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Symptom Management and Supportive Care

The Assessment and Management of Delirium in Cancer Patients

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Key Words. Delirium • Neoplasms • Palliative care • Diagnostic techniques and procedures • Antipsychotic agents

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Summarize the current evidence regarding strategies for the assessment and management of delirium in advanced cancer.
2. Outline the medications most commonly implicated for drug-induced delirium.
3. Compare the various pharmacological agents available for use in managing cancer-related delirium.

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ABSTRACT

Delirium remains the most common and distressing neuropsychiatric complication in patients with advanced cancer. Delirium causes significant distress to patients and their families, and continues to be underdiagnosed and undertreated. The most frequent, consistent, and, at the same time, reversible etiology is drug-induced delirium resulting from opioids and other psychoactive medications. The objective of this narrative review is to outline the causes of delirium in advanced cancer, especially drug-induced delirium, and the diagnosis and management of opioid-induced neurotoxicity. The early symptoms and signs of delirium and the use of delirium-specific assessment tools for routine delirium screening and monitoring in clinical practice are summarized. Finally, management options are reviewed, including pharmacological symptomatic management and also the provision of counseling support to both patients and their families to minimize distress. ***The Oncologist*** 2009;14:1039–1049

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1083-7159/2009/$30.00/0 doi: 10.1634/theoncologist.2009-0122

Introduction

"Most delirious patients are considered either dull, stupid, ignorant, or uncooperative. It is only when their behaviour and content of thought are grossly deviant that an abnormal mental state is recognised, although ids [sic] not always correctly identified as delirium" [1].

Despite the passage of time since Engel and Romano's description of delirium caused by global brain dysfunction in their classic paper in 1959, delirium continues to be frequently underdiagnosed or misdiagnosed by health care professionals [2–4] and continues to be inadequately treated [5].

Delirium remains the most common and devastating neuropsychiatric complication in patients with advanced cancer [2, 6], although a delirium episode is reversible in up to 50% of cases [7, 8]. Delirium causes significant distress to patients and their families [9, 10]. In a recent study of 99 patients with advanced cancer who had recovered from delirium, 74% remembered their delirium episode [11]. Patients who recalled their delirium episode reported a higher level of distress than patients with no recall [11]. Delirium impairs patient communication, thus challenging the assessment of pain and other symptoms [2]. Delirium also causes significant morbidity, increasing the length of hospital stay and also increasing the risk for falls and associated sustained injuries [12, 13]. The development of delirium prognosticates a greater likelihood of death [14].

The purpose of this review is to update oncologists on the clinical assessment and management of this syndrome, with a focus on drug-induced delirium.

Definition and Prevalence

Delirium is defined as a disturbance of consciousness with reduced ability to focus, sustain, or shift attention, with changes in cognition or perceptual disturbances that occur over a short period of time and tend to fluctuate over the course of the day, with an organic etiology [15].

Delirium is present in 26%–44% of advanced cancer patients at the time of admission to an acute care hospital or palliative care unit, and >80% of patients with advanced cancer develop delirium in the last hours and days before death [8, 16, 17].

According to the level of psychomotor activity, three clinical delirium subtypes have been described: hyperactive, hypoactive, and mixed (with alternating features of both hyperactive and hypoactive delirium) [18, 19]. However, in many studies to date, the true nature of the psychomotor abnormality has been difficult to determine because of its fluctuation (observed more in longitudinal studies) and also the potentially confounding effect of medications used to treat delirium. Patients with hyperactive delirium are more likely to receive psychotropic medications and may have a better prognosis than patients with hypoactive delirium [20]. Hypoactive delirium may be more resistant to pharmacological treatment [21]. The majority of delirium episodes are either of the hypoactive or mixed subtype [22, 23]. Lawlor et al. [24], in a prospective study, found that delirium was mixed in 48 of 71 (68%) patients. The hyperactive and mixed subtypes are highly associated with drug-induced delirium, whereas predominantly hypoactive delirium is associated with dehydration and encephalopathies [25].

