Chapter

Introductory Chapter: Delirium in Palliative Care

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1. Introduction

This introductory chapter aims at presenting an overview of delirium in palliative care. In this setting, it is one of the most frequent, but often misunderstood and difficult to treat, symptoms. Moreover, this is a matter of paramount importance as delirium is associated with a heightened rate of falls, increased cognitive and functional damage, and important patient and family psychological discomfort. In these particularly vulnerable patients, distress — expressed as a feeling of fear, anguish, humiliation — can be deleterious and is ethically unacceptable. Delirium is further associated with increased healthcare costs [1].

The term delirium derives from the Latin word deliria which literally means "to come out of the trace". It refers to a serious change in the mental state that leads to confusion and reduced awareness of the environment. This change is often accompanied by perceptual symptoms, such as hallucinations, or by cognitive symptoms such as disorientation and memory loss [2]. Nevertheless, rather than a symptom, delirium is a complex neurocognitive syndrome characterized by brain dysfunction with perturbations in the degree of consciousness, attention, thinking, perception, memory, psychomotor behavior, emotional sphere, and sleep–wake rhythm [3]. These clinical features differentiate delirium from a state of agitation that can be due to other undetected symptoms or physical needs (e.g., pain or full bladder).

2. The extent of the problem

In the palliative care setting, delirium represents a frequent clinical condition. In patients with advanced cancer, for instance, research showed that its prevalence varies from 13 to 88% [4]. Despite on admission delirium prevalence ranges between 13 to 42%, the higher prevalence occurs in the last 24 to 48 hours of life (terminal delirium), when the phenomenon becomes part of the complex picture of multiorgan dysfunction [5]; in this context, delirium is particularly difficult to treat, and it is considered as the predominant symptom for starting terminal sedation [1]. Overall, the reversibility is about 30% [6] and failure to respond to treatment may become indicative of a worse prognosis already after the first week of palliative care [7].

Despite its high prevalence and clinical significance, delirium is poorly sought; of note, Rainsford et al. [8] demonstrated that the diagnosis of delirium was performed only in 30% of in-hospice patients.

3. Mechanism and causes

The genesis of delirium is multifactorial. In general, all conditions that can induce a neuroinflammatory process are potential causes of delirium. Through the action of cytokines, chemokines, tumor necrosis factor-alpha, and other inflammatory agents (e.g., interleukin (IL)-1, and IL-6), a cascade of events is activated; it culminates in endothelial and microvascular damage and alterations of the blood–brain barrier. Again, disorders of neurotransmitter pathways such as the dopamine and acetylcholine systems, involving respectively dopamine excess or acetylcholine depletion, have a key role in the pathophysiology of delirium [9]. Further, in clinically ill patients, the impairment of cerebral oxidative metabolism is another potential mechanism to be considered [10].

Although drugs such as opioids, anticholinergic drugs, steroids, chemotherapies and metabolic disorders such as metabolic encephalopathy, nutritional deficiencies, electrolyte disturbances, dehydration are the main inducers of delirium, many conditions can provoke delirium. These causes include constipation, infections, hematological changes, paraneoplastic syndromes, brain neoplasms, central nervous system (CNS) secondarisms, seizure disorders, hypoxia, hypo/hypercarbia, and environmental factors. Several acronyms are commonly used to memorize and recognize potential causes. Sometimes the cause of the delirium cannot be found (**Table 1**).

I WATCH DEATH	Infections Withdrawal Acute metabolic causes Trauma CNS pathology Hypoxia Deficiencies Endocrinopathies Acute vascular Toxins or drugs Heavy metals
DELIRIUM	**D**rugs **E**lectrolyte disturbances **L**ack of drugs withdrawals **I**nfection **R**educed sensory input **I**ntracranial infection **U**rinary/fecal retention **M**yocardial/pulmonary causes
THINK	**T**oxic Situations such as shock, dehydration, deliriogenic medications, organ failure **H**ypoxemia **I**nfections **I**mmobilization **N**on-pharmacological interventions **K** or electrolyte problems
DIMES	**D**rugs **I**nfections **M**etabolic **E**nvironmental **S**tructural

Adapted from Bush [3].

Table 1.
Acronyms used to memorize possible causes of delirium in palliative care.

