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## **Delirium and depression: Inter-relationship and overlap in elderly people**

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### **Abstract**

Delirium and depression are complex neuropsychiatric syndromes that are common in the elderly and associated with a variety of poor healthcare outcomes. Accurate detection is key to providing optimal care for these conditions but is complicated by their considerable clinical overlap. This includes shared symptom profiles as well as comorbidity. Careful assessment of symptom character as well as the context and course of disturbances can allow for more accurate diagnosis. Prior depressive illness is a common finding in patients with delirium, while depressive illness is a recognised sequel of delirium. Evidence points to similar pathophysiological mechanisms involving disturbances in stress and inflammatory responses, monoaminergic and melatonergic functions, that in turn point to avenues for therapeutic intervention. Development of better tools for systematic assessment for delirium and depression in populations at high risk by virtue of age, diminished cognitive reserve and frailty is a key target to achieve improved healthcare outcomes.

### **Keywords**

delirium; depression; overlap syndrome; cognition; elderly

### **Introduction**

Delirium is a serious acute neuropsychiatric disorder that is common in hospitalised populations, occurring in approximately 1 in 5 general hospital admissions.<sup>1,2</sup> It is associated with significant adverse outcomes including prolonged hospitalisation, increased nursing home placement, functional decline, long term cognitive impairment and increased mortality.<sup>3-5</sup> Despite this, it remains understudied and poorly recognised in everyday practice with typically 50% of cases missed or misdiagnosed across healthcare settings.<sup>6</sup> Although characterised as a neurocognitive disorder,<sup>7</sup> delirium is a complex syndrome

consisting of a range of cognitive and non-cognitive features.<sup>8</sup> The non-cognitive features include disruptions to sleep-wake cycle, motor activity as well as disturbances in mood and affective expression.<sup>9,10</sup>

Major depression is common in the elderly with point prevalence estimated at 4.6-9.3% with an additional 2-3 times as many (4.5-37.4%) experiencing sub-threshold depressive symptomatology.<sup>11</sup> Hospitalised samples indicate rates as high as 45% of elderly inpatients.<sup>12</sup> A variety of medical morbidities are associated with elevated risk for depression (e.g. Parkinson's disease, Cerebrovascular disease, Diabetes) with depression prevalent in 20- 30% of patients with dementia,<sup>11</sup> and although late life depression is associated with a twofold increase in dementia risk, it remains unclear whether it is an actual risk factor for dementia or a prodromal marker.<sup>13,14</sup>

Depression and delirium are potentially related in several ways. Overlap may indicate comorbidity in patients who are frail and/or share risk factors for neuropsychiatric disturbances and are thus prone to complex multiple morbidity. It may also merely reflect a lack of phenomenological precision that occurs with syndromal diagnoses. Conversely, the widespread disruption of neural networks that characterises delirium may also incorporate affective centres in vulnerable or predisposed subjects such that the presence of prominent affective features may assist in identifying a subset of patients who can benefit from targeted therapeutic interventions. Similarly, patients with mood disorders can have prominent cognitive disturbances that may extend to include the range of features that characterise delirium. The frequency of mood disorders and delirium, especially in elderly populations with pre-existing cognitive impairments is such that a combination of these factors is likely to underpin the perceived overlap, but a better understanding of this interrelationship offers the prospect of improved outcomes in everyday clinical practice.

The purpose of this review is to examine the literature relevant to delirium and depression. In particular, we focus on the extent of the overlap, possible explanations for the inter-relationship and its implications for clinical practice and research efforts.

## Search Strategy and Selection Criteria

A search of Medline was conducted for English language publications between January 1, 1980 and January 1, 2014. Key search terms included 'delirium', 'depression', 'confusion', 'affect', 'mood', 'affective', 'mania' and 'mood disorder'. 2597 articles were identified. The search was refined to include only studies of adult populations and where the key search terms were in major headings of the publication, which identified 429 publications. Relevant articles were identified from a review of these abstracts. Age limited to adults. Case reports and reviews were excluded. A hand-search of references listings of the selected papers was used to identify any additional publications (See Figure 1 for search strategy and results).

