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Relationship between delirium and depression in old age

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Summary

BACKGROUND: Depression is the most prevalent affective syndrome in old age. Delirium is a common and serious adverse event in elderly patients and is associated with significant cognitive and functional decline and early institutionalisation. Both disorders have shared symptoms and signs. Recent studies suggest that depression is an independent risk factor for delirium, and depression symptoms may also represent sequels of delirium. It is important to identify patients at risk of delirium, in order to apply preventive strategies and to address the consequences of incident delirium. In this narrative review we discuss the complex relationship between depression and delirium in old age.

METHODS: A literature search was conducted using following databases: PsycINFO, Embase, PubMed, Google scolar, Web of science and AgeLine using key words “delirium”, “depression”, “overlap" and "risk factor”.

MAIN FINDINGS: Delirium and depression are complex psychiatric syndromes that are common in old age and associated with poor outcomes. This study gives a general overview about the relationship between depression and delirium. Prior depression is not a rare finding in patients suffering from delirium, and depressive symptoms are frequently observed as sequel of delirium. If delirium occurs, differential diagnosis may be particularly challenging in people with depression. Studies suggest similar pathophysiology, such as disturbances in inflammatory and stress responses. Accurate detection of depression and delirium is a key target to achieve improvement of outcomes and to provide optimal healthcare.

CONCLUSION: The literature suggests an inter-relationship between depression and delirium. Symptoms of depression may contribute an increased risk of delirium and delirium may be a predictor of depression. However, the relationships between the two conditions regarding common underlying pathomechanisms and clinical aspects remain imprecisely defined and requires more study.

Keywords: *delirium, depression, neuropsychiatry, dementia*

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Introduction

Delirium is an acute neurocognitive disorder. It is a serious neuropsychiatric syndrome that is common in elderly people [1]. Rates of delirium are highest among hospitalised older people [2]. The aetiology of delirium is often multifactorial with complex interrelations between predisposing and precipitating factors [3]. Neurodegenerative and cerebrovascular diseases are among the most important predisposing factors [3, 4]. The prevalence of delirium at hospital admission ranges from 14–24% and the incidence of delirium arising during hospital stay ranges from 6–56% among general hospital populations aged 65 years and older [4]. Delirium is associated with significant adverse outcomes including functional decline, prolonged hospitalisation, long-term cognitive impairment and increased risk of mortality [5, 6]. Nonetheless, delirium is often unrecognised by physicians and nurses in their daily practice, with almost 50% of cases missed or misdiagnosed mainly because of its fluctuating course and the lack of formal cognitive assessment methods. The diagnosis of delirium is essentially clinical and is based on bedside evaluation of key features [5, 7–9].

Depression in the elderly is a common psychiatric disorder. The prevalence of major depression in adults aged 55 years or older is estimated at 2%, and its prevalence rises with increasing age. Moreover, 10% to 15% of older adults have clinically significant depressive symptoms without suffering from severe depression syndrome [10]. Many medical morbidities are associated with an elevated risk for depression in old age, such as Alzheimer’s disease, Parkinson’s disease and cerebrovascular diseases. Moreover, recent studies show that late-life depression is associated with increase in dementia risk [11]. Major depression in cognitively intact older medical inpatients is associated with sustained poor physical and mental health status [12].

Some recent studies have addressed the inter-relation between depression and delirium, and discussed evidence of both depression as a risk factor for delirium and delirium as a risk factor for depression. Patients with depression can have prominent cognitive symptoms that may include delirium features [13]. The similarity and the overlap of

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symptoms of delirium and depression lead to frequent misdiagnosis [14].

The aim of this review is to summarise literature relevant to the relationship between delirium and depression regarding both symptom overlap and shared pathophysiological mechanisms, and their implications for clinical practice.

Search strategy

We searched the following major databases: PsycINFO, Embase, PubMed, Google scolar, Web of science, AgeLine. Keyword search strategies designed to exhaustively cover the literature included: "delirium", "depression", "overlap", "risk factor" to identify articles studying interrelationship between delirium and depression, such as *evidence of both depression as a risk factor for delirium and also delirium as a risk factor for depression, misdiagnosis de delirium as depression, overlap syndrome and early detection and therapy.* Additionally, reference lists of selected articles were reviewed to identify potentially relevant studies. We used the search terms in various groupings as key words or medical subject headings when appropriate.

