Drug-associated delirium in cancer patients

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1. Delirium definition and clinical characteristics

Delirium is a disorder of consciousness and attention; it is one of the most common neurological complications seen in general in the medically ill hospitalised patient, and is also common in the medical oncology ward [1,2]. Delirium seen in different settings contributes to defining the diagnoses of diverse specificities: postoperative delirium, delirium in the ICU, withdrawal delirium or delirium tremens, terminal restlessness and others.

Before considering specific clinical contexts or diagnoses it is necessary to recognise the general characteristics of delirium as a syndrome and its clinical implications. There is now almost universal agreement on the definition of delirium, or acute confusional state, according to the DSM. However, acute confusional state is a synonym of delirium and is still a useful clinical definition, particularly in non-English-speaking countries. Delirium is a syndrome and not a disease, and its pathophysiology has not been fully elucidated. Different theories have favoured alternatively the failure of a common final pathway – mainly regulating the cholinergic projection to the cerebral cortex – or a more diffused or multifocal impairment of different areas in the CNS which contribute to maintaining the normal level of vigilance and attention.

Clinically, delirium is an altered state of consciousness with reduced awareness of self and of the environment, which may present with inability to think and talk clearly and rationally; at times there are hallucinations, delusions, disorientation with respect to time and space, altered sleep-wakefulness cycle and cognitive impairment. Psychomotor agitation can be present in the hyperactive deliria, but hypomotor deliria will show psychomotor retardation and somnolence. One extremely important clinical aspect of delirium is fluctuation of the clinical presentation; symptoms can change suddenly, often under repetitive conditions (such as in the classic nocturnal worsening often described in the elderly with cognitive impairment and called in the past ‘sundowning’). These sudden changes from a near-to-normal mental state to frank delirium often surprise nursing and medical staff and find them unprepared in front of the patient and a distressed family.

The clinical presentation of delirium varies, and no defined association of symptoms and signs can be considered specific [3]. For the purposes of diagnosis and clinical evaluation it is easier to use the DSM criteria as they give a systematic approach to the core clinical elements [4]. All four of the following criteria have to be fulfilled to make a diagnosis.

Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain and shift attention; to fulfil this criterion the levels of both consciousness and attention need to be affected.

Change in cognition (such as memory deficit, disorientation and language disturbances) or perception disturbances that are not better explained by a pre-existing established or evolving dementia. Testing cognitive function with simple bedside examinations such as the MiniMental test is often enough to describe disorientation with respect to time and space, difficulties in performing calculations and in writing and simple memory tests. In the elderly with previous cognitive failure or being already demented it may be difficult to distinguish a failure in cognition as part of a chronic condition from a newly developing delirium (Table 1). Perceptual disturbances are illusions and hallucinations. Most often hallucinations are visual, but they are present only in a percentage of delirious patients and their absence is not a determinant for the diagnosis [3].

The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. This criterion specifically aims to distinguish delirium from chronic conditions, particularly from dementia (Table 2), but in elderly patients with longstanding medical complications it may be difficult to differentiate the contribution of pre-existing neurological factors and incident acute factors. This distinction may be academic in
many cases but it is relevant, as described below, to explain many complex cases. Also in the case of advanced cancer patients, with multiple clinical problems and polypharmacy, delirium can be a long-lasting complication either characterising the final phase of the disease or being a reversible condition [5].

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition. This last criterion conceptually distinguishes delirium from primary psychiatric disease (mainly acute psychosis) (Table 1). In the old taxonomy this criterion was included in the construct of organic brain disorder or of recognising an organic cause of psychiatric symptoms. This terminology is no longer accepted by the latest DSM versions, but it can be used to clarify the scope of criterion 4.

Based on the clinical presentation, delirium is distinguished into hypoactive, hyperactive and mixed types. The hyperactive deliria are usually associated with delusions and hallucination, disruptive or agitated behaviour and often worsening of symptoms during the night. Hypoactive deliria, in contrast, show a somnolent detached state of consciousness and may be missed or mistaken for depression if the patient is not assessed more carefully with formal mental task testing. Mixed hyper- and hypoactive presentations are most frequent and the transition from hyperactive to hypoactive delirium, stupor and coma can be seen as one of the ways of dying.