## Epidemiology

Affective symptoms are common to both depression and delirium with affective lability reported in 43-86% of all episodes of delirium.<sup>8,10,15</sup> More sustained mood disturbances in delirium have also been reported; Leonard et al<sup>16</sup> found that core depressive symptoms such

as low mood and anhedonia were frequent in delirious subjects - 54% of subjects had one of these features and 38% had both. Farrell and Ganzini<sup>17</sup> reported low mood, anhedonia, feelings of worthlessness or guilt, loss of appetite and sleep disturbance in over 50% of the delirious subjects who had been referred with suspected depression. Moreover, 52% had frequent thoughts of death and 24% had thoughts of suicide.

Similarly, depressive illness frequently includes many of the cognitive disturbances that occur in delirium, especially in older subjects. The most consistent deficits occur with respect to executive function, processing speed, selective attention and the acquisition and retrieval of new information.<sup>18</sup>

Other work has explored the overlap condition of delirium and depression. This occurs commonly in hospitalized older persons. Based on estimates from previous studies, approximately 5-12% of older hospitalized patients meet diagnostic criteria for both conditions, with an even greater number having symptoms of both.<sup>16,19</sup> However, large-scale epidemiologic studies to document the co-occurrence of these conditions are lacking.

The adverse outcomes associated with delirium have been well documented, including increased mortality, institutionalization, healthcare costs, functional and cognitive decline.<sup>1,3</sup> Mortality risk at three months increased by 11% for every 48 hours of active delirium in elderly medical inpatients<sup>20</sup> thus highlighting the importance of timely diagnosis and treatment. Depressive symptoms are an important factor in missed or delayed diagnoses and likely contributed to poor outcomes in these prior studies. Moreover, the overlap syndrome has been associated with a strikingly worse prognosis than either condition on its own. In a large prospective cohort of 456 medical patients, Givens et al<sup>19</sup> documented that patients with the overlap syndrome of delirium and depression had a 5-fold increased risk of nursing home placement or mortality, and 3-fold increased risk of functional decline at one-month than patients with neither condition. Both delirium and depression contributed independently and additively to the adverse outcomes.

## Diagnostic considerations

### Diagnostic criteria for delirium and depression appear in Table 1

Both delirium and depression are syndromally defined and include cognitive and neuropsychiatric elements. However, the emphasis differs with delirium considered primarily a neurocognitive disorder, while depressive illness has sustained mood disturbance at its core.<sup>7,21</sup> This distinction is complicated by the fact that within the concepts of delirium and mood disorder there exist a range of presentations that include agitated depression, hyperactive delirium, psychomotor retarded depressive illness, hypoactive delirium, Bell's mania, and depressive pseudo-dementia that describe combined mood and cognitive elements. While affective disturbances are acknowledged to occur with delirium in DSM-5 and ICD 10 diagnostic criteria (e.g., anxiety, fear, depression, irritability, anger, euphoria and apathy), they are not considered core elements. Moreover, most delirium assessment tools have limited inclusion of affective symptoms to avoid confounding, other than lability of affect (DRS-R98),<sup>22</sup> inappropriate mood (Intensive Care Delirium Screening Checklist (ICDSC)),<sup>23</sup> and apathy (Delirium-O-Meter).<sup>24</sup>

The GDS-15 is the most commonly used scale for depressive symptoms in the studies we identified. It has been widely used in studies of elderly at risk of depression<sup>25-26</sup> but diagnostic accuracy is lower in patients with mild-moderate cognitive impairment and the self-report nature is problematic in patients with dementia.<sup>27</sup> The Cornell Scale for Depression in Dementia (CSDD)<sup>28</sup> is a clinician rated scale that is more accurate than the GDS for assessment of depression in subjects with significant cognitive impairment<sup>29</sup> but lacks sensitivity to change which impacts upon its suitability for serial assessments. Future studies of depressive symptoms in delirious subjects require greater clarity regarding optimal assessment methods that account for cognitive impairment and comorbid physical conditions.

