

## Delirium as a marker of vulnerability in the elderly

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### Abstract

Delirium is the clinical expression of an acute cerebral dysfunction caused by various noxious insults. Its prevalence is very high in the elderly, especially in the hospital setting, and in geriatric patients it can be the clinical manifestation of almost every acute disease. Delirium is associated to a number of adverse clinical and functional outcomes, to a higher risk of cognitive decline, institutionalization, and short- and long-term mortality. It is thus necessary to increase the attention on this issue: in fact, it is clearly demonstrated that delirium can be prevented in a large proportion of cases.

Delirium is not only a marker of patient vulnerability and clinical instability, but also an index of the quality of care and the efficiency of its organization. By systematically assessing the presence of delirium during the whole length of hospital stay, physicians may closely monitor the patient's clinical status. The aims of this review are to review the current clinical practice in delirium, focusing particularly on elderly individuals. The topics covered include epidemiology and outcomes, causes, clinical features and diagnosis, prevention and treatment. Finally, implications for clinical practice are discussed.

### Introduction

The observation that acute illnesses of young and elderly patients may present in different ways has been recognized since a long-time by geriatric medicine. For instance we can consider the acute myocardial infarction and/or infections. It is perfectly logical, for every newly graduated physician, to suspect one of these illnesses when symptoms and signs, such as chest pain, cough, fever and dyspnoea, present in a young adult. However, these symptoms are not always present in an

older adult with the same clinical illnesses.<sup>1,4</sup> Some years ago, Besdine observed that *when an elderly person gets sick the first sign of a new disease (or of the relapse of a chronic one) is rarely a single specific symptom that helps identifying the organ or the tissue in which the disease occurs.*<sup>5</sup> In most cases, the presenting symptoms of a new disease are atypical and are the expression of the incipient failure of a body-system, generally a *locus minoris resistentiae*. Among atypical symptoms of elderly patients, delirium is one of the commonest.

Delirium is a geriatric syndrome encompassing an array of neuropsychiatric symptoms,<sup>6</sup> which represents a disarrangement of the cerebral function in response to one or more pathophysiological stressors.<sup>7,8</sup>

The aims of this review are to discuss the current clinical practice in delirium, focusing on older individuals. The topics covered include epidemiology and outcomes, causes, pathophysiology, diagnosis, prevention and treatment.

### Epidemiology and outcomes of delirium

The frequency of delirium varies according to the settings in which it occurs. In general medical and old age medicine wards, prevalent delirium (*i.e.*, already present on admission) ranges from 18 to 35%; this proportion should be added to the incident delirium (*i.e.*, developing during hospital stay), yielding an overall occurrence in these settings of 29-64%.<sup>9</sup> In general, up to 50% of older subjects have delirium during the hospital stay.<sup>9,10</sup> The prevalence of delirium is high even in surgical settings, with proportion ranging from 10 to 74%<sup>9</sup> and in Intensive Care Units, where prevalence may reach 80% in patients undergoing mechanical ventilation.<sup>11-13</sup> Delirium is also common in rehabilitation and post-acute care facilities, where it is present in nearly one out of five patients on admission.<sup>14,15</sup> Delirium is less common in the community (1-3%),<sup>9</sup> but it should be taken into account that its onset usually brings the patient to emergency care. Here, the prevalence of delirium ranges from 9.6 to 12.3%, according to different studies.<sup>16-19</sup>

Delirium is associated with a number of adverse clinical outcomes, including increased risk of institutionalization and higher mortality.<sup>12,20,21</sup> In hospital settings, delirium is associated with a nearly double risk of death at 2 years follow-up, independent of important confounders, such as age, sex, comorbidity and dementia.<sup>21</sup> It is worth noting that not only delirium per se (as an episode), but duration of delirium, increases the risk of mortality. In a prospective cohort study of patients undergoing surgical repair of hip fracture, Bellelli found

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that each day of post-operative delirium in a orthogeriatric unit increased the hazard of dying at 6 months by 17%, after adjusting for covariates.<sup>22</sup> Delirium is also associated with increased risk of cognitive impairment and/or progression to dementia. In a population of 533 individuals from the Vantaa 85+ study, Davis showed that delirium increased the risk of incident dementia [odds ratio (OR) 8.7, 95% confidence interval (CI) 2.1-35] and was also associated with worsening dementia severity (OR 2.8, 95% CI 1.4-5.5).<sup>23</sup> Similar results of the facilitating role of delirium in leading to cognitive impairment and or dementia have been found in other studies including patients with dementia and in a critically ill population.<sup>24-26</sup> Finally, delirium is severely distressing for patients, carers and healthcare providers, including nurses and physiotherapists.<sup>27-29</sup>

