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 hypoactive 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

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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	Spared unless in severe cases	Spared
Attention	Impaired	Initially spared	Can be impaired
Cognition	Impaired	Impaired	Can be impaired
Hallucinations	Usually visual	Often absent	Often auditory
Delusions	Poorly systematised and fleeting	Often absent	Sustained and systematised
Psychomotor activity	Increased, reduced mixed with alternating course	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	Abnormal[a]	Abnormal[a]	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	
Hospital palliative care unit	42.0	45.0
Palliative care programme including home care	28.0	–
Dying cancer patients in specialised palliative care unit		80

Modified from Caraceni and Grassi [2].

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 conscious-

ness 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 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 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 signs, 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 multi-drug chemotherapy (cytarabine, cisplatin, gemcitabine, vinorelbine, FOLFOX regimen and methotrexate) and of the new biological therapies such as anti-angiogenetic antibodies and others (bevacizumab, rituximab, bortezomid and motesanib) [12]. The syndrome usually includes seizures, cortical vi-

sual 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

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
Liver 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

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 $\geqslant 5$ 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.

4.2. Opioids

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 $\geqslant 90$ 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.

Table 5 – Case reports of delirium associated with drug toxicity. Modified from Caraceni and Grassi [2].
Pychotropics: Clozapine Diphenydramine Fluoxetine Mianserin Promethazine Lithium Risperidone
Antibiotics, antimalarials and antivirals: Ciprofloxacin Clarithromycin Mefloquine Ofloxacillin Acyclovir Gamcyclovir
Drug combinations: Benzodiazepine/clozapine combination Flecainamide/paroxetine combination Diphenhydramine/linezolide combination Paroxetine/benztropine combination Lithium/neuroleptic combination Tacrine/ibuprofen interaction Ethanol/niacin coingestion Sertraline/haloperidol/benztropine combination
H-2 receptor blockers: Famotidine (six cases) Ranitidine Ranitidine and cimetidine
Opioids: Fentanyl Oxycodone Morphine Hydromorphone
Antiblastic: Paclitaxel Vincristine Ifosfamide Cytosine arabinoside Cisplatin Methotrexate Thiotepa Etoposide Nitrosurea
Biological drugs used in cancer: Bevacizumab Rituximab
Other: Diet pills (phentermine) Amiodarone Cyclosporin Donepezil Herbal medicine loperamide, theales and valerian Levodopa Nizatidine Omeprazole Paclitaxel Steroids Tacrine Ziconotide Zolpidem

Table 6 – Drugs with anticholinergic activity in each category. The agents are listed from the more pronounced to less pronounced anticholinergic potency.
Prototypical anticholinergics: Belladonna alkaloids Atropine Scopolamine Hyoscine butylbromide Robinul
Antidepressants: Amytriptiline Imipramine Desimipramine Nortriptyiline Paroxetine Trazodone Mirtazapine
Antihistamines: Marzine Diphenhydramine Promethazine Biperidene Trihexyphenidyl Cimetidine Ranitidine
Neuroleptics: Chlorpromazine Flufenazine Clozapine Prochlorperazine Trifluorperazine Olanzapine Thioridazine Haloperidol Quetiapine Risperidoone Ziprasidone
Anti-Parkinsonian: Amantadine, Levodopa Other: Metoclopramide Baclofen Entacapone

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 discontinuation 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 necessary. Usually at least a week or two of therapy is needed to develop psychiatric complications [28]. 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, tachypnea, 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 (SRRI 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 the 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].

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

Drug	Combinations
Fluoxetine	Carbamazepine
	Pentazocine
	MAOIs
	Moclobemibe
	Nefazodone
	Tramadol
	Mirtazapine
Fluvoxamine	Alone
	Nefazodone
Paroxetine	Risperidone
	Moclobemide
Sertraline	Isocarboxazide
	Nortriptyline
	Tranylcypromine
	Erythromycin
	Buspirone
	Loxapine
Tryptopan	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

MOAIs, monoamine oxidase inhibitors.