## Assessment in clinical practice

Although the symptoms of delirium and depression are relatively lacking in specificity, careful assessment of the context of symptoms can allow for accurate attribution whereby delirium is typically more acute in onset and more likely to be linked to acute physical illness, while depressive symptoms typically develop more gradually (weeks) and are linked to psychological stressors. Depressive illness may exhibit diurnal fluctuation in symptom intensity but rarely fluctuate with the intensity or rapidity of delirium. Disturbances to mood are typically more sustained in depressive illness and where disturbances of consciousness occur, these tend to be less profound compared to the qualitative disturbance of delirium that impairs awareness of the immediate environment. Neurobehavioural and psychotic symptoms are also common to both depression and delirium but their character and context typically differs; in delirium psychotic features are often simple and relate to the immediate environment, while psychotic mood disorders classically include complex mood-congruent psychotic features involving themes of guilt or nihilism. Sleep-wake cycle is the most common non-cognitive function disturbed in delirium and is reported in 97-99% of all delirious episodes.<sup>8,10</sup> Moreover, the character of disturbances differs with sleep-wake cycle fragmentation or even complete reversal in approximately three quarters of delirious patients, while depression more typically includes initial or late insomnia. As such, careful history taking, augmented by a collateral source where possible, aligned to thorough examination and investigation for acute medical conditions are crucial to accurate diagnosis. Specific assessment tools such as the DRS-R98 and / or EEG can assist these efforts in more complex cases.<sup>30</sup> Table 2 outlines relatively distinguishing and overlapping features of delirium and depression.

There is considerable overlap in presentation between hypoactive delirium and depression with psychomotor retardation with both including decreased amount and speed of activity and speech, though the onset of such symptoms may be more insidious in depression.<sup>31</sup> This overlap is important as the prognosis of hypoactive delirium is generally considered to be worse than for other clinical subtypes.<sup>32</sup> Agitation, which may be a feature of delirium, is more frequently associated with late life depression<sup>33</sup> while conversely, increasing age is associated with relatively hypoactive presentations of delirium.

## Misdiagnosis of delirium as depression

Delirium is commonly the actual diagnosis in referrals to consultation-liaison psychiatry for assessment of suspected depression, with reports ranging from 6% to 52% cases representing such misdiagnoses.<sup>17,34-36</sup> Although these studies do not adequately account for possible comorbidity and include many complex diagnostic challenges, equally, referrals to psychiatric consultation liaison services represent a small proportion of cases of delirium that occur in hospital settings and the full extent of misdiagnosis is likely to be considerably greater than that described in these studies.

Misdiagnosis reflects a range of factors including limited awareness of delirium as an entity, the absence of formal screening in everyday practice, as well as the complexity of the syndrome which is typically highly fluctuating and can include presentations (e.g. hypoactive clinical subtype) that are phenomenologically very similar to depressive illness. Moreover, there is a lack of consensus as to the best scales to use for assessment and diagnosis.<sup>37</sup> Factors that have been directly linked to misdiagnosis include atypical presentation, inexperience of the diagnosing clinician and a documented past psychiatric diagnosis.<sup>35,38</sup> In addition, women with misdiagnosed delirium are more commonly labelled as depression, while men are more likely to receive an unspecified diagnosis.<sup>35</sup>

Distinguishing the two conditions can be difficult, especially where delirium presents with hypoactive features. The presence of depressive symptoms in the absence of core delirium symptoms suggest a diagnosis of depressive illness, whereas, presence of depressive symptoms in a patient with delirium carry less diagnostic certainty and may reflect mood changes in delirium rather than a discrete depressive illness.<sup>16,32,39</sup> Other confounding factors are the overlap between symptoms of physical illness and depression or delirium, such as weight loss, fatigue, reduced energy, reduced appetite and psychomotor retardation, which may occur independently of depression or delirium. Other reasons for the misdiagnosis are the overlap of the two syndromes, as documented in recent studies.

## Etiologic considerations

### Depression as a risk factor for delirium

At least 17 previous studies have examined depression as a risk factor for delirium (See Appendix Table 2). Sample sizes ranged from 34 – 11,745 patients. Fifteen studies included general adult populations and 16 focused on older adult populations (aged 60+). Study settings included postoperative (n=12), general medical (n=4), and nursing home (n=1). The increased risk for delirium in patients with depression ranged from 1.3 to 9-fold.<sup>40,41</sup> Active depressive illness<sup>42-44</sup> and number of pre-operative depressive symptoms on the GDS-15 influenced both incidence and duration of postoperative delirium.<sup>45</sup> Both a history of depression and presence of subclinical levels of depression are risk factors for delirium.<sup>40</sup> Specific symptoms of depression may contribute to increased risk of delirium. Psychological symptom burden rather than physical symptom burden was associated with an increased incidence and longer course of postoperative delirium.<sup>46</sup> Dysphoric mood and hopelessness rather than withdrawal and apathy were more strongly associated with delirium.<sup>47</sup>

Two previous studies did not support current depression as a risk factor for delirium.<sup>48,49</sup> However, the latter study did find that a past psychiatric diagnosis, most commonly depression, was predictive of delirium.