### Causes of delirium

Although a single factor can lead to delirium, usually delirium is multifactorial in elderly people. The multifactorial model of the cause of delirium has been well validated and it is now widely accepted. According to the Inouye's model,<sup>30</sup> onset of delirium depends on complex inter-relationships between patients with several predisposing factors and exposure to noxious insults or precipitating factors. Thus, in vulnerable patients, such as those with underlying dementia and multimorbidity, a seemingly benign insult, *e.g.*, a dose of a sedative or a hypnotic drug-might be enough to precipitate delirium. Conversely, in a young, healthy patient, delirium will develop only after expo-

sure to a series of noxious insults, such as general anaesthesia and major surgery.<sup>30</sup> In terms of clinical practice, this observation is fundamental since it suggests that addressing of a single risk factor is unlikely to resolve delirium, and that multifactorial aetiologies need to be searched. Inouye identified four predisposing (*i.e.*, sensory impairment, cognitive impairment, severity of acute illness and dehydration) and five precipitating factors (*i.e.*, physical constraints, malnutrition, recent prescription of >3 new drugs, bladder catheter and iatrogenic events).<sup>30</sup> Disability, depression, previous stroke, alcohol abuse and multiple chronic illnesses have also been considered as predisposing,<sup>9</sup> while electrolytes' imbalance, urinary retention, constipation, trauma and surgical interventions as precipitating factors.<sup>9</sup>

Drugs are also a potential cause of delirium. In a systematic review, Clegg found that delirium risk increases especially with the use of opioids (OR 2.5, 95% CI 1.2-5.2) and benzodiazepines (OR 3.0, 95% CI 1.3-6.8).<sup>31</sup> In line with this notion, the American Geriatric Society recommends not to using benzodiazepines or other sedative-hypnotics for older adults as a first choice for insomnia, agitation, or delirium.<sup>32</sup>

## Pathophysiology of delirium

The pathophysiological mechanisms underlying delirium are still incompletely elucidated. Historically, Engel and Romano investigated electroencephalogram (EEG) abnormalities varying with the onset of cognitive dysfunction. Their research, focused on a generalized slowing of the EEG traces. The authors speculated that delirium was possibly caused by a global alteration of the neuron metabolism, and hypothesized a decreased cortical excitation.<sup>33</sup> Since then, a series of other experiments and theories have been proposed,<sup>34-36</sup> including cerebral hypoperfusion,<sup>37</sup> excessive oxidative stress,<sup>38</sup> alterations of serotonergic, dopaminergic, and GABA-ergic neurotransmission systems,<sup>39-41</sup> systemic and neuroinflammation leading to blood-brain-barrier disruption,<sup>42</sup> and alteration of the cellular maintenance processes.<sup>43</sup> A recent review by Maldonado proposed seven distinct and complementary mechanisms, including the *neuroinflammatory, neuronal aging, oxidative stress, neurotransmitter deficiency, neuroendocrine, diurnal dysregulation, and network disconnectivity* hypotheses.<sup>44</sup> The review also suggests that many mechanisms included in these theories lead to a final common outcome associated with an alteration in neurotransmitter synthesis, function, and/or availability that mediates the behavioral and cognitive

changes observed in delirium. In general, the most commonly described neurotransmitter changes associated with delirium include deficiencies in acetylcholine and/or melatonin availability, excess in dopamine, norepinephrine, and/or glutamate release; and variable alterations (*e.g.*, either a decreased or increased activity, depending on delirium presentation and cause) in serotonin, histamine, and/or g-aminobutyric acid.