4. Clinical features

According to the type of psychomotor activity, there are three subtypes of delirium:

- Hyperkinetic form. It features agitation, restlessness, with or without hallucinations.

- Hypokinetic form. It is improperly referred to as "quiet delirium" or "acute encephalopathy". This type is featured by apathy, declined responsiveness, reduced psychomotor function, withdrawn attitude, lethargy, and drowsiness.

- Mixed form. The person may exhibit a fluctuation between the hypoactive and hyperactive subtypes where there is an alternation between the hypokinetic form and the hyperkinetic form.

In palliative care, the hypoactive and mixed are the most frequent subtypes of delirium. The lack of tangible agitation and the erroneous belief that the patient is drowsy because of illness, drugs administered, or an underlying depressed habitus, make this subtype very often misunderstood. This is a serious care gap as hypoactive delirium is frequently associated with perceptual disturbances and distress [11].

5. Diagnosis

According to the recently updated guidelines of the National Institute for Health and Clinical Excellence (NICE), the assessment of delirium should be performed in all hospitalized patients who are at risk of experiencing it, including oncological and terminally ill patients (respectively up to 88% and 50% incidence) [12]. Despite this and other recommendations, the lack of a systematic assessment for delirium is a serious issue.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V, 2013) [2] defined delirium based on four criteria, namely:

- An alteration of consciousness characterized by a reduced ability to focus, maintain or shift attention.

- A cognitive change (such as memory deficit), language alteration, and the development of a perceptual disorder (such as delusion) that are not dependent on a pre-existing condition of dementia.

- A development of the disorder in a short time with daily fluctuations.

- Evidence collected from the medical history, physical examination and laboratory investigations that show that the disorder is caused by physical conditions resulting from a serious pathology, problems of alcohol abuse or drug intoxication, or withdrawal.

Of note, despite DSM-V is the gold standard for the diagnosis of delirium, it cannot be easily administered by non-psychiatrist personnel including nurses. This is a great limitation as nurses have constant contact with the patient throughout the day, and they could efficiently evaluate modifications in the patient's attention and

awareness over time. Furthermore, diagnostic instruments for delirium are mostly based on the DSM-III or IV. Thus, many efforts are being made to validate updated versions or to develop new tools [13].

In addition to the DSM-V, the International Classification of Diseases (ICD) classification from the World Health Organization (WHO) is conventionally adopted. The 11th Revision (ICD-11) defined delirium as a neurocognitive disorder characterized by '*disturbed attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (i.e., reduced orientation to the environment) that develops over a short period of time and tends to fluctuate during the course of a day, accompanied by other cognitive impairment such as memory deficit, disorientation, or impairment in language, visuospatial ability, or perception. Disturbance of the sleep-wake cycle (reduced arousal of acute onset or total sleep loss with reversal of the sleep-wake cycle) may also be present. The symptoms are attributable to a disorder or disease not classified under mental and behavioural disorders or to substance intoxication or withdrawal or to a medication*' [14]. Thus, this approach includes more details on non-cognitive features, and it seems to better address the problem of the diagnostic and pathophysiological difference between delirium and states of dementia.

Practically, suspicion of delirium can be induced by changes or fluctuations in usual behaviors. These fluctuations can occur in the day's course, although more severe symptoms usually manifest during the evening and the night. The diagnosis of delirium requires healthcare professionals who are trained and competent in the diagnosis of delirium. It can be made by referring to tools or simple cognitive tests, for example by having the patient recite the days of the week or the months of the year. Among the most commonly used instruments, there are the Confusion Assessment Method (CAM) [15] and the Delirium Observation Screening (DOS) scale [16]. Although the choice of tool to be used depends on the level of training of the staff, commonly used tests may require a short training period. About CAM, the training manual is available at the website of the American Geriatrics Society [17]. On the contrary, the DOS can be administered without specific training.

The CAM method was also validated in palliative care [18]. It consists of a 9-item questionnaire and a diagnostic algorithm encompassing four items/features. In particular, the features "acute onset and fluctuating course" and "inattention" are needed, along with "disorganized thinking" or "altered level of consciousness" [3]. The DOS scale is a 13-item tool. Since each item can be scored 0 or 1, the total score can range from 0 to 13 and a score of ≥3 indicates delirium. Similar to CAM, it was validated in palliative care patients [19].