2. Frequency and assessment

The frequency of delirium is high in the acutely hospitalised patient population, with a prevalence which may be around 10% in the medical ward (excluding the cases of postoperative delirium). The most relevant patient populations seen by oncologists are summarised in Table 2, which shows that the frequency of this complication can not only increase in more advanced disease, but also that it is common in the elderly and as well as in the general oncology ward [6,7].

The diagnosis of delirium should be based on clinical observation and examination, and can be aided by the systematic use of screening tools to detect cognitive failure, such as the Minimental state examination, or tests specifically

| Table 1 – Main differential diagnoses of delirium. |
|----------------|----------------|----------------|----------------|
| Clinical features | Delirium | Dementia | Acute psychosis |
| Onset | Acute | Slow | Acute |
| Circadian course | Fluctuating | Stable | Stable |
| Level of consciousness | Affected | Sparred unless in severe cases | Sparred |
| Attention | Impaired | Initially spared | Can be impaired |
| Cognition | Impaired | Impaired | Can be impaired |
| Hallucinations | Poorly systematised and fleeting | Often absent | Often auditory |
| Delusions | Increased, reduced mixed with alternating course | Often absent | Sustained and systematised |
| Psychomotor activity | Often normal | Can vary, with bizarre behaviour depending on the psychosis |
| Involuntary movements | Asterixis, myoclonus or tremor can be present in some subtypes | Absent in most forms | Absent |
| EEG | Abnormala | Abnormala | Normal |

EEG, electroencephalogram.
*See text for more details.

| Table 2 – Frequency of delirium in different patient populations admitted to hospital, hospice or home palliative care programme. |
|----------------|----------------|----------------|
| Population | Prevalence (%) at admission | Incidence (%) during admission |
| Elderly ≥65 admitted to acute hospital unit | 10.5 | 31.3 |
| Elderly ≥70 admitted to acute hospital unit | 25.0 | |
| Elderly ≥70 admitted to acute hospital unit | 18.0 | |
| Medical oncology unit | 18.0 | |
| Medical oncology unit | 16.5 | |
| Hospice | 28.0 | 42.0 |
| Palliative care unit including home care | 45.0 | |
| Dying cancer patients in specialised palliative care unit | 80 | |

Modified from Caraceni and Grassi [2].
Table 3: Diagnostic and etiological directions in case of delirium in the oncological patient (excluding postoperative delirium).

| Action                                      | Assessment                                                                 |
|---------------------------------------------|-----------------------------------------------------------------------------|
| Rule out structural brain lesions           | Oncological history, neurological examination, brain imaging if unclear     |
| Rule out seizures, non-convulsive status epilepticus | When brain lesions are known or suspected EEG may be necessary |
| Rule out acute psychotic reactions          | History of psychiatric disease, young age, psychogenic unresponsiveness or catatonia |
| Identify potentially toxic agents           | Specific (chemotherapy toxicity, brain RT, high-dose ifosfamide, antivirals, immunosuppressive agents) |
| Consider posterior reversible encephalopathy (MRI required) | All generic psychoactive drugs |
| Reduce the risk of drug interactions       | Any drug can be involved; check metabolic pathways in the hepatic microsomal oxidising system |
| Check metabolic factors and vitamin deficiency | Renal failure, hepatic failure, electrolyte imbalance, hypoxia, acidosis, B1 (thiamine) deficit |
| Think of rarer conditions                  | Paraneoplastic neurological syndromes (usually associated with unknown or initial neoplastic disease) |

EEG, electroencephalogram; MRI, magnetic resonance imaging; RT, radiotherapy.

designed to screen potential delirium cases, such as the Nursing Delirium Screening Test (NuDESC). In the validation study by Gaudreau et al [8], the NuDESC proved sufficiently sensitive to be used as a screening tool in oncology, although recently a study on the detection of postoperative delirium in the elderly showed that sensitivity was too low in this population [9]. Still, a more careful and systematic approach [10] adopted by the nursing staff is a reasonable strategy and is to be recommended in oncology and particularly in palliative care settings such as a hospice. The diagnosis finally relies on the DSM criteria and requires specific expertise. The main differential diagnoses and their characteristics are listed in Table 1.