## Diagnosis of delirium

Delirium has been recognized for at least two millennia with the term *delirium* deriving from the Latin *lira* meaning to wander from one's furrow. Prior to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III,<sup>45</sup> acute generalized disturbances of brain function were described by a myriad of labels (*e.g.*, acute organic brain syndrome, acute confusional state, brain failure, toxic encephalopathy and intensive care psychosis).<sup>46</sup> However, these terms do not represent distinct scientific entities and should therefore avoided in clinical practice.<sup>47</sup> Delirium should now be viewed as the umbrella term subsuming these multiple synonyms, allowing to improve communication among clinicians and researchers and, consequently, to improve its management. From 1980, year of publication of the DSM-III edition,<sup>45</sup> the DSM-IV firstly<sup>48</sup> and the DSM-IV-Text Revised version<sup>49</sup> some years later, have sensibly supported the growth in the field of delirium diagnosis, providing a highly inclusive description

of this syndrome and enabling physicians to improve detection. Currently, the fifth version of the DSM criteria (DSM-5) (Table 1)<sup>6</sup> is considered the gold-standard reference for the diagnosis of delirium, despite a recent study has shown that the way to adhere its criteria (*i.e.*, in a *overly-strict* or *relaxed* manner) may lead to different diagnostic sensitivity of clinicians.<sup>8</sup> The DSM-5 classification also includes an *attenuated delirium syndrome*, when the symptoms of delirium are not severe enough for a more specific diagnosis.<sup>4</sup> Key diagnostic features include an acute onset and fluctuating course of symptoms, inattention, impaired consciousness, and disturbance of cognition (*e.g.*, disorientation, memory impairment, language changes).<sup>6</sup> Occasionally, disturbance in sleep-wake cycle, perceptual disturbances (hallucinations or illusions), delusions, psychomotor disturbance (hypoactivity or hyperactivity), inappropriate behavior, and emotional lability are part of delirium.<sup>9</sup> Delirium may present in hyperactive, hypoactive, or mixed forms. In its hyperactive form, it is manifested as severe confusion and disorientation, developing with relatively rapid onset and fluctuating in intensity. In its hypoactive form, it is manifested by an equally sudden withdrawal from interaction with the outside world. Although these two forms are distinctive clinically, patients can wax and wane between them during the course of a day or the course of the disorder (mixed type). The mainly hypoactive form is more common in elderly patients, and has been generally associated with a worse prognosis.<sup>50</sup>

Delirium is essentially a clinical diagnosis, which means that this disorder is constantly at

**Table 1. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 edition criteria.**

- |                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A) A disturbance in attention ( <i>i.e.</i> , reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)                                                                                                                                                                   |
| 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                                                                                                                        |
| C) An additional disturbance in cognition ( <i>e.g.</i> , memory deficit, disorientation, language, visuospatial ability, or perception)                                                                                                                                                                                               |
| D) The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma                                                                                                         |
| E) 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 ( <i>i.e.</i> , due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies |

### Specify whether:

*Substance intoxication delirium*: this diagnosis should be made instead of substance intoxication when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention

risk to be undetected. Recognition of delirium, indeed, necessitates brief cognitive screening, astute clinical observation and accurate informant's interview, *i.e.*, a list of procedures and practices, which do not represent the routine approach to older patients of most clinicians in their everyday routine practice. As a result, delirium may result undetected in up to 80% of cases.<sup>16</sup> There are several possible explanations for this. Inouye has shown that the presence of sensory impairment, dementia, older age and the hypokinetic variant of delirium increase the odds of delirium to be undetected by nurses.<sup>17</sup> In this study, the simple clinical observation, without using standardized diagnostic tools led to a rate of underrecognition which was around 70%, significantly lower if compared to the rate of delirium detected by a team of researchers trained in the use of diagnostic tools.<sup>17</sup> However, also untrained physicians tend to frequently overlook delirium.<sup>51</sup>

There are more than twenty-four diagnostic tools for delirium, the most commonly used is the confusion assessment method (CAM).<sup>52</sup> The CAM has been validated in high-quality studies of more than 1000 patients, showing sensitivity of 94%, specificity of 89%, and high interrater reliability.<sup>9</sup> It has been translated into at least 12 languages and in the last years it has been adapted for use in Intensive Care Units (ICUs)<sup>53</sup> and Emergency Departments.<sup>54</sup> However, cognitive testing and training are recommended for optimum use, implying that lack of formal training and education may lead to unacceptable rates of underdiagnosis.

