed but discussion is beyond the scope of this review. These more biologically-oriented explanations may help us to understand how a depressive episode (depressive illness) could arise in the setting of particular disorders. They are less helpful in clarifying the onset of depressive symptoms, which occur commonly in many illnesses, including many non-neurological ones. The wide range of medical conditions, as well as hearing and visual deficits, which are associated with depression, suggests that the meaning of the illness for the sufferer is as important as the precise body system involved (Murphy, 1982). Prince *et al* (1998) have shown that disablement, and more specifically handicap – the disadvantage imposed by a physical impairment and disability – is the most important risk factor for depression in older people at home.

The highest prevalence of depressive disorders in older people is found in residential and nursing homes, medical wards for the elderly and among older people in receipt of extensive home care support (Ames, 1988; Banerjee *et al*, 1996). The usual explanation is that this simply reflects the concentration of disablement found in these settings. However, the concept of handicap (the disadvantage to the individual caused by a disability) provides another perspective. It is possible that some caring environments disadvantage older people by depriving them of benefits available to others with a similar level of disability who reside elsewhere. Some care settings may therefore be aetiological agents for depression. This has implications for prevention.

Lastly, a large number of physical disorders (some occult at presentation of depression), drugs and iatrogenic factors are associated with the onset of depression. The main ones are listed in Table 2. The elderly are particularly prone.

Care-giving

This deserves special attention as a risk factor of depression, as there are opportunities for prevention, identification and treatment. In one study (Ballard *et al*, 1996) a quarter of carers of people with dementia were depressed, and many had persistent symptoms. Factors associated with depression in carers were

depression in the designated patient and problem behaviours arising from him or her.

Epidemiological findings

Epidemiological research has not demonstrated that ageing *per se* is associated with an increased risk of developing depression (Robert *et al*, 1997). Any apparent age effect is explained by the additional risk caused by disability and ill health in those with depression (Robert *et al*, 1997; Prince *et al*, 1998).

Palsson *et al* (1999) found that measures of brain atrophy were similar in depressed and mentally healthy older subjects derived from a population sample, so it may be unwise to extrapolate from hospital studies, which comprise most of those cited in this review, to the community at large. However, in an epidemiological study, Cervilla & Prince (1997) found associations between depression and exposure to social supports deficits and threatening life events, which were considerably stronger for subjects without cognitive impairment than for those with it. This lends support to two pathways to depression in the elderly, one via organic brain disease and another via social stress and deficient social support.

Incident studies are useful in separating factors which might be aetiological from those which are of prognostic importance. An example is gender.

Although most cross-sectional studies find that female gender is a risk factor, in one study (Schoevers *et al*, 1999) this was not true. An explanation is that gender is a prognostic and not a risk factor. Female gender may be associated with chronicity, which may inflate the finding of a gender bias in cross-sectional research.

Green *et al* (1992) found that lack of life satisfaction, feelings of loneliness, and smoking were associated with depression. Multivariate analysis identified loss of someone close within the previous six months as a further factor. In a prospective community study, Schoevers *et al* (1999) identified bereavement of a spouse, health problems and comorbid organic deterioration (from baseline) as risk factors for the incidence of depression. More complex interactions were noted. For example, being married or having adequate social support significantly reduced the impact of reduced functional ability (at baseline) in triggering depression over time.

Precipitating factors

Box 2 lists the main types of precipitants, which can be categorised as either recent life events or chronic stressful conditions. Murphy (1982) found that 48%

Table 2. Medical illnesses and centrally acting drugs that may cause organic mood syndromes

Medical conditions	Centrally acting drugs
Endocrine / metabolic	Antihypertensive drugs
Hypo-/hyperthyroidism	Beta-blockers
Cushing's disease	Methyldopa
Hypercalcaemia	Reserpine
Sub-nutrition	Clonidine
Pernicious anaemia	Nifedipine
Organic brain disease	Digoxin
Cerebrovascular disease/stroke	Steroids
Central nervous system tumours	Analgesic drugs
Parkinson's disease	Opioids
Alzheimer's disease	Indomethacin
Multiple sclerosis	Anti-parkinsonism drugs
Systemic lupus erythematosus	L-dopa
Occult carcinoma	Amantadine
Pancreas	Tetrabenazine
Lung	Psychotropic drugs
Chronic infections	Neuroleptics
Neurosyphilis	Benzodiazepines
Brucellosis	Miscellaneous
Neurocysticercosis	Sulphonamides
Myalgic encephalomyelitis	Oral contraceptives
Acquired immune deficiency syndrome	

Box 2. Precipitating factors in depression of later life*Life events*

Bereavement
 Separation
 Acute physical illness
 Medical illness or threat to life of someone close
 Sudden homelessness or having to move
 into an institution
 Major financial crisis
 Negative interactions with family member
 or friend
 Loss of 'significant other' (including a pet)

Chronic stress

Declining health and mobility; dependence
 Sensory loss; cognitive decline
 Housing problems
 Major problems affecting family member
 Marital difficulties
 Socio-economic decline
 Problems at work; retirement
 Caring for a chronically ill and dependent
 family member

of elderly patients with depressive disorder ($n=119$) had experienced at least one severe life event in the preceding year, compared with 23% of a control group. Neither these percentages nor the types of adverse events are very different from other adult age groups, save for ill health, which is a more common precipitant in older people. Major social difficulties (as distinct from abrupt life events) lasting for two years or more were also significantly associated with depression.