3. Diagnostic procedures

As with any new neurological sign or symptom, in a patient with cancer a change in mental status requires a neurological examination and, if available, neurological consultation. In the case of neurological findings suggesting a structural brain lesion, imaging should be performed. In a patient with cancer, depending on the stage of the disease, it is not rare for delirium, even without focal neurological symptoms, to be an initial presentation of brain or meningeal metastases, as demonstrated in 15% of patients in one case series [11].

Encephalitis of infectious origin can occur particularly in immunocompromised patients and occurs not infrequently after bone-marrow transplantation conditioning chemotherapy.

Cancer patients are at increased risk of posterior reversible encephalopathy syndrome (also known as posterior reversible leukoencephalopathy), a syndrome that is probably caused by damage to the brain vasculature and is found in association with immunosuppressive therapies ( cyclosporine, tacrolimus), as a complication of transplant, high-dose multidrug chemotherapy (cytarabine, cisplatin, gemcitabine, vinorelbine, FOLFOX regimen and methotrexate) and of the new biological therapies such as anti-angiogenetic antibodies and others (bevacizumab, rituximab, bortezomib and motesanib) [12]. The syndrome usually includes seizures, cortical visual deficit and headache, but at presentation changes in mental status, or delirium, can dominate the clinical picture.

When seizures are not associated with obvious generalised or focal convulsions, the differential diagnosis of delirium can be difficult. In fosfamide encephalopathy obtundation of consciousness and myoclonus reflect a continuous seizure-like activity in the electroencephalogram (EEG).

Patients with a history of psychiatric disorders can develop acute psychotic reactions, especially when confronted with serious medical illness such as cancer, with clinical presentations such as unresponsiveness and catatonia that can be confused with delirium. These patients are usually young, and the clinical context helps to exclude the most common causes or risk factors of delirium. True paraneoplastic neurological syndromes presenting with altered mental state (limbic encephalitis) are indeed very rare; specific expertise is required for their diagnosis and they are usually found in association with initial cancer with the onset of the neurological syndrome preceding the diagnosis of cancer [13].

Table 3 summarises the elements which can guide clinical reasoning and a diagnostic strategy when faced with a cancer patient with delirium that is not occurring after surgery and general anaesthesia. The clinical context, risk factors, prognosis, associated symptoms and goals of care will influence the diagnostic path and completeness or futility of any interventions eventually required.

4. Pathophysiology, risk factors and aetiology

The complex pathophysiology of delirium is beyond the scope of this chapter [14], but it is important to remember that the brainstem, thalamic and hypothalamic projections into the cortex are implicated in the regulation of normal vigilance and in modulating the level of consciousness between the physiological states of wakefulness and sleep. This system has a neurotransmitter organisation, including acetylcholine, dopamine, serotonin, histamine and γ-aminobutyric acid.
Drug toxicity, in the setting of medical therapy or abuse, is an extremely frequent cause of delirium (Table 5). The ability to identify one drug as a cause for delirium depends on anecdotal clinical observation, pharmacological knowledge and clinical studies. One recent systematic review of the literature supports the association of psychoactive medications, considered together, and use of opioids, which have an independent increased risk of developing delirium in cancer patients [18]. Another review focusing on patients at risk of developing delirium (elderly patients admitted to hospital for medical reasons or in the postoperative period) suggests avoiding the use of benzodiazepines in this population [19].

Experimental human studies demonstrated that anticholinergic drugs such as scopolamine, ditran and atropine can cause delirium depending on dosage [20]. Lower doses usually produce somnolence (scopolamine 0.3–0.8 mg), higher doses (atropine 5 mg, scopolamine = 1 mg) agitated florid delirium; paradoxical effects of low doses have also been demonstrated.