A new tool, which has recently been validated in the screening for delirium of older patients is the 4AT test<sup>55</sup> (Figure 1). The 4AT was developed because, none of the delirium screening tools existing appeared to have all the following features important in routine, non-specialist care: brevity (generally <2 min), no special training required, simple to administer (including in people with visual or hearing impairment), does not require physical responses, allows for assessment of *untestable* patients (those who cannot undergo cognitive testing or interview because of severe drowsiness or agitation) and incorporates general cognitive screening to avoid the need for separate tools for delirium and other causes of cognitive impairment.<sup>55</sup> In a prospective study of 236 elderly patients consecutively admitted to an acute geriatric ward and a department of rehabilitation, the 4AT has shown good sensitivity (89.7%) and specificity (84.1%) for delirium. Furthermore, the areas under the receiver operating characteristic curves for delirium diagnosis were 0.93 in the whole population, 0.92 in patients without dementia and 0.89 in patients with dementia, suggesting that the 4AT is highly specific in excluding delirium in patients without dementia and highly sensitive in highlighting delirium in patients with dementia.<sup>55</sup>

## Non-pharmacological and pharmacological prevention of delirium

Primary prevention with non-pharmacological multicomponent approaches is widely accepted as the most effective strategy for delirium. A recent metanalysis to evaluate available evidence on multicomponent non-pharmacological delirium interventions in

reducing incident delirium and preventing poor outcomes associated with delirium, identified 14 high-quality trials published from January 1, 1999 to December 31, 2013, for a total number of 4267 patients.<sup>56</sup> Overall, the studies demonstrated significant reductions in delirium incidence (OR, 0.47; 95% CI, 0.38-0.58), with four randomized or matched trials reducing delirium incidence by 44% (OR, 0.56; 95% CI, 0.42-0.76). These results are even more striking considering that the multicomponent non-pharmacological interventions

<b>[1] ALERTNESS</b>		
<i>This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.</i>		
Normal (fully alert, but not agitated, throughout assessment)		0
Mild sleepiness for <10 seconds after waking, then normal		0
Clearly abnormal		4
<b>[2] AMT4</b>		
<i>Age, date of birth, place (name of the hospital or building), current year.</i>		
No mistakes		0
1 mistake		1
2 or more mistakes/untestable		2
<b>[3] ATTENTION</b>		
<i>Ask the patient: "Please tell me the months of the year in backwards order, starting at December". To assist initial understanding one prompt of "What is the month before December?" is permitted.</i>		
Months of the year backwards	Achieves 7 months or more correctly	0
	Starts but scores <7 months/refuses to start	1
	Untestable (cannot start because unwell, drowsy, inattentive)	2
<b>[4] ACUTE CHANGE OR FLUCTUATING COURSE</b>		
<i>Evidence of significant change or fluctuation in: alertness, cognition, other mental function (e.g., paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24 h</i>		
	No	0
	Yes	4
<b>4 or above:</b> possible delirium +/- cognitive impairment		
<b>1-3:</b> possible cognitive impairment		
<b>0:</b> delirium or cognitive impairment unlikely (but delirium still possible if [4] information incomplete)		
<b>4AT SCORE</b> <input type="text"/>		
<b>GUIDANCE NOTES</b>		
Information and download: <a href="http://www.the4at.com">http://www.the4at.com</a>		
The 4AT is a screening instrument designed for rapid and sensitive initial assessment of cognitive impairment and delirium. A score of 4 or more <i>suggests</i> delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. Items 1-3 are rated <i>solely on observation of the patient at the time of assessment</i> . Item 4 requires information from one or more source(s), <i>e.g.</i> , your own knowledge of the patient, other staff who know the patient ( <i>e.g.</i> , ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.		
<i>Alertness:</i> Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. <i>AMT4 (Abbreviated Mental Test - 4):</i> This score can be extracted from items in the full AMT if done immediately before. <i>Acute Change or Fluctuating Course:</i> Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, <i>Are you concerned about anything going on here?; Do you feel frightened by anything or anyone?; Have you been seeing or hearing anything unusual?.</i> In general hospital settings psychotic symptoms most often reflect delirium rather than functional psychosis (such as schizophrenia).		

Figure 1. The 4AT test (available from: <http://www.the4at.com>).

were also able to significantly decrease the rate of falls, and, although in a non significant manner, the length of hospital stay and the rate of institutionalization.<sup>56</sup> Overall, these reduced complications of delirium and falls could save an estimated \$15 billion to \$17 billion annually.<sup>57</sup>

Historically, the most famous approach is the Hospital Elder Life Program (HELP),<sup>58</sup> a multi-component intervention strategy including reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilisation, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations. The programme, which has shown to be effective in diverse settings and populations,<sup>59-60</sup> should be implemented by a skilled interdisciplinary team, assisted by either nursing staff or trained volunteers.