The differential diagnosis of delirium includes dementia and depression, and other psychiatric disorders. In dementia, in contrast to delirium, there is little or no clouding of consciousness, and the onset is insidious. However, the symptoms of Lewy Body dementia (comprising cognitive impairment, visual hallucinations, delusions, and parkinsonism) do fluctuate. Patients with dementia may also commonly present with a superimposed delirium. Hypoactive delirium, with somnolence and withdrawal, may be misdiagnosed as depression. Hyperactive delirium may be mistaken for manic and psychotic episodes, anxiety, or akathisia. Increased expression of pain in an agitated patient may be misinterpreted and inappropriately treated as a pain syndrome, with the resulting increased opioid administration exacerbating the delirium severity [26], rather than correctly identified as disinhibition because of delirium.

Pathophysiology and Causes

The cholinergic hypothesis describes a deficiency of acetylcholine and an excess of dopamine as mediators for delirium [27]. Other neurotransmitter hypotheses postulate the role of glutamate, serotonin, cortisol, and endogenous opioid [3, 28, 29]. The role of cytokines is attracting recent interest, especially interleukin (IL)-1, IL-6, and IL-8, and also interferon and tumor necrosis factor [30, 31]. It has been suggested that IL-6 has a role in hyperactive delirium [32]. Transient thalamic dysfunction has been postulated as a mechanism for drug-induced delirium [33]. Future research may identify pathophysiological mechanisms specific for other delirium subtypes.

The organic etiology of delirium is usually multifactorial, with a median of three (range, one to six) precipitants per delirium episode [7] (Fig. 1).

On multivariate analysis, one small prospective study in 145 oncology admissions found the following five risk factors for the development of delirium: advanced age, cognitive impairment, low albumin, bone metastases, and hematological malignancy [34]. However, often a specific cause remains unidentified. Predisposing factors increase a

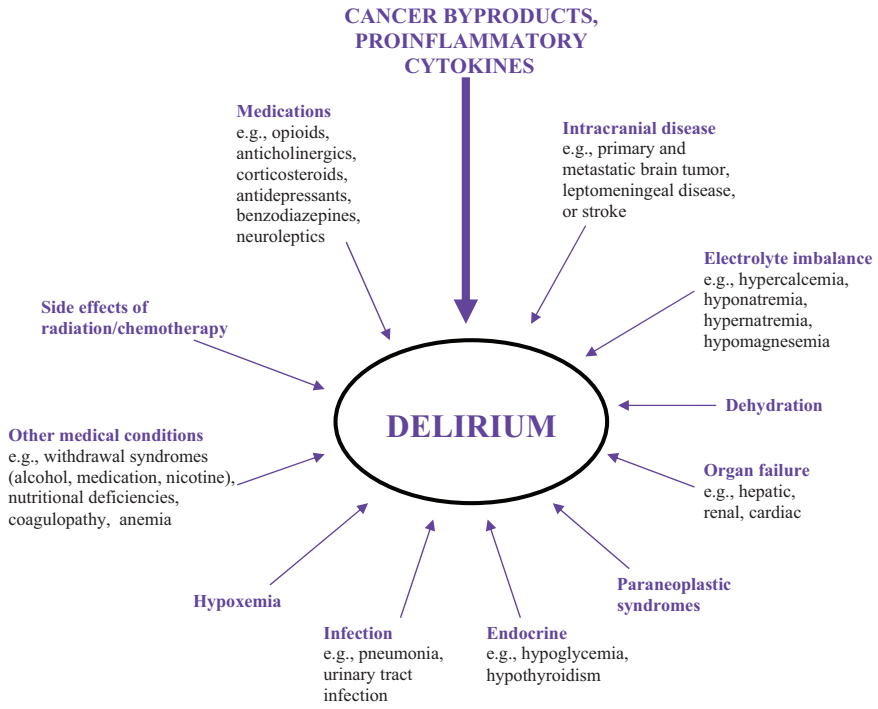

Figure 1. Factors contributing to delirium in cancer patients.

patient's baseline susceptibility for developing delirium. Examples are pre-existing cognitive impairment, such as dementia, and reduced sensory input because of poor vision or deafness.