In fact the list of drugs with anticholinergic activity is very long (Table 6), and such drugs should be used with caution, especially in the elderly with poor general conditions, multiple medical problems and polypharmacy. Unfortunately all these conditions are commonly found in cancer patients of advanced age, with progressive disease and who need appropriate palliative therapy for symptom control. Appropriate selection of drugs with simplified metabolic pathways and lack of interference would reduce the risk of adverse reactions.

### Table 4 – Factors associated with the risk of developing delirium resulting from multivariate analysis in cancer. Modified from Caraceni and Simonetti [17].

| Potentially specific predisposing factors:                       |          |
|---------------------------------------------------------------|----------|
| Advanced age                                                  |          |
| Previously impaired cognition                                  |          |
| History of delirium                                           |          |
| Metastatic CNS lesion                                         |          |
| Non-specific factors associated with disease progression/      |          |
| deterioration of general function:                           |          |
| Functional impairment                                         |          |
| Severity of illness                                           |          |
| Low albumin                                                   |          |
| Bone metastases                                               |          |
| Haematological malignancies                                   |          |
| Potentially specific incident factors:                        |          |
| Metabolic abnormalities                                       |          |
| Metastases to brain or meninges                                |          |
| Opioids (dose-related)                                        |          |
| Benzodiazepines                                               |          |
| Corticosteroids (dose-related)                                |          |

(GABA). An imbalance in some of these neurotransmitters is thought to have a primary role in delirium pathophysiology. An impaired cholinergic transmission from the brainstem and enhanced dopaminergic tone are also thought to play a causal role in delirium [14]. All drugs with anticholinergic activity are sedating and can cause delirium. The cholinergic hypothesis can also explain the increased susceptibility to delirium of the elderly and of patients with cognitive impairment or dementia, considering that all these situations are characterised by a reduced function of the cholinergic central activating system.

Delirium may have many causes, but in most cases a multifactor model can best explain its pathophysiology, with the combination of some predisposing conditions and incident noxious factors. This model was suggested by clinical observation in early studies on the syndrome [15] and has been confirmed by well-conducted cohort studies demonstrating that the combination of specific baseline conditions – such as advanced age, cognitive impairment, dementia and severity of illness - was associated with an increased incidence of delirium when combined with new factors, occurring during the hospital stay, in elderly patients [16]. Among incident factors, infections and medications were noted. The results, summarised in Table 4 [17], can be interpreted by classifying the associated factors such as structural lesion or functional abnormalities potentially impairing specific CNS functions (brain metastases, previous cognitive failure), being direct or indirect indicators of progression of the disease (metastases), or of poor general condition and toxic factors (benzodiazepines, opioids and steroids).

#### 4.1. The role of drug toxicity

Opioids are very important drugs for the quality of life of cancer patients, and their role in the management of pain and other symptoms cannot be underestimated. Opioids have CNS side-effects which include sedation, impairment of cognitive functions [21] and delirium. The central side-effects of opioids are usually dose-related and can be the main dose-limiting side-effects in dose titration to obtain better pain control. High doses of opioids are associated with myoclonus, delirium, hyperalgesia and eventually seizures [22,23]. Symptoms of CNS toxicity can also occur at low doses in individual cases [24,25]. Recently an independent statistical association with the use of doses >90 mg of oral morphine per day was found to be associated with an increased risk of developing delirium [18]. This means that we have to carefully monitor the mental status of patients on significant opioid doses and seek for signs or symptoms of CNS toxicity such as myoclonus and hallucinations. Conversely, the mistake should not be made of blaming opioids for any complication. Most cases of delirium will be recognised in complex situations and with multiple factors together with, if not alternative to, opioid toxicity alone.