Proactive geriatric consultation is another successful approach that has been assessed in a randomised controlled trial on patients with hip fracture.<sup>61</sup> According to this program, geriatrician provides advices and recommendations before and after surgery on the basis of ten structured modules, including hydration, pain management, nutrition, and mobilisation. Other non-pharmacological interventions have demonstrated that systematic detection of delirium, educational programs and training to nurse and medical health staff and caregivers, and early mobilization and rehabilitation are effective in reducing delirium.<sup>9</sup>

However, despite a critical mass of evidence and the efforts made by researchers to disseminate the results of these trials, policies to speed the implementation of such programs in the everyday clinical practice are nowhere on the horizon. Increasingly, efforts to prevent adverse events for older adults in the hospital seem stymied in a pernicious *know-do* gap: as the evidence grows, the state of implementation is not keeping up.<sup>57</sup> In Italy, there are not hospitals yet, which have adopted primary prevention programs such as HELP or have implemented standardized approaches to prevent delirium. According to a recent survey on physicians, nurses, psychologists and physiotherapists working in geriatric, internal medicine and neurological hospital's wards, both the knowledge of delirium and the competence to manage it is poor or very poor.<sup>62</sup>

Another problem with non-pharmacological primary prevention is that it has not shown to be effective in patients at low-risk for delirium,<sup>63</sup> indirectly suggesting the lack of specificity of this approach. Additionally, it is unclear whether single component interventions may result effective in preventing delirium. To address this problem, a recent systematic overview of systematic reviews of comparative studies concerning non-pharmacological intervention to treat or prevent delirium in older

patients found that only staff education, reorientation protocol and Geriatric Risk Assessment MedGuide software resulted effective in preventing delirium, albeit a wide confidence interval, likely due to the fact that only one study has been performed for each of them.<sup>63</sup>

There are more than a dozen studies of pharmacological prevention of delirium, none of them reporting a clear efficacy of the intervention over placebo. The review by Inouye<sup>9</sup> has included sixteen trials: in 6 trials, rates of delirium did not differ significantly between groups, in 8 trials, treatment reduced delirium rates but this reduction either had no effect on clinical outcomes (*i.e.*, ICU admission, length of hospital stay, complications, or mortality) or clinical outcomes were not measured, while in two of the trials, treatment resulted in potentially worse outcomes compared with placebo.<sup>9</sup> Haloperidol has been used in a study of delirium prevention among patients undergoing hip fracture surgical repair: the results showed that delirium incidence did not change after treatment while the duration of delirium decreased.<sup>64</sup> Olanzapine was found to reduce the incidence but increased the duration and severity of delirium (without reported clinical outcomes), and rivastigmine resulted in increased duration and mortality.<sup>9</sup> Based on these results, pharmacological prevention of delirium is not recommended by authoritative guidelines.<sup>65</sup>

Recently, in a multicenter, rater-blinded, randomized placebo-controlled trial performed in a cohort of 67 patients admitted to intensive care units and acute wards of 4 university hospitals and 1 general hospital, Hatta and colleagues<sup>66</sup> showed that ramelteon, an agonist of melatonin approved by the Food and Drug Administration for the treatment of insomnia, was effective to reduce the incidence of delirium in comparison to placebo. Taken at the dosage of 8 mg, ramelteon was associated with a lower risk of delirium (3% *vs* 32%), with a relative risk of 0.09 (95% CI, 0.01-0.69). Even after risk factors were controlled for, ramelteon was still associated with a lower incidence of delirium. This finding supports a possible pathogenic role of melatonin neurotransmission in delirium; however, further studies are needed to confirm its efficacy.

## Management of delirium

The treatment of delirium relies mainly on two different but complementary approaches: the first is to search and treat the underlying presumed acute causes; in addition to this approach the optimization of brain conditions is required. This involves ensuring that the patient with delirium has adequate oxygenation, hydration, nutrition, and normal levels

of metabolites, that drug effects are minimized, constipation treated and pain treated. It is worth noting that these activities are not less relevant than identifying the causes of delirium, both because brain is in a threatening condition during delirium and because physicians are able to identify the causes of delirium only in 70% of cases.<sup>7</sup> In line with this concept, physical restraints should be avoided as they can increase agitation and risk of injury.<sup>9</sup> In order to avoid the use of restraints some patients may require constant supervision. Detection and management of mental stress is also very important, as well as counseling for caregivers and proxies.<sup>28</sup> Various acronyms have been created in order to remind causes of delirium, such as DELIRIUMS (drugs, eyes/ears, low oxygen, infection, retention of urine or stool/restraints, ictal, undernutrition/underhydration, metabolic, subdural/sleep deprivation)<sup>67</sup> or VINDICATE (vascular, infections, nutrition, drugs, injury, cardiac, autoimmune, tumors, endocrine).<sup>68</sup> Brain neuroimaging may be sometimes helpful, but generally is indicated only in patients with history of recent fall, when an infectious or cerebrovascular event is suspected, or when both arousal is deeply impaired and focal signs are evident at the neurological examination.<sup>53</sup>