Drug-Induced Delirium

The most commonly implicated medications are opioids (see section below on opioid-induced neurotoxicity), corticosteroids, benzodiazepines, and anticholinergics [7, 25, 35, 36] (Table 1). In addition to delirium, other features of anticholinergic drug toxicity are mydriasis, hyperthermia, fever with no sweating, flushed appearance, dry skin, and urinary retention.

In a prospective cohort study in 261 cancer hospital inpatients, Gaudreau et al. [35] found that the risk for delirium doubled if the daily dose equivalent (DDE) of s.c. morphine was >90 mg/day or if the DDE of lorazepam was >2 mg/day. A DDE >15 mg/day of oral dexamethasone led to a 2.7 higher risk for the development of delirium, but no association with anticholinergics was found in that study [35].

Opioid-induced neurotoxicity (OIN) is a syndrome of neuropsychiatric side effects seen with opioid therapy. Table 2 outlines the risk factors for this syndrome. OIN can occur with all known opioid agonists that are used in cancer pain management, including morphine, hydromorphone, oxycodone, fentanyl, and methadone [37, 38]. Meperidine, an opioid analgesic that is not recommended for the management of cancer pain, produces a high rate of neurotoxicity because approximately 60% of it is metabolized to normeperidine. Leipzig et al. [39] found that 77% of cancer patients receiving opioids had an impaired mental status. The features of OIN are severe sedation, hallucinations, cognitive impairment, delirium, myoclonus, seizures, hyperalgesia, and allodynia. These symptoms can develop as a single feature or in any combination and order. Hallucinations tend to be visual or tactile, with visual hallucinations occurring in almost half of hospice inpatients [40]. Patients with a history of seizures, cerebral metastases, or metabolic abnormalities may have a predisposition to developing tonic-clonic OIN-associated seizures. The oncologist must

Table 1. Medications that contribute to delirium [7, 25, 28, 35, 36]

Category	
Psychoactive	Opioids, benzodiazepines, anticholinergics, tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics, nonbenzodiazepine hypnotics
Antineoplastic	
Other	Corticosteroids, antihistamines, H_2 blockers, antibiotics (quinolones), metoclopramide, anticonvulsants, certain antivirals