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
	Desimipramine
CYP3A4 Inhibitors	Drugs metabolised by CYP3A4 whose plasma levels can increase when combined with inhibitors
All imidazole antifungals	Fentanyl
Fluoxetine	Alfentanyl
Norfloxacine	Methadone
	Alprazolam
	Midazolam

The number of potential pharmacological interactions is extremely large and variable according to clinical conditions and antineoplastic, supportive and combined therapies. Dexamethasone, anticonvulsants and cisplatin or asparaginase have specific interactions, to give only one example. In cases of delirium, a specific review of drugs and their metabolism is mandatory. Conversely the choice of drugs with the least metabolic interference potential is to be recommended. Guidelines to treat pain and depression, for instance, should recommend as first choice morphine, mirtazapine or citalopram, while TCAs should not be used as first choice in combination with morphine because of their strong anticholinergic effects and also because they increase morphine bioavailability [33]. However, oral gabapentin has been shown to increase oral morphine bioavailability [34], but the clinical impact of this observation has never been clarified.

4.6. Alcohol and drug withdrawal

Patients with known alcohol and or drug abuse, in particular chronic use of benzodiazepines, should be considered at risk of withdrawal in the case of reduced or suspended intake of alcohol when admitted to the hospital or hospice. Alcohol withdrawal delirium should be treated with benzodiazepines; in severe cases (delirium tremens) this can be life-threatening and requires specialist advice or intensive care. More subtle cases can result from the sudden discontinuation of the chronic use of benzodiazepines in patients with reduced ability to swallow when admitted to a care facility, which may go unnoticed without a very careful assessment of the patient history.

4.7. Delirium as a complication of the terminal phase of advanced cancer

In patients with advanced cancer undergoing palliative care and admitted to a hospice, delirium episodes are particularly frequent; this can be expected from the progressive accumulation of the risk factors described, and indeed the prevalence of delirium tends to increase as the terminal phase of illness approaches, reaching 80% in the last days of life, and it is *per se* a prognostic factor of shortening life expectancy [7,35]. On the other hand, in palliative care units and in hospices delirium episodes can be reversible – owing to modifiable etiologies, such as drugs and infections – in as many as 50% of the cases [5,36]. It is therefore of extreme importance to assess delirium reversibility in advanced disease, to direct treatment goals and family counselling. When a single drug toxicity can be identified the probability of reversing toxicity is also high [36], but on the other hand when the clinical situation is complex – due to multiple concurrent factors, organ failure and in an advanced phase of the disease – reversibility is less likely and delirium can be viewed as one aspect of the terminal phase of the illness. In this last case, not only can it be impossible to modify the eventual contribution of drugs to the delirious state, it could also be futile or even inappropriate if comfort and quality of dying is the goal of care. Interventions directed at dealing with and managing the impact of delirium on family distress and anxiety are particularly appropriate at this time [37].

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 cases of fatal cardiac arrhythmia following haloperidol administration.

Pharmacological treatment of delirium aims at patient tranquilisation, 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 medicine consultant, depending on the clinical conditions and setting [17].

6. Conflict of Interest

The author has no conflict of interest relating to this article.

REFERENCES

[1] Caraceni A, Scolari S, Simonetti F. The role of the neurologist in oncology a prospective study. J Neurol 1999;246(Suppl. 1). I/68.

[2] Caraceni A, Grassi L. Delirum: acute confusional stated in palliative medicine. 2nd ed. Oxford: Oxford University Press; 2011.

[3] Meagher DJ, Moran M, Bangaru R, et al. Phenomenology of delirium. Assessment of 100 adult cases using standardized measures. Br J Psychiatry 2007;190:135–41.

[4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Text revision. DSM IV-TR. Washington: American Psychiatric Press; 2000.

[5] Leonard M, Raju B, Conroy M, et al. Reversibility of delirium in terminally ill patients and predictors of mortality. Palliat Med 2008;22:848–54.

[6] Ljubisavjevic V, Kelly B. Risk factors for development of delirium among oncology patients. Gen Hosp Psychiatry 2003;25:345–52.

[7] Hosie A, Davidson MP, Agar M, Sanderson CR, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. Palliat Med 2012;27:486–98.

[8] Gaudreau J, Gagnon P, Harel F, Tremblay A, Roy M. Fast, systematic and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005;29:368–75.

[9] Neufeld K, Leoutsakos J, Sieber F, et al. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. Br J Anaesth 2013. http://dx.doi.org/10.1093/bja/aet167.

[10] Gaudreau J, Gagnon P, Harel F, Roy M. Impact on delirium detection of using a sensitive instrument integrated into clinical practice. Gen Hosp Psychiatry 2005;27:194–9.

[11] Tuma R, DeAngelis LM. Altered mental status in patients with cancer. Arch Neurol 2000;57:1727–31.