Among the other tools, there is the 5-item Nursing Delirium Screening Scale (Nu-DESC) [20]. As Bush et al. [21] highlighted, it offers poor sensitivity for detection of the hypoactive form and is not validated in palliative care. Other tools are the NEECHAM Confusion Scale [22], the 13-item Delirium Rating Scale (DRS) [23] and the Memorial Delirium Assessment Scale (MDAS). This latter was also validated in palliative care [24].

6. Prevention

Prevention is based on early recognition of any precipitating causes. Pharmacological interventions, including antipsychotics, are not recommended as prophylactic strategies. For this purpose, the NICE guidelines recommend only non-pharmacological interventions [12]. Avoiding polypharmacy, in particular delirogenic drugs such as benzodiazepines, opioids, and corticosteroids is of paramount importance for delirium prevention. Moreover, in all frail patients, and even more in the presence of risk factors for delirium, multi-component preventive

interventions must be implemented. These approaches are based on temporal–spatial reorientation, mobilization programs, sleep hygiene, maintenance of adequate hydration, and provision of visual and hearing aids, if used by the patient.

7. Therapy

Treatment of delirium often requires the combination of pharmacological (e.g. *major* tranquilizers) and non-pharmacological (reorientation, communication, and sleep hygiene) interventions tailored to the patient.

7.1 Causal therapy

Clinical and physical assessment including appropriate laboratory and radiological investigations can help identify the cause of the delirium. Moreover, rapid recognition and treatment of the underlying cause can often avoid resorting to more complex symptomatic pharmacological and non-pharmacological strategies. Treatment of the underlying cause may include:

- Correction of potential fluid or electrolyte disturbances
- Removal of potential pharmacological agents
- Removal of potential physical issues
- Adequate pain assessment (also looking for non-verbal signs in cognitively impaired individuals) and management [25]

For evaluating the delirogenic potential of drugs, optimizing the medication use, the DEL-FINE score can be used. Drugs (and drug withdrawal) are assigned a score ranging from "three = strong delirogenic potential" to "zero = no delirogenic potential". For instance, a score of three is assigned to amitriptyline, atropine, clomipramine, and the withdrawal of benzodiazepines, ethanol, and opioids [26].

Nevertheless, the causal treatments can often be difficult as, even when the root cause is identified, it cannot be reversible. Therefore, symptomatic treatments are often used. These treatments include pharmacological therapy and non-pharmacological strategies.

7.2 Symptomatic treatment

Drugs useful for managing delirium may include antipsychotics and in selected cases benzodiazepines including diazepam, lorazepam, and midazolam. The latter class of drug can be indicated in the case of alcohol withdrawal or epilepsy delirium. Other drugs such as α-2 receptor agonists, psychostimulants, cholinesterase inhibitors, and melatonergic drugs are also used although no recommendations have been released so far.

About antipsychotics, it was demonstrated that both conventional (e.g., haloperidol) and atypical antipsychotics including olanzapine, risperidone, quetiapine, aripiprazole are effective in the treatment of delirium. Of note, the efficacy and safety of haloperidol at low doses (up to 10 mg/day) are comparable to those of atypical antipsychotics such as risperidone, olanzapine, and quetiapine [27].

In palliative care, haloperidol is one of the most used drugs. It is commonly administrated for the treatment of delirium and for the prevention and/or

treatment of nausea/vomiting (including the opioid-induced ones) [28]. Even if it represents the preferred drug in the treatment of delirium, its use is limited by concern for side effects. Usually, the onset of extrapyramidal disorders is dose-dependent and cardiotoxicity — QTc prolongation or torsades de pointes (with a QTc > 450–500 ms immediate drug withdrawal is recommended) — generally rarely occurs for low doses [29]. However, in patients under palliative care, many factors such as the severity of the underlying disease and organ damage, comorbidities, cachexia, hypoproteinemia, advanced age, and polytherapy can increase the risk of side effects. For example, haloperidol pharmacokinetics (**Table 2**) mostly depends on CYP2D6 functioning.