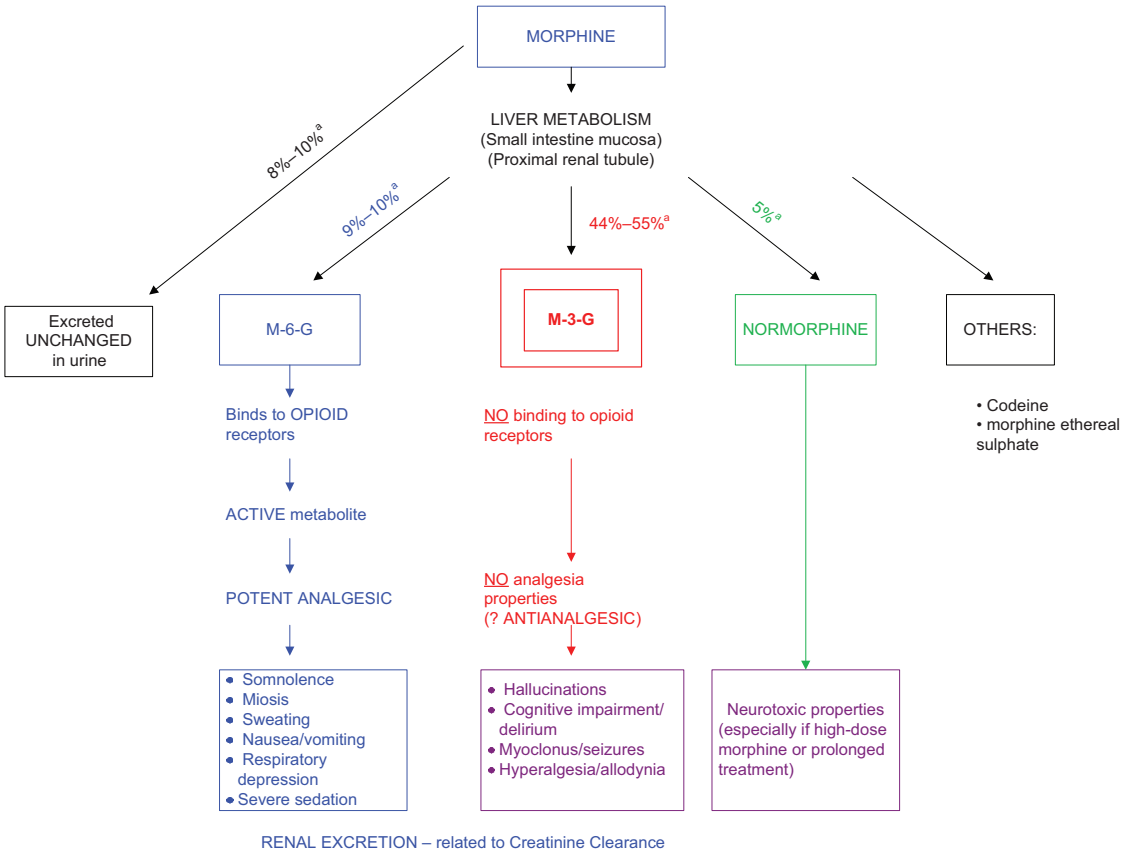

Figure 2. Morphine metabolism [37, 41, 44]. [a]The percentage breakdown of metabolites remains the same for all routes of administration.

Abbreviations: M-3-G, morphine-3-glucuronide; M-6-G, morphine-6-glucuronide.

remain vigilant because any patient prescribed opioids is at potential risk for developing OIN.

Opioid-induced central nervous system (CNS) adverse effects are related to the anticholinergic actions of opioids, with inhibition of central cholinergic activity in multiple cortical and subcortical regions of the brain, in addition to an imbalance in CNS cholinergic and dopaminergic systems [29]. The accumulation of toxic opioid metabolites has also been implicated (Fig. 2). Using the example of morphine as the "gold standard" opioid, the major metabolite (44%–55%), morphine-3-glucuronide (M-3-G), has no μ-opioid binding and consequently no analgesic properties [37, 41]. M-3-G is thought to be responsible for the cluster of OIN symptoms described above. However, the evidence for this is conflicting. Gong et al. [42], in 1992, reported that M-3-G did not produce excitatory and antianalgesic effects in rats, and Penson et al. [43] more recently, in 2001, did not induce neurotoxicity when small i.v. doses of M-3-G were injected into healthy volunteers. Normorphine, another nonopioid-binding neurotoxic metabolite, accounts for only approximately 5% of morphine metabolism [44]. However, this mediator may play a more prominent role in patients receiving high-dose or prolonged treatment with morphine. It is unknown to what extent morphine-6-glucuronide (M-6-G) contributes to OIN.

Opioid neurotoxicity is also thought to involve endocytosis of opioid receptors and also activation of N-methyl-D-aspartate receptors, where the neurotransmitter is glutamate [29]. It has been suggested that inhibition of glycine in dorsal horn neurons leads to myoclonus and hyperalgesia [29]. It has also been proposed that the neurotoxic effect of opioids may occur via a nonopioid receptor–mediated mechanism [45].

Evaluation

For didactic purposes, we separately discuss the clinical features and assessment of delirium and the evaluation of contributory factors. However, in daily clinical practice, this process takes place in a fully integrated fashion.

Clinical Features of Delirium

Early diagnosis is important, because this enables not only earlier treatment but also provision of education and support to the patient and family.