### **Delirium as a risk factor for depression**

Seven prospective studies examined delirium as a risk factor for subsequent depression. These studies examined diverse populations, including elderly hip fracture (n=4), cardiac surgery (n=1), stem cell transplant (n=1), and burn unit (n=1) patients for follow-up periods ranging from two-weeks to two years. Six studies found a positive association between delirium and subsequent depressive symptoms. Dolan et al<sup>50</sup> reported those with delirium were 1.5 times more likely to exhibit depressive symptoms at two year follow up. Three studies reported significantly higher scores on depression rating scales in the delirious groups at follow up between one and four months post delirium.<sup>51-3</sup>

### **Pathophysiological overlap**

There have been no studies directly assessing the relationship between etiological and biological parameters and symptoms of delirium and depression. As such, possible overlap with respect to pathophysiology is inferred from our knowledge of each condition separately. A variety of physiological mechanisms are implicated in delirium, most of which are also thought to be relevant to depression. This reflects the complexity of both conditions with widespread disruption of neural networks. These overlapping neurobiologies may explain the close inter-relationship between the conditions.

The principal neurophysiological disturbances linked to delirium relate to alterations in monoamine neurotransmission and abnormal stress and inflammatory responses – all of which are also proposed as mechanisms in depressive illness. In delirium, indirect evidence from studies of causative factors and treatment effects, along with more direct evidence from cerebrospinal fluid studies has implicated dopaminergic-cholinergic imbalance as a common final neural pathway.<sup>54,55</sup> Other evidence points towards aberrant interactions between inflammatory mechanisms and the limbic-hypothalamic-pituitary-adrenocortical axis (LHPA) in delirium. The effect of peripheral inflammatory mediators on brains already compromised by the effects of aging or dementia is greater than in less compromised states. In support, high levels of plasma cortisol,<sup>56</sup> and dexamethasone non-suppression<sup>57</sup> have been reported in delirium and may contribute to a prolonged or exaggerated stress response.<sup>58,59</sup> Moreover, studies have linked altered expression of various cytokines to delirium.<sup>60</sup> Similarly, disturbed monoamine function and over-activity of the hypothalamic-pituitary-adrenal axis (HPA) are well-established mechanisms in the pathophysiology of depression<sup>61</sup> with considerable evidence for the role of cytokines and inflammatory processes in depression.<sup>62</sup>

The fluctuating course and disturbed sleep and motor activity in delirium suggest disruption of circadian function. Disturbed melatonergic activity has been reported in delirium.<sup>63,64</sup> Vulnerability to delirium proneness may be elevated in those with compromised circadian regulation whereby acute physiological stress can precipitate a cycle of escalating circadian disruption manifesting as a delirious episode.<sup>65</sup> Circadian disturbances are also linked to

depressive illness and supported by the use of melatonergic antidepressants and symptoms such as diurnal mood variation and sleep disturbance. However, in both conditions circadian changes may be secondary to impaired perception of environmental zeitgebers that regulate circadian function.<sup>66</sup>

A proposed model for the relationship between delirium and depression is shown in Figure 2. Ultimately, a combination of (i) host factors such as baseline cognition, physical status and genetic predisposition (ii) altered stress axis and systemic inflammatory responses and (iii) the nature of the insult (physical stressors linked to delirium with psychological more likely to result in depression) render the individual susceptible to developing neuropsychiatric morbidity with depression, delirium or, in the most vulnerable individuals, features of both-the 'overlap syndrome'.

## Therapeutic considerations

The substantial overlap between delirium and depression has important implications for management. Accurate, timely diagnosis of delirium is especially urgent because it is frequently a manifestation of serious underlying morbidity. Moreover, pharmacological intervention warrants careful consideration of whether mood disturbance is part of delirium (which may be best managed non-pharmacologically by focusing upon treatment of the delirium and its underlying cause) versus a comorbid or primary diagnosis of depression. Where a discrete depressive illness is evident, anti-depressant agents with anticholinergic properties should be avoided as they may aggravate delirium symptoms. Older antidepressant agents (such as tricyclic agents) have well recognised anticholinergic effects, but the anticholinergic potential of newer agents can be underestimated - paroxetine, for example, has greater propensity for anticholinergic side effects in comparison to other selective serotonin reuptake inhibitors.<sup>67</sup>