Results

Epidemiological aspects

The overall prevalence of delirium in the general population is 1–2%, but this increases with age, reaching 14% for adults over the age of 80. Delirium affects 14–24% of all hospitalised subjects. Among older adults, delirium occurs in 15–53% of patients post-surgery, in over 70% of those in the intensive care unit (ICU), and up to 60% of those in nursing homes [7, 9]. Among those requiring critical care, delirium is a risk factor for death within the next year [15]. Mood lability and other affective symptoms are reported in over 50% of delirium cases. Fifty-four percent of subjects suffering from delirium have depressed mood or anhedonia and 38% have both symptoms. Moreover, 24% of these patients show suicidal thoughts during delirium. About 8% of older hospitalised individuals meet the diagnostic criteria of overlap condition of delirium and depression [16].

Aetiological considerations

Neurophysiological alterations associated with delirium relate to neurotransmission and neuroendocrine imbalances, and an abnormal inflammatory response. These are also considered as pathological mechanisms of depression [17, 18].

Emerging evidence implicates hypothalamic-pituitary-adrenal axis (HPA) disturbances in the pathophysiology of delirium [19, 20]. It was suggested that an increase of preoperative cortisol levels can participate in the pathogenesis of cognitive dysfunction during postoperative delirium [21]. Likewise, a disturbed HPA axis is a well-established mechanism in the pathophysiology of depression [22] and Alzheimer's disease [23], and may represent a pathophysiological factor shared between delirium and depression, with particular relevance in the presence of Alzheimer's disease.

Moreover, studies provide evidence that points towards a strong link between increased production of inflammatory mediators and delirium. The pro-inflammatory cytokine interleukin-8 was reported to strongly correlate with delirium severity [24, 25]. Studies have also shown that increased cytokine production in central nervous system plays an important role in the pathogenesis of depression [26], as well as in neurodegenerative diseases such as Alzheimer's disease [27], which in turn is a strong risk factor for delirium [18].

Depression as predictor of delirium

Symptoms of depression may contribute to an increased risk of delirium. A recent systematic review discussed evidence of both depression as a risk factor for delirium and also delirium as a risk factor for depression. Based on the review of studies including old adults in postoperative, general medical and care institutions settings, the risk of delirium was estimated 1.3 to 9 times higher in patients with diagnosed depression [13]. Mood symptoms rather than physical symptoms of depression were associated with increased incidence and longer duration of delirium [13, 28, 29]. Schneider et al. demonstrated that psychological symptoms such as mood symptoms predicted delirium, since the exclusion of somatic items did not change the significance of the predictive value of the Hamilton Depression Scale (HAMD). Furthermore, the inclusion of only the somatic HAMD items in the statistical analysis did not show the significant predictive value of the depression scale [28]. The study of McAvay et al. suggested that depressed mood and hopelessness are predictive factors for incident delirium occurring during hospitalisation, whereas apathy-vigour symptoms of depression were not associated with the onset of delirium [29].

Preoperative depression influences both incidence and duration of postoperative delirium. Depression symptoms in subjects with mild syndromes not fulfilling the criteria of depression were also associated with postoperative delirium in elderly patients [30, 31]. A study in non-cardiac surgical patients of various ages found that subclinical preoperative depression was predictive of postoperative delirium [32]. In a recent prospective cohort study we found that participants with preoperative Geriatric Depression Scale (GDS) scores >5 had a higher risk of postoperative delirium than those with lower scores. Together, these results show that even very mild depression syndromes are associated with increased risk of delirium [33].

In the elderly, depression and brain white matter changes are common [34]. White matter alterations have been detected in major depressive disorder patients, in, for example, the frontal lobe, hippocampus, temporal lobe, thalamus, striatum and amygdala [35]. Depressive disorder and white matter hyperintensities are interactively associated with the poor performance of multiple cognitive functions. Neuroimaging studies have reported widespread structural abnormalities, suggesting that a dysfunctional frontal-limbic circuit is involved in the pathophysiological mechanisms of depression [34]. On the other hand, the study of Shioiri et al. suggests that the abnormalities of the microstructure in the deep white matter predispose patients to delirium and may account for the underlying mechanism of age-related vulnerability to delirium [36]. Seven recent studies show that white matter hyperintensities were associated with the occurrence of postoperative delirium [37]

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Delirium as predictor of depression

Recent studies provided evidence that delirium in elderly patients is associated with various long-term sequelae, which include affective disturbances. A systematic review on neuropsychiatric symptoms after delirium found that the prevalence of depressive symptoms was almost three times higher in patients with delirium than in patients without delirium (22.2% vs 8.0%, risk ratio 2.79) [38]. Slor et al. reported that in-hospital delirium is associated with an increased burden of depressive symptoms 3 months after discharge in elderly patients. Symptoms of depression in patients with previous in-hospital delirium cannot be fully explained by persistent subsyndromal delirium [39]. Fann et al. reported significantly higher scores on depression rating scales and persistent stress at 30 days follow up after delirium [40]. The study of Dolan et al. found that patients with delirium were 1.5 times more likely to develop depression at 2-year follow up. Olofsson et al. performed a study including 61 patients operated on for femoral neck fractures. Four months after surgery, they reported that patients who developed delirium were more often depressed, had poorer psychological well-being and more medical complications than the participants without delirium [41].