Table 2. Factors predisposing to opioid-induced neurotoxicity (OIN)

● Opioid factors—large dose, extended treatment time, rapid dose escalation, reduced nociceptive input
● Dehydration
● Renal failure
● Infection
● Borderline cognitive impairment/delirium
● Use of other psychoactive drugs, e.g., benzodiazepine and nonbenzodiazepine hypnotics, tricyclic antidepressants
● Older age
● Previous episode of OIN

An essential feature for the clinical diagnosis of delirium of the *Diagnostic and Statistical Manual of Mental Disorders IV-TR* (DSM-IV-TR) criteria is a disturbance of consciousness [15]. Noncore clinical features of delirium include sleep–wake cycle disturbance, altered psychomotor activity, and emotional lability. Patients may exhibit prodromal features including anxiety, restlessness, irritability, disorientation, and sleep disturbances [46]. Patients may have disorganized thinking and disjointed unintelligible speech. The altered perceptions that may occur include misperceptions, illusions, delusions, and hallucinations [47]. Clinical features include neurological motor abnormalities: tremor, asterixis, myoclonus, and tone and reflex changes [47]. Dysgraphia may also occur [48]. Other neurological abnormalities that may be present include constructional apraxia, dysnomia, and aphasia [47]. Generalized slowing of the electroencephalogram is a classic finding [1].

Delirium Assessment Tools

Delirium is frequently underdiagnosed in the clinical setting, even by experienced physicians and nurses [3]. One study reported that physicians and nurses missed the diagnosis 23% and 20% of the time, respectively [2]. A similar underdiagnosis may occur in patients admitted to clinical trials [49].

Historically, the Mini-Mental State Examination (MMSE) [50] was used in multiple studies on cognitive failure in cancer patients with delirium [2, 8, 51–53]. However, the MMSE only assesses cognitive function. For example, two delirious patients with an MMSE score of 14 of 30 can range from being completely lethargic to completely agitated and unmanageable. Better tools are needed to assess perceptual abnormalities, psychomotor changes, delusions, and other delirium features. Multiple validated delirium-specific assessment tools are now available [54, 55]. Some instruments, such as the Confusion Assessment Method (CAM) [56], are diagnostic only and used mainly for screening. Such tools cannot be used to monitor patients because they do not give a severity rating. Instruments that measure delirium severity, in addition to being diagnostic tools, include the Memorial Delirium Assessment Scale (MDAS) [57, 58] and the brief observational Nursing Delirium Screening Scale (NuDESC) [59], derived from the Confusion Rating Scale (CRS) [60].

A brief description of three delirium assessment tools used in clinical practice follows.

CAM

The CAM [56] is based on the DSM-III-R criteria. Although it is a brief, four-item diagnostic algorithm that takes <5 minutes to administer, it does require training in its use. It has recently been validated in the palliative care setting [61].

MDAS

The MDAS [57] is a 10-item, four-point, clinician-rated instrument (possible range, 0–30). It was originally designed to measure severity but can be used as a diagnostic tool using a cutoff total MDAS score ≥7 of 30 [58]. This is a validated instrument [58]. The objective cognitive testing items (items 2, 3, and 4) should be completed first because this achieves a higher rate of completion and allows assessment time for the more observational or subjective items [62].

NuDESC

The NuDESC [59] is an observational five-item scale (possible range, 0–10) that includes the four items of the CRS [60] and an additional assessment of psychomotor retardation. Each symptom (disorientation, inappropriate behavior, inappropriate communication, illusions, or hallucinations, as well as psychomotor retardation) is rated 0–2 according to its presence and severity. It is a low burden tool that takes <2 minutes to complete, and can be used for screening and monitoring delirium severity. The NuDESC has been validated and is reported to have a sensitivity of 85.7% and a specificity of 86.8% [59].

Further Clinical Assessment

The assessment of delirium also includes the investigation of all potential precipitating factors for the delirium episode (as shown in Fig. 1) in order to identify reversible causes. Medication history for both new and continuing drugs should be reviewed. Predisposing factors that increase the patient's baseline susceptibility for developing delirium may also be identified, such as pre-existing cognitive im-

Table 3. Management of opioid-induced neurotoxicity (OIN)

● Initial opioid selection (e.g., avoid opioids with active metabolites in patients with known renal failure)
● Hydration (oral/parenteral: i.v. or s.c.)
● Opioid dose reduction with or without coanalgesic/adjuvant
● Opioid switch/rotation The equianalgesic dose of the new opioid should be reduced by 30%–50%, e.g., morphine → hydromorphone, oxycodone, methadone, or fentanyl
● Stop contributing drugs, e.g., hypnotics
● 75%–80% of episodes of drug-induced delirium resolve by action of opioid rotation and discontinuation of other drugs
● Psychostimulants
● Symptomatic treatment with neuroleptics, e.g., haloperidol
● Consider benzodiazepine for myoclonus, e.g., clonazepam [67]
● Reassurance and explanation

pairment or reduced sensory input with poor vision or deafness. Urinary retention and constipation may aggravate agitation, especially in the elderly.