[12] Staykov D, Schwab S. Posterior reversible encephalopathy syndrome. J Int Care Medicine 2012;27:11–24.

[13] Graus F, Dalmau J. Paraneoplastic neurological syndromes. Curr Opin Neurol 2012;25:795–801.

[14] Gaudreau J, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. Med Hypotheses 2005;64:471–5.

[15] Lipowski ZJ. Etiology. Delirium: acute confusional states. New York, Oxford: Oxford University Press; 1990. p. 109–40.

[16] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852–7.

[17] Caraceni A, Simonetti F. Palliating delirium in patients with cancer. Lancet Oncol 2009;10:164–72.

[18] Gaudreau J, Gagnon P, Roy M, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712–8.

[19] Clegg A, Young J. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing 2011;40:23–9.

[20] Itil T, Fink M. EEG and behavioral apects of the interaction of anticholinergic hallucinogens with centrally active compounds. Prog Brain Res 1968;28:149–68.

[21] Kurita G, Lundorff L, Pimenta C, Sjøgren P. The cognitive effects of opioids in cancer: a systematic review. Support Care Cancer 2009;17:11–21.

[22] Hagen N, Swanson R. Strychnine-like multifocal myoclonus and seizures in extremely high-dose opioid administration: treatment strategies. J Pain Symptom Manage 1997;14:51–8.

[23] Okon T, George M. Fentanyl-induced neurotoxicity and paradoxic pain. J Pain Symptom Manage 2008;35:327–33.

[24] Caraceni A, Martini C, De Conno F, Ventafridda V. Organic brain syndromes and opioid administration for cancer pain. J Pain Symptom Manage 1994;9:527–33.

[25] Bruera E, Schoeller T, Montejo G. Organic hallucinosis in patients receiving high doses of opiates for cancer pain. Pain 1992;48:387–99.

[26] King S, Forbes K, Hanks G, Ferro C, Chambers E. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med 2011;25:525–52.

[27] Breitbart W, Stiefel F, Kornblith AB, Pannullo S. Neuropsychiatric disturbance in cancer patients with epidural spinal cord compression receiving high dose corticosteroids: a prospective comparison study. Psychooncology 1993;2:233–45.

[28] Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: neuropsychiatric complications. Cancer Invest 1989;7:479–91.

[29] Bernard SA, Bruera E. Drug interactions in palliative care. J Clin Oncol 2000;18:1780–99.

[30] KuKanich B, Hubin M. The pharmacokinetics of ketoconazole and its effects on the pharmacokinetics of midazolam and fentanyl in dogs. J Vet Pharmacol Ther 2010;33:42–9.

[31] Levin TT, Bakr MH, Nikolova T. Case report: delirium due to a diltiazem–fentanyl CYP3A4 drug interaction. Gen Hosp Psychiatry 2010;32(648):e9–e10.

[32] Tsao Y, Gugger J. Delirium in a patient with toxic flecainide plasma concentrations: the role of a pharmacokinetic drug interaction with paroxetine. Ann Pharmacother 2009;43:1366–9.

[33] Ventafridda V, Ripamonti C, DeConno F, et al. Antidepressants increase bioavailability of morphine in cancer patients (letter). Lancet 1987;1:1204.

[34] Eckhardt K, Ammon S, Hofmann U, et al. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Anesth Analg 2000;91:185–91.

[35] Scarpi E, Maltoni M, Miceli R, et al. Survival prediction for terminally ill cancer patients: revision of the palliative prognostic score with incorporation of delirium. Oncologist 2011;16:1793–9.

[36] Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes and outcome of delirium in patients with advanced cancer. Arch Intern Med 2000;160:786–94.

[37] Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. Psychosomatics 2004;45:107–13.

[38] Lonergan E, Britton A, Wyller T. Antipsychotics for delirium. Cochrane database of systematic reviews; 2007:Art.No:CD005594. doi: 10.1002/14651858.CD005594.

[39] National Guidelines for Seniors' Mental Health: The Assessment and Treatment of Delirium. <http://www.ccsmh.ca/en/guidelinesusers.cfm>; 2006. (accessed 03.05.08).

[40] Casarett D, Inouye S. Diagnosis and management of delirium near the end of life. Ann Intern Med 2001;135:32–42.

[41] Cook IA. Guideline Watch. Practice guideline for the treatment of delirium. *Am Psych Assoc*; 2004. Available from <http://focus.psychiatryonline.org/content.aspx?bookid=28&sectionid=1681952>.