Clinical considerations

The accurate diagnosis of both delirium and depression is crucial for the choice of the appropriate treatment. The co-occurrence of delirium and depressive symptoms is not a rare condition. Overlap of symptoms is also common, in particular for the hypoactive form of delirium. Thus, medical staff have to exclude delirium in any patient suspected of a depression episode with an acute onset or fluctuating symptoms. Careful history taking and a proper clinical examination are crucial to accurate diagnosis. Furthermore, intervention may require interdisciplinary support teams of psychiatrists and geriatric specialists to keep patients optimally supported [16].

Delirium in its hyperactive form is more easily detected, especially in the acute care setting, because it is typically associated with agitation, irritability, combative outbursts and psychotic symptoms, which are disturbing to caregivers. However, it may be misdiagnosed, for example as psychosis or agitation as part of a behavioural syndrome related to dementia. The hypoactive form is more common and often underdiagnosed or misdiagnosed as depression because somnolence, apathy and cognitive impairment are more difficult to distinguish from other physical or psychiatric illnesses. Diagnosis and differential diagnosis is even more challenging when delirium and/or depression occur in persons with dementia. Finally, the mixed subtype of delirium, which includes characteristics of both hyperactive and hypoactive forms, may be misdiagnosed as agitation and disorganised thinking related to depression [42].

Symptoms of delirium and depression are partially similar. Nevertheless, delirium is more acute in onset, whereas depression develops more gradually. The fluctuation in symptom intensity is much more remarkable in delirium than in depression. On the other hand, depression frequently includes cognitive symptoms that also occur in delirium, especially in the elderly. These cognitive deficits consist mainly of executive dysfunction, disturbance of processing speed and short-term memory loss [13]. Attentional deficit, disorientation and other cognitive symptoms are typically more intense in delirious patients. Consciousness disturbances are a common part of delirium symptoms but rarely occur in depression. Mood disturbances tend to be more continuous in depression. Reversal or fragmentation of the sleep-wake cycle is common in delirium. The character of disturbances differs in depressive patients, who suffer typically from sleep-onset or late insomnia. Psychotic symptoms are also common in both conditions, but in delirious patients psychotic manifestations tend to be related to the surroundings, whereas in depression psychotic features are linked to negative emotions [13, 42, 43].

Inter-relationship in clinical practice

Misdiagnosis of delirium as depression

Delirium, especially the hypoactive clinical subtype in elderly people, is commonly misdiagnosed as depression. Many factors may lead to misdiagnosis, such as lack of knowledge about the diagnostic criteria and of systematic screening, atypical clinical presentation of delirium, the fluctuation of symptoms and the ability of non-psychiatric staff to accurately diagnose delirium at the time of consultation. In everyday practice, distinguishing depressive symptoms from delirium with hypoactive features may be difficult. Another confounding factor leading to misdiagnosis is the overlap of depression and delirium [13, 16, 44, 45]. In addition, delirium may co-occur with depression. Distinguishing delirium from depression has an important impact on patient outcomes and choice of treatment. Delirium reflects an underlying and potentially severe medical condition. The consequences of misdiagnosis are often severe and wide ranging, affecting both patient and health professional. Prompt intervention and search for its causes is the method of choice. Therefore a clinician who misdiagnoses delirium as depression may delay its causal treatment and proper management [16, 42, 46, 47]. Armstrong et al. observed an increase in psychiatric consultations for delirious patients in ICUs because of suspected depression. They suggested that this may be due to the fact that ICU staff are so routinely exposed to delirious patients, and that they therefore see delirium as a typical event of the unit experience and thus miss the delirium altogether [48].

Overlap syndrome

Delirium and depression have substantial clinical overlap. They can exist simultaneously in the same patient and often confer increased risk for each other. Studies have provided evidences that the co-occurrence of delirium and depression is associated with a considerably worse prognosis than either disorder separately. The study of Givens el al. showed that patients with the overlap syndrome of depression and delirium have more risk of functional decline, early nursing home placement and death than patients with neither disorder [16].