Renal failure can make more difficult the choice of an opioid and increase the risk of delirium due to the accumulation of toxic metabolites. Drugs which exhibit the safest pharmacological profile, when renal failure occurs, are buprenorphine, fentanyl, alfentanil, remifentanil and sufentanil [26]. However, simple clinical measures include the choice of an opioid with least pharmacological interactions (morphine is the first choice), providing hydration if metabolite accumulation occurs because of reduced renal clearance, reduction of the dose and substitution of the opioid if toxicity is suspected. A palliative care consult is helpful to optimise opioid pharmacotherapy in these cases.

4.3. Steroids

The use of steroids is very common in cancer patients. High doses and prolonged administration can induce delirium, also called in the past steroid psychosis [27]. Also sudden discon- tinuation of steroids can cause hypocortisol syndrome and delirium. It is very important that steroids are given for a limited amount of time and tapered slowly when no longer nec-

The symptoms can range from depression to mania and psychosis. The true incidence of mental changes related to steroid administration in palliative care is unknown. High doses are often reported to cause euphoria.
4.4. Serotonin syndrome

This significant toxic reaction became more frequent with the spread in the use of serotonin selective inhibitors (SSRIs, e.g. paroxetine) such as antidepressants. It is usually seen after the addition of a serotonergic drug to a drug regimen already containing serotonin-enhancing drugs, and it combines signs of encephalopathy (confusion, restlessness, myoclonus, hyper-reflexia, rigidity and coma) and of autonomic instability (fever, diaphoresis, diarrhoea, flushing, tachycardia, tachypnoea, blood-pressure changes, midriasis, shivering and tremor). It may be fatal or may have a more benign course. Interactions of different drugs, often used in cancer patients, should be monitored (SSRI with tramadol, ketobemidone and venlafaxine). Table 7 lists a number of cases reported in the literature of drug combinations leading to serotonin syndrome. Caution should therefore be exercised not only in the use of the drugs reported but with all agents with serotonergic action, such as duloxetine and tapentadol, in particular when considering their use in combination with other serotonergic agents.

4.5. Drug pharmacological interactions

The role of metabolic interactions as a cause of toxicity is more and more likely as the number of drugs increase and the general patient condition deteriorates. The induction or inhibition of hepatic enzyme metabolism is an important source of variability in drug effects and can lead to unexpected toxic reactions. The P450 system comprises a family of more than 20 isoenzymes, among which the CYP 2D6 and CYP 3A4 metabolise 80% of known drugs. A relatively recent review [29] reports on a number of examples of drugs commonly used in oncology and palliative care that have high or moderate probability of interacting with the same metabolic pathways and of leading to unexpectedly high or low levels of a drug, with the consequence of under- or over-dosing; examples of such drugs include methadone, codeine, oxycodone, haloperidol, tricyclic antidepressants (TCAs), SSRIs, monoamine oxidase (MAO) inhibitors, benzodiazepines, macrolides, azoles, rifampin and antifungals. Table 8 shows a list of interactions that can be particularly relevant in the management of symptoms in cancer patients.

However, the clinical role of drug interaction in producing specific effects may be very difficult to ascertain; laboratory in vitro data may not be applicable to the clinical situation, while in vivo other circumstances may be operating to change the effect that was expected on the basis of laboratory data. For instance, in dogs the co-administration of ketoconazole and midazolam resulted as expected in a reduced elimination of midazolam but did not affect the elimination of fentanyl [30]. Case reports suggest that these interactions are indeed at times important [31,32].

| Drug Combinations | Drug Combinations |
|-------------------|-------------------|
| Fluoxetine        | Carbamazepine     |
|                  | Pentazocine       |
|                  | MAOIs             |
|                  | Moclobemide       |
|                  | Nefazodone        |
|                  | Tramadol          |
|                  | Mirtazapine       |
| Fluvoxamine       | Alone              |
|                  | Nefazodone        |
| Paroxetine        | Risperidone       |
|                  | Moclobemide       |
| Sertraline        | Isocarboxazide    |
|                  | Nortriptyline     |
|                  | Tranylcypromine   |
|                  | Erythromycin      |
|                  | Buspirone         |
|                  | Loxapine          |
| Tryptophan        | Fluoxetine        |
|                  | Non-selective MAOIs |
|                  | Clomipramine      |
| Venlafaxine       | Alone              |
| Trazodone         | Buspirone         |
|                  | Nefazodone        |
| Moclobemide       | Citalopram        |
|                  | Imipramine        |
| Meperidine        | Iproniazid        |
|                  | MAOIs             |
|                  | Moclobemide       |
| Phenelzine        | 3,4-Methylenedioxy-methamphetamine |
| Dextrometorphan   | Non-selective MAOIs |
| Dothiepine        | Alone              |