Patients with a significant degree of overlap between delirium and depressive symptoms may represent a sub-group of patients that benefit from treatment targeted at both conditions, although this is an important area for future clinical trials. The circadian disturbance apparent in delirium and depression may prove a useful target of intervention. Al-Aama et al<sup>68</sup> demonstrated a useful effect of melatonin in the prevention of delirium, while Hatta and colleagues<sup>69</sup> found a marked reduction in delirium incidence among elderly general medical and ICU patients treated prophylactically for a week with a nocturnal dose of the melatonin agonist ramelteon. Melatonergic agents such as agomelatine are already commonly used in depression.<sup>68</sup> ECT remains an important treatment option for severe and / or treatment resistant depressive illness<sup>70</sup> and, although it has been suggested as a treatment for resistant delirium tremens, it is not generally recommended in the treatment of delirium.

## Other aspects / controversies

Our understanding of the overlap between depression and delirium can be enhanced by large studies that focus upon longitudinal assessment of both syndromal illness as well as individual neuropsychiatric and cognitive disturbances that can occur in these conditions. Such work can clarify not only the true extent of overlap between these conditions, but also

allow for the identification of features that are relatively specific for each state. In turn, this information can inform efforts to optimally assess for depressive symptoms in patients with high rates of neurocognitive disorders such as delirium and dementia. The limitations of the GDS and CSDD emphasise the need for alternate methods for assessment, including tools that are tailored specifically for this purpose.

Although both delirium and depression can include cognitive impairment, the extent to which these compare remains unclear. The exact nature of cognitive impairments in depressive illness is unclear and includes a range of possible explanations, with some studies suggesting that the psychomotor retardation and slowed processing speed in depression may account for some of the apparent cognitive impairment.<sup>71</sup> Clarifying how cognition is differently affected in delirium versus depression can inform efforts to reliably identify these conditions as many aspects of cognitive function are particularly suited to systematic and reliable assessment.

Important caveats to note in interpretation of studies assessing the role of depression as a risk factor for delirium (and vice versa) is the need to account more consistently for the presence of pre-existing depressive illness and the confounding effect of shared risk factors in the form of physical and psychological stressors and vulnerabilities conferred by cognitive impairment and frailty, as these have not been adequately examined or adjusted for in prior work. Dissecting such relationships requires detailed longitudinal studies of patient populations who are at risk for these conditions.

Recent studies have highlighted the prognostic significance of interactions between delirium and depression. These findings may reflect a number of possible mechanisms; (i) the additive effects of comorbidity with additional neuropsychiatric burden and more widespread CNS dysfunction, (ii) combined symptoms may reflect the impact of physical and psychological stressors on a functionally more vulnerable CNS with diminished neuronal reserve, (iii) depressive states with prominent cognitive disturbance are typically at the more severe end of the affective spectrum, and (iv) delirium characterised by prominent symptoms of mood disturbance may reflect a more prognostically-severe form of the condition. Further research can specifically explore these possibilities which in turn can inform therapeutic efforts.

Most of the literature examining affective disorders and delirium focuses on depressive features. However, at the opposite end of the spectrum, 'delirious mania' is defined as 'a syndrome of acute onset of the excitement, grandiosity, emotional lability, delusions and insomnia characteristic of mania, with the disorientation and altered consciousness characteristic of delirium'.<sup>72</sup> Lee et al,<sup>73</sup> in a small case series found that delirious and manic symptoms resolved at different rates. Weintraub and Lippmann<sup>74</sup> described possible explanations for delirious mania in elderly patients including delirium mimicking a presentation of mania and delirium evolving into mania. However, the relationship between delirium and mania remains imprecisely defined and requires more systematic study.



## Conclusions

Although affective changes and cognitive impairment are well-recognised elements of both delirium and depressive illness, these disorders are typically considered as distinct entities. A significant amount of comorbidity is expected due to the high prevalence of delirium, depression and other causes of cognitive impairment in elderly populations, but the relationship between depression and delirium may extend to include more complex interactions, including shared aetiological and pathophysiological mechanisms. Both conditions are syndromally defined which may account for some phenomenological overlap and detailed longitudinal studies exploring affective and cognitive symptoms before, during, and after delirium are needed to clarify features that are relatively distinguishing of mood versus delirious states. These distinguishing features need to be emphasised in assessment procedures used in the study of delirium, as well as in more general studies of neuropsychiatric profile in populations at high risk of these conditions. Moreover, identifying precise symptoms of overlap and the temporal sequence of symptoms can help to distinguish co-morbidity and causal relationships. Prognostically, clinical presentations that include elements of both states are more likely to be linked to adverse outcomes such that careful consideration is needed to identify optimal management responses in everyday clinical practice.