Depression and delirium can postpone functional recovery after hospitalisation, perhaps due to increased difficulty in participation in rehabilitation programmes. Therefore, recognition of the increased risk for adverse outcomes in hospitalised patients with the overlap syndrome may help post-hospitalisation planning [16, 47].

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Table 1: Distinguishing clinical features of delirium and depression.

Delirium
– Acute onset – Marked disturbance in attention and awareness – Altered consciousness – Reduced orientation to the environment – Disorganised thinking – Symptoms tend to fluctuate in severity during the course of a day – Underlying somatic cause
Major depression
– Insidious onset – Sustained depressed mood – Loss of interest or pleasure – Worthlessness or guilt – Thought of death or suicidal ideation
Overlapping features
– Cognitive impairment – Mood changes – Sleep disturbance – Loss of energy and fatigue – Agitation – Delusions or hallucinations

As discussed above, there is a considerable overlap between depression syndrome and hypoactive delirium (table 1). Both conditions include underactivity, apathy, and decreased amount and speed of speech, though the onset of such symptoms could be more insidious in depression. As the prognosis of hypoactive delirium is considered to be worse than that of other subtypes, accurate differential diagnosis and, in the case of delirium, a search for its causes are particularly important [13].

Prevention, early detection and therapy

Co-occurrence of depressive symptoms and delirium increase the likelihood of long-term adverse outcomes such as functional decline, institutionalisation, cognitive impairment and increased risk of mortality [5, 6]. Thus, prevention, early detection and proper management of these disorders may help clinicians to improve long-term outcomes.

Subsyndromal delirium may present with affective changes (subjective or observed) and, as delirium and depression can coexist, medical staff should perform a delirium screen for all older patients presenting with newly developed depressive symptoms. Although there is very little specific evidence on effective prevention and treatment of delirium related to depression, some recommendations to reduce delirium incidence and severity, and the consequences of concurrent delirium and depression may be considered, including (a) considering old age patients with depression as at risk for delirium, (b) implementing staff education on both depression and delirium in old age, (c) using delirium screening instruments, (d) treating depression before interventions that may trigger delirium, in particular surgery [4, 49], (e) considering both delirium cognitive sequelae and depression to improve rehabilitation outcome [50].

Conclusion

Delirium and depression are complex neuropsychiatric disorders that are common in old age. Both conditions have similar pathophysiological mechanisms and are associated with poor healthcare outcomes. Management of both conditions is complicated by their considerable clinical overlap. Distinguishing delirium from depression is a key target to achieve improved outcomes. Careful and systematic assessment of symptoms leads to accurate detection, which is necessary to provide optimal care.

The studies considered in this review and their main findings are summarised in tables 2 and 3, respectively.

Disclosure statement

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Table 2: Summary of studies.

Study	Study population	Total number of patients	Number of delirium patients	Delirium prevelance	Age of delirium patients (years)	Delirium measure	Psychiatric measure	Psychiatric outcome
Guenther et al. [3]	Patients ≥50 years scheduled for cardiac surgery	215	67	31%	Range 71–75	CAM-ICU	GDS MMSE	Cognitive function
Guenther et al. [6]	ICU patients	125	75	60%	Range 71–75	CAM-ICU	GDS MMSE	Activities of daily life
Ely et al. [15]	ICU patients receiving mechanical ventilation	275	183	81.7%	Mean± SD: 56 ± 17	CAM-ICU	None	6-month mortality
Givens et al. [16]	Patients aged 70 and older who were not delirious at hospital admission	459	23 had the overlap syndrome 39 had delirium alone	5.0% overlap syndrome 8.5% delirium alone	Mean± SD: 80.0 ± 6.5	CAM	GDS	Activities of daily life Nursing home placement Death
Casey et al. [25]	Adult patients who were scheduled for major elective non-intracranial, non-cardiac surgery	114	39/108	36.1%	Mean 69.5	CAM or CAM-ICU	None	Neurofilament light is associated with delirium
Schneider et al. [28]	Patients undergoing elective surgeries that exceeded 90 min.	47	17	36.2%	Mean ± SD: 66.8 ± 7.1	DRS DSM-IV criteria	HAMD MMSE	Predictive indicators for the development of postoperative delirium
McAvay et al. [29]	Patients aged 70 and older who were admitted to the general medicine service	416	36	8.6%	Mean± SD: 82.3 ± 6.6	CAM	GDS MMSE	Risk for incident delirium
Kazmierski et al. [30]	Patients undergoing cardiac surgery with cardiopulmonary bypass	563	91	16.3%	Mean 67	DSM-IV	DSM-IV MINI MMSE	Risk for incident delirium
Kazmierski et al. [31]	Patients admitted for open heart surgery	260	30	11.5%	Mean 62	DSM-IV	DSM-IV MINI MMSE	Risk for incident delirium
Smith et al. [32]	Patients undergoing major noncardiac surgery	998	35	3,5%	Mean 63.9	CAM	BDI Standardised battery of cognitive measures	Risk for incident delirium
Eshmawey et al. [33]	183 patients aged >50 years undergoing elective cardiac surgery	183	60	32.8%	Mean± SD: 75.5 ± 8.8	CAM-ICU	GDS	Predictors for incident delirium
Shioiri et al. [36]	Patients who underwent scheduled cardiac operations	116	19	16.4%	Mean 73.1	DSM-IV	BDI MMSE	Risk factor for delirium
Radinovic et al. [47]	Individuals with hip fracture without delirium consequently enrolled in a prospective cohort study	277	88 (delirium alone) 60 (overlap syndrome)	(31.8%) (21.7%)	Mean± SD: 73.7 ± 7.9 79.7 ± 6.7	CAM	GDS	Number of reinterventions, 1-month mortality, reinterventions plus 1-month mortality, number of hospital-acquired complications severity of complications, and length of hospital stay.