Non-pharmacological treatments are the first measure in delirium, unless there is severe agitation that places the person at risk of harming oneself or others. Avoiding unnecessary tubes and catheters, involving family members, having recognizable faces at the bedside, having means of orientation available (such as a clock and a calendar) may be crucial in improving the situation.<sup>9,65</sup> If this is insufficient, verbal and non-verbal de-escalation techniques may be required to offer reassurances and calm the person experiencing delirium, and only if de-escalation techniques fails or are inappropriate pharmacological treatment is indicated.<sup>65</sup> The T-A-DA method (*tolerate, anticipate, don't agitate*)<sup>69</sup> is a promising technique proposed by Flaherty for the non-pharmacological management of people with delirium, based on 13 years of experience at the Delirium Rooms of two acute hospitals. The philosophy relying on this approach is to create a restraint-free environment for the delirious patients: all unnecessary attachments are removed (IVs, catheters, NG tubes), which allows for greater mobility, and patient behavior is tolerated even if it is not considered normal as long as it does not put the patient or other people in danger.<sup>69</sup> Obviously, this technique requires that patients have close supervision to ensure that they remain safe.<sup>69</sup> Importantly, the staff try to anticipate patient's behavior, so that caregivers can plan required care, and staff is trained to avoid actions or behavior which may cause agitation.<sup>69</sup>

The use of drugs to control hyperactive symptoms of delirium is a strongly debated issue. Antipsychotics, particularly haloperidol, are the most commonly used drugs and certainly the most studied.<sup>65</sup> However, evidence of efficacy is weak and it is even weaker for the atypical antipsychotics, such as risperidone, olanzapine and quetiapine.<sup>9,65</sup> However, the National Institute for Health and Clinical Excellence advise for the use of haloperidol or olanzapine when there are psychotic symptoms or an agitated/aggressive behavior, which put at risk the patients or the health-care staff.<sup>65</sup> Benzodiazepines lack a reliable evidence base<sup>70</sup> and can themselves cause delirium or worsen it.<sup>32</sup> However, if delirium is due to alcohol withdrawal or benzodiazepine withdrawal or if antipsychotics are contraindicated (*e.g.*, in Parkinson's disease or neuroleptic malignant syndrome), then benzodiazepines might be considered as an alternative treatment.<sup>9</sup> Similarly, people with dementia with Lewy bodies may have significant side-effects to antipsychotics, and should either be treated with a small dose or not at all.<sup>65</sup> In the past the antidepressant trazodone has been proposed for the treatment of delirium, but it carries a risk of oversedation, and its use has not been well studied.<sup>71</sup>

## Conclusions

Delirium is a geriatric syndrome with a significant impact on the health status of older patients. It is highly prevalent among hospitalized patients and its occurrence is burdened by a series of negative outcomes and the elevated healthcare costs. However, this clinical condition is still undetected and sometimes trivialized by physicians, nurses and healthcare operators.

Therefore, comprehensive efforts to educate clinicians, academic students, healthcare staff and public about delirium, including about the disorder's importance, recognition, risk factors, prevention, and management, will be crucial to remedy under-recognition and mismanagement. Students and clinicians should be educated to think delirium as an emergency rather than a *normal* condition of the elderly or a problem related exclusively to alcohol consumption.

Delirium should also be taught in Medical School as the sixth vital sign<sup>72-73</sup> and may be regarded as a paradigm of care for the frailest old people. In fact, by daily monitoring the presence or absence of delirium during the whole length of hospital (or long-term care) stay, physicians may be enabled in identifying the people in whom the plan of care is failing from those in whom it begins to be effective. Delirium may also be useful to provide physi-

cians with some prognostic information, since persistent delirium is associated with increased risk of mortality.<sup>22</sup> Finally, delirium is as a potent and well recognized indicator of health-care quality across many settings,<sup>74</sup> and creation of incentives for system-wide process improvement to address the disorder will result in high-quality old age medical care overall.<sup>9</sup>

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