Protective factors

Several factors – biological, psychological and social – seem to exert a buffering effect (see Box 3). They may therefore protect an older person from developing depression in the face of the precipitating events discussed above.

Box 3. Protective (buffering) factors*General medical care*

Correcting physical deficits (eg sensory loss)
 Optimising general health
 Good nutrition
 Physical fitness

Coping behaviours

Adaptive, integrated personality
 Capacity for confiding relationships
 Active coping styles to overcome adversity
 (as opposed to helplessness)

Social supports

Adequate social network
 Tangible social support
 Positive perceptions of support
 Confiding relationships
 Religious/spiritual beliefs

Since ill health is a major risk factor for depressive disorder in older people, maintaining optimum health is a worthwhile goal. Although evidence is scant, there is an emerging view that fitness and exercise programmes may play a preventive role in older people. Individuals with more integrated personalities and active coping styles are less prone to depression, as are those with robust social support systems – whether informal (Murphy, 1982), family-oriented or formal (Koenig *et al*, 1998) – although it is probably the perception (that is, quality) of support that matters more than the actual amount of it.

Factors in relapse and recurrence

Depression is prone to relapse and recurrence. Hence, a previous history of depression is a potent risk factor (Schoevers *et al*, 1999). Factors implicated in relapse or recovery are best considered as prognostic rather than aetiological; among the more important are treatment adequacy in the continuation and maintenance phases, respectively.

Conclusions

Each episode of depression arises out of a unique combination of a personal susceptibility to depression and, usually, a precipitant or several precipitants which trigger it. "My boss always taught me to ask, 'Why has this person developed depression now?' ". This apocryphal remark makes good clinical sense – it prompts enquiry into not only the biological realm but also the psychosocial. Another aphorism is "Depression is depression at any age". Largely, this is true, but there is emerging evidence

of a subtype of late-life depression, often with vascular rather than genetic risk, associated with late age of onset, deep white matter hyperintensities on MRI and subcortical changes. The clinical picture is one of apathy, limited depressive ideation, poor insight and high morbidity. The vascular hypothesis is not proven but generates testable hypotheses of aetiology, which, if supported, would lead to innovative treatments in late-life depression. Although there is some overlap in changes in neurotransmitters with ageing and in later-life depression, there are also inconsistencies, and epidemiological data do not, in any case, support ageing as a risk factor for depression. The search for a specific marker, such as a neuroendocrine test, has so far been disappointing. Rather, those most at risk of depression are socially isolated elderly people, those with sensory impairment and others with significant handicap from physical disorder. Currently, there is probably an overemphasis on the biological causation of late-life depression, and there are dangers in drawing too many conclusions from unrepresentative samples. Epidemiological data may provide a corrective. Emerging data suggest different pathways to depression, in which the impact of stressors known to trigger depression may be modified by patterns of vulnerability which may vary from individual to individual. Proposed factors include genetic, organic and environmental ones.

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Multiple choice questions

- Risk factors for depression in late-life include:
 - a greater genetic risk
 - decreased plasma MHPG (3-methoxy-4-hydroxyphenylglycol)
 - increased platelet monoamine oxidase B activity
 - increased platelet serotonin uptake sites
 - hypoactivity of the hypothalamic–pituitary–adrenal axis.
- Structural changes which have been reported in late-life depression include:
 - frontal lobe volume reduction
 - white matter hyperintensities
 - parietal lobe infarction
 - reduced volume of the red nucleus
 - reduced volume of the caudate nucleus.
- Symptoms of the newly proposed 'vascular depression' include:
 - psychomotor agitation
 - increased levels of guilt
 - reduced insight
 - visual field deficits
 - apathy.
- The following have been shown to be associated with depression onset:
 - warfarin
 - stroke
 - haemophilus pneumonia
 - calcium channel blockers
 - Alzheimer's disease.
- The following events have a definite association with onset of later-life depression:
 - social difficulties lasting more than two years
 - disputes with neighbours
 - being a carer
 - loss of a pet
 - paranoid personality.

MCQ answers

1	2	3	4	5
a F	a T	a F	a F	a T
b T	b T	b F	b T	b F
c T	c F	c T	c F	c T
d F	d F	d F	d T	d T
e F	e T	e T	e T	e F

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