**Table 7 – Serotonin syndrome reported in cases of administration of serotonin reuptake inhibitors alone or in combination with other serotonergic substances.**

**Table 8 – Potential drug interactions with potential elevation of blood plasma levels of central nervous system active agents.**

| CYP2D6 inhibitors | Drugs metabolised by CYP2D6 whose plasma levels can increase when combined with inhibitors |
|-------------------|--------------------------------------------------------------------------------------------|
| Cimetidine        | Oxycodone |
| Desimipramine     | Tramadol |
| Fluoxetine        | Haloperidol |
| Paroxetine        | Risperidone |
| Haloperidol       | Fluoxetine |
| Sertraline        | Paroxetine |
| Venlafaxine       | Venlafaxine |
|                   | Desimipramine |

| CYP3A4 Inhibitors | Drugs metabolised by CYP3A4 whose plasma levels can increase when combined with inhibitors |
|-------------------|--------------------------------------------------------------------------------------------|
| All imidazole antifungals | Fentanyl |
| Fluoxetine        | Alfenyl |
| Norfloxacin       | Methadone |
|                   | Alprazolam |
|                   | Midazolam |
5. Delirium management

Screening of potential etiologies, starting with an accurate medication list, is the first step in delirium management; consequently a first recommendation is to withdraw all medications that are not absolutely necessary. Very often finding the aetiology is delayed, and the time to recovery after modifying etiological factors can be significant. In a number of cases, as already discussed above, the multifactor pathophysiology can be part of a complex clinical picture which does not allow for recovery or is even part of the dying process. All of these conditions require symptomatic management – in particular to control hallucinations, delusions and psychomotor agitation – be it temporary until recovery or continuously until death. The first-line pharmacological intervention for delirium is neuroleptics, and haloperidol is the first-choice drug according to all clinical guidelines [38–41]. In patients with mild to moderate delirium, oral medication may be indicated, but more difficult cases will require parenteral administration. Haloperidol initial dose can vary from 0.5 to 1 mg, orally or parenterally b.i.d., according to patient age, and should be titrated in the following hours depending on the severity of delirium symptoms. Titration of the dose is a fundamental step before a real lack of clinical response can be documented, as many treatment failures are failing this recommendation. Parenteral haloperidol can be used via intramuscular administration. This can be necessary in patients without an IV line and with very disruptive behaviour, otherwise an IV infusion can also be adopted. The use of haloperidol should be preceded by cardiac monitoring with electrocardiography (ECG), according to some national regulations, while its intravenous infusion is not officially approved, although commonly used in different settings of care. Prolongation of the Q–T interval on the ECG may contraindicate the use of haloperidol. This caveat is based on reports of fatal cardiac arrhythmia following haloperidol administration.

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Pharmacological treatment of delirium aims at patient tranquillisation, abolishing hallucinations and delusions, reducing psychomotor agitation, and improving night-time sleep. Haloperidol, risperidone or olanzapine, while sharing a strong tranquilising action, are not primarily sedating drugs and haloperidol has the least sedating properties among all the neuroleptics. If required, more sedating neuroleptics can be used: for example quetiapine (25–50 mg b.i.d.), eventually giving a higher dose at bed-time. If this approach fails, more specific drugs can be added to control symptoms by keeping the patient sedated, including antihistamines, benzodiazepines and eventually alfa-2 agonists (clonidine, dexmedetomidine). All these regimens require specialist advice, be it from the neurologist, psychiatrist or palliative care specialist.
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