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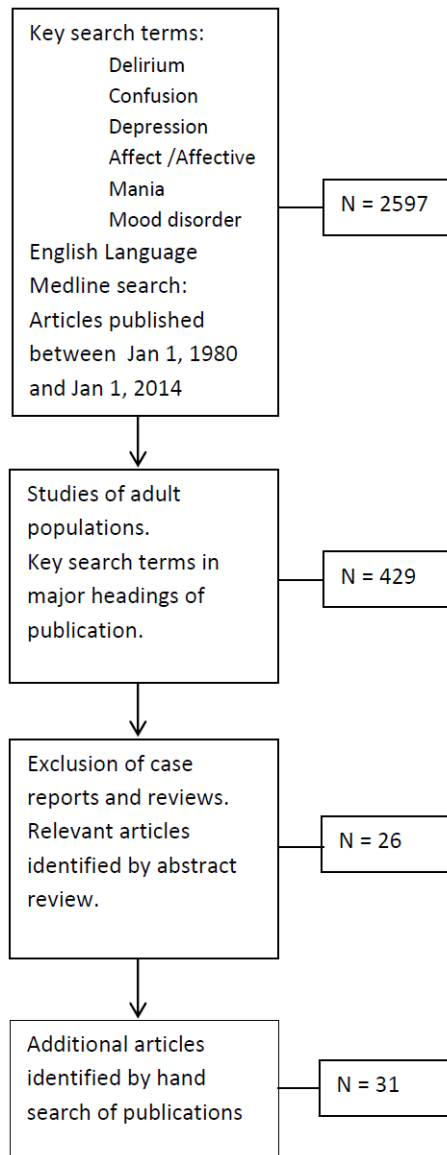
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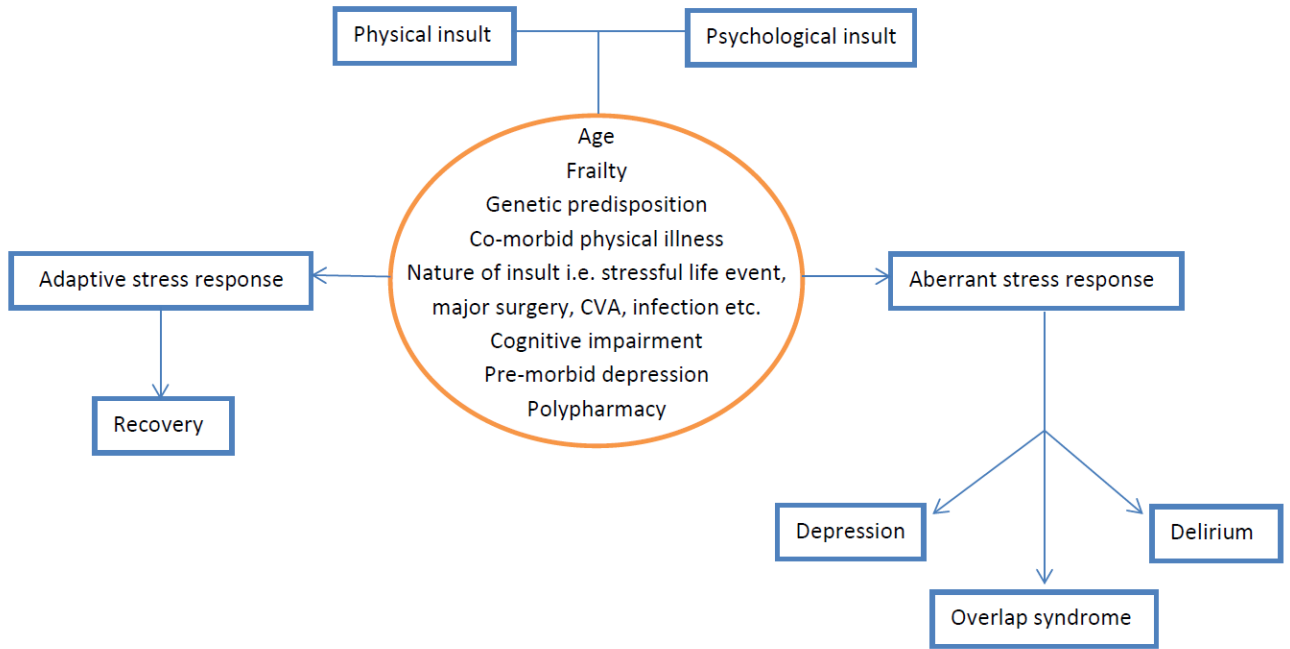
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**PANEL****Pearls / take home messages**