CAM: Cognitive Assessment Method, GDS: Geriatric Depression Score, SD: standard deviation, BDI: Beck Depression Inventory; HAMD: Hamilton Depression scale, DRS: Delirium Rating Scale, DSM: Diagnostic and Statistical Manual of Mental Disorders, MINI: MINI neuropsychiatric interview

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Table 3: Summary of findings.

Study	Outcome	Main findings
Guenther et al. [3]	Risk factors for delirium	Older age, higher Charlson's comorbidity index, lower Mini-Mental State Examination (MMSE) score, length of cardiopulmonary bypass and systemic inflammatory response syndrome in the intensive care unit were independently associated with delirium.
Guenther et al. [6]	Activities of daily life	Postoperative delirium did have an impact on activities of daily life when lasting 2 days or longer. MMSE ≤26 points, duration of aortic clamping and length of delirium are associated with decline in activities of daily life.
Ely et al. [15]	6-month mortality	Delirium was an independent predictor of higher 6-month mortality and longer hospital stay even after adjusting for relevant covariates including coma, sedatives, and analgesics in patients receiving mechanical ventilation.
Givens et al. [16]	Activities of daily life, nursing home placement, death	The overlap syndrome of depression and delirium is associated with significant risk of functional decline, institutionalisation, and death.
Casey et al. [25]	Neurofilament light is associated with delirium.	Delirium is associated with exaggerated increases in neurofilament light and that may contribute to the pathogenesis of delirium itself.
Schneider et al. [28]	Predictive indicators for the development of postoperative delirium	Preoperative depression symptoms and perioperative transfusions/infusions had significant predictive value for the development as well as for the severity of postoperative delirium.
McAvay et al. [29]	Risk for incident delirium	Assessing symptoms of dysphoric mood and hopelessness could help identify patients at risk for incident delirium
Kazmierski et al. [30]	Risk for incident delirium	Major depression, cognitive impairment, advanced age, anaemia, atrial fibrillations, prolonged intubation and postoperative hypoxia were independently associated with delirium after cardiac surgery.
Kazmierski et al. [31]	Risk for incident delirium	Independent predictors for delirium included cognitive impairment, atrial fibrillation, a history of peripheral vascular disease major depression and advanced age
Smith et al. [32]	Risk for incident delirium	Preoperative executive dysfunction and depressive symptoms are predictive of postoperative delirium among non-cardiac surgical patients.
Eshmawey et al. [33]	Predictors for incident delirium	Higher preoperative depression score is associated with an increased risk of postoperative delirium. Preoperative plasma cortisol level does not seem to be a predictor of delirium after surgery.
Shioiri et al. [36]	Risk factor for delirium	The abnormalities in the deep white matter and thalamus that were mainly accelerated by aging may account for the vulnerability to postoperative delirium.
Radinovic et al. [47]	Number of reinterventions, 1-month mortality, reinterventions plus 1-month mortality, number of hospital-acquired complications severity of complications, and length of hospital stay.	Depressive symptoms and delirium increase the likelihood of adverse outcomes after hip fracture in a step-wise manner when they coexist

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