About doses, in mild delirium with no underlying psychiatric illness haloperidol can be used at the dose of 0.5–1 mg bid, both oral or subcutaneous (0.25–0.5 mg for elderly patients). In moderate delirium, the dose can be doubled. In severe and terminal delirium the dose is 0.5–4 mg both oral or subcutaneous (possibly repeated every 45–60 min) with a maximum of 2–20 mg/day.

Among the other antipsychotics, risperidone (0.5–4 mg/day) could be useful in patients requiring high doses of haloperidol or at high risk of developing haloperidol-induced extrapyramidal or cardiac effects. Olanzapine (2.5–10 mg/day, orally or i.m.) has an efficacy comparable to haloperidol but can induce sedation due to its antihistaminergic action; thus, it is not recommended in elderly patients with dementia or hypoactive delirium, although its use can be beneficial for the regulation of the sleep–wake rhythm [30]. Quetiapine (from 12.5–25 mg/day up to an average dose of 50–175 mg/day) has an intense antihistaminergic activity which can worsen confusion. It can also cause hypotension. Finally, the first-generation antipsychotic agent levomepromazine is also used to address intractable nausea or vomiting, and for severe delirium in the last days of life. This phenothiazine is administered orally or by subcutaneous bolus injection (10–25 mg, repeatable as required after 2 hours) or continuous subcutaneous infusion (25–100 mg/day).

It must be emphasized that the efficacy of antipsychotics and other pharmacological interventions for the treatment of delirium in palliative care is still under debate [31, 32]. The use of antipsychotics and/or other medications becomes inevitable for the management of hyperactive or mixed delirium with severe agitation and anxiety but they must be given short-term and at the lowest effective dose. Symptomatic therapy of delirium is also mandatory if it becomes a source of suffering.

T1/2	*p.o.*: after a single dose (e.g., 2–4 mg) 14.5–36.7 hrs; up to 21 days after chronic administration *i.v.*: 10.1–26.2 hrs *i.m.*: 20.7 hrs (decanoate i.m.: 21 days)
Onset of action	*p.o.*: > 1 hr. *s.c.*:10–15 min *i.v.*: seconds
Duration of action	*s.c.*: up to 24 hrs *i.v.*: 4–6 hrs
Vd	9.5–21.7 L/kg
PPB	92%
Cl	0.9–1.5 l/kg/h

Abbreviations: p.o., oral; i.m., intramuscular; s.c., subcutaneous; i.v., intravenous; Vd: Volume of distribution; PPB, Plasma protein binding; Cl, Clearance.

Table 2.
Main haloperidol pharmacokinetics.

7.3 Non-pharmacological strategies

Non-pharmacological approaches such as behavioral and educational interventions, and cognitive activities as well as methods aimed at improving sleep, vision, and hearing functioning, are useful for addressing the issue of delirium. Encouraging family visits is another effective non-pharmacological strategy to be strengthened.

Communication strategies play a role of fundamental importance. Among the many examples reported, those proposed by the Mother Élisabeth Bruyère health care organization seem to be simple and effective. According to these suggestions, it is mandatory to use a calming voice, speak slowly and in short simple sentences, present one idea at a time and if needed, repeat the sentence. It is also suggested to avoid contradicting the person, accepting his/her arguments. Finally, rapid movements or gestures that can be misinterpreted as aggressive must be avoided [33].

8. Conclusion

Although clinical experience and scientific evidence underline that delirium can lead to multiple clinical and healthcare problems and that its timely recognition and treatment can induce a remission of the clinical picture, screening of cognitive conditions and delirium remains an unmet need. As the efficacy of pharmacological treatments has not yet been proven, greater efforts must be focused on prevention and early diagnosis. In short, the strategies to be adopted for prevention are quite codified. It is crucial to recognize potential risk factors and, since according to the ICD-11, delirium is essentially featured by disturbed attention and awareness, a careful evaluation of changes in usual behaviors is mandatory. The suspicion, in turn, must direct towards the administration of validated tools. Although the effectiveness of antipsychotics and other pharmacological treatments is still questioned, the use of these drugs is especially necessary for the treatment of hyperactive or mixed delirium featuring severe agitation and self or hetero-injurious behaviors. The hypoactive subtype, although very frequent, is little recognized and requires multicomponent non-pharmacological approaches.

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