- Depression and delirium are common complications in hospitalised elderly and account for considerable morbidity and mortality
- Depression and delirium often co-exist and act as risk factors for each other but their distinction is important in identifying optimal treatment
- Because of their common overlap, in the hospital setting, the clinician should rule-out delirium in any patient suspected of depression
- Careful history taking that focuses upon the context and character of symptoms, complemented by focused investigation can allow for accurate diagnosis in the majority of cases
- Where present, symptoms of delirium tend to dominate and take diagnostic precedence as delirium frequently indicates serious and urgent physical morbidity
- In older persons, avoid treatment of depression with highly anticholinergic agents which may aggravate cognitive impairment or co-occurring delirium



**Figure 1.**  
Process of article selection



**Figure 2.**  
Proposed common pathway of depression and delirium



**Table 1**

## DSM-5 Criteria for Major Depressive Disorder and Delirium

DSM-5 Criteria for Major Depressive Disorder	DSM-5 Criteria for delirium
<p><b>A.</b> Five or more out of nine symptoms (including at least one of depressed mood and loss of interest or pleasure) in the same 2-week period. Each of these symptoms represents a change from previous functioning.</p> <ol style="list-style-type: none"> <li><b>1.</b> Depressed mood (subjective or observed)</li> <li><b>2.</b> Loss of interest or pleasure</li> <li><b>3.</b> Change in weight or appetite</li> <li><b>4.</b> Insomnia or hypersomnia</li> <li><b>5.</b> Psychomotor retardation or agitation (observed)</li> <li><b>6.</b> Loss of energy or fatigue</li> <li><b>7.</b> Worthlessness or guilt</li> <li><b>8.</b> Impaired concentration or indecisiveness</li> <li><b>9.</b> Thoughts of death or suicidal ideation or attempt</li> </ol> <p><b>B.</b> Symptoms cause significant distress or impairment</p> <p><b>C.</b> Episode not attributable to a substance or medical condition</p> <p><b>D.</b> Episode not better explained by a psychotic disorder</p> <p><b>E.</b> There has never been a manic or hypomanic episode</p>	<p><b>A.</b> A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).</p> <p><b>B.</b> The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</p> <p><b>C.</b> An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</p> <p><b>D.</b> The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.</p> <p><b>E.</b> There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies</p>

**Table 2**

Distinguishing and overlapping features of delirium and depression

<b>Highly distinguishing features of delirium</b>	<b>Overlapping features</b>
Fluctuating course	Affective changes
Acute onset	Sleep disturbance
Altered consciousness	Underactivity
Marked Inattention	Apathy
Underlying physical cause	Agitation
Disorientation	Impaired speed of information processing
Disorganised thinking	Delusions / hallucinations
Poor comprehension	Impaired memory

**Table 3**

## Key areas for future research focus

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**Epidemiology:**

Large studies across therapeutic settings and age groups to ascertain the extent of overlap between delirium and mood disorders, and exploring the impact of each separately and in combination upon healthcare outcomes

**Diagnosis and Assessment / Phenomenology:**

Identification specific features (both cognitive and neuropsychiatric) of delirium and depression that are relatively distinguishing of the conditions, and which can be incorporated into assessment tools to enhance the accuracy of detection.  
Clarification of the relevance of other neurocognitive disorders (e.g. dementia, MCI) upon clinical presentation of delirium, depression and overlap states.

**Causation:**

Investigation of the extent to which delirium and depression share risk factors and how pathophysiological mechanisms in these states overlap and relate to treatment and outcomes.

**Treatment:**

Therapeutic trials assessing the impact of various psychotropic agents (antidepressants, antipsychotics) specifically on mood disturbances occurring in delirium.

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