In addition to the use of a delirium-specific tool, a multidimensional assessment of the patient's symptom burden, using a validated instrument such as the Edmonton Symptom Assessment System [63] enables the identification and quantification of other significant symptoms that are impacting the delirium episode.

Clinical Management

The multimodal management of delirium includes nonpharmacological and environment management strategies, in addition to neuroleptic and other medications, while simultaneously identifying and treating underlying causes when appropriate. Comprehensive management should involve a multidisciplinary team. The patient's delirium severity and response to treatment need to be monitored regularly.

Treatment of Underlying Causes

Because 50% of delirium episodes in advanced cancer are reversible, possible contributors to delirium (as shown in Fig. 1) should be appropriately treated. For drug-induced delirium, all implicated medications should be discontinued or undergo a dose reduction if cessation of the implicated medication is not possible. Opioid rotation should be instigated if opioid discontinuation is not possible [64–66]. See Table 3 for further management of OIN [67]. Most effects of OIN resolve within 3–5 days of introduction of opioid rotation and hydration. There have been some case reports examining the effect of treatment of opioid-induced delirium with acetylcholinesterase inhibitors [68], but currently there is no supporting evidence for their effectiveness from controlled trials [69].

Pharmacological Treatment of Delirium Symptoms

There is limited research evidence from clinical trials, so this review reports current best practice. Neuroleptics are considered to be first-line agents [20, 70]. They are usually used as a short-term measure to relieve perceptual disturbance or agitation while reversible causes are investigated and treated, and include haloperidol and atypical antipsychotics (Table 4) [20, 68–80]. There is no research evidence to date to support particular dosing schedules and practice. Clinical trials are needed to better inform current practice.

Haloperidol is the most commonly used and the most studied neuroleptic [70, 81]. It is a potent dopamine D_2 receptor antagonist with few anticholinergic side effects. However, there is limited randomized controlled trial evidence for its use in the management of delirium [20]. In the 2004 Cochrane review on drug therapy for delirium in terminally ill patients, only one study met the review criteria [82]. This was the seminal double-blind, randomized comparison trial by Breitbart et al. [52] of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in 30 hospitalized AIDS patients. Chlorpromazine and haloperidol were found to be equally effective. There was a small but significant decline in cognitive function over time with chlorpromazine. This study highlighted the importance of not treating delirium with a benzodiazepine as a single agent, unless delirium is secondary to sedative or alcohol withdrawal, because the lorazepam arm was stopped early because of side effects (excessive sedation, increased confusion, disinhibition, and ataxia).

By 2007, there were three studies eligible for the Cochrane review examining antipsychotics in delirium [83], comparing haloperidol with risperidone, olanzapine, and placebo. The review concluded that haloperidol at a dose of <3.5 mg/day, risperidone, and olanzapine were equally effective.

Haloperidol has the advantage of versatile routes of administration: oral, s.c., i.m., and i.v. It is rarely sedating. Because the average oral bioavailability of haloperidol is approximately 60% [84], parenteral doses are about twice as potent as oral doses. High concentrations of haloperidol and reduced-haloperidol, the active metabolite of haloperidol, increase the frequency and severity of extrapyramidal side effects (EPSs) [84]. Parenteral administration of halo-

Table 4. Guide to medications used for symptomatic treatment of delirium in advanced cancer patients

Conventional neuroleptics [22, 72]
Haloperidol
Chlorpromazine
Methotrimeprazine (levomepromazine)—not available in the U.S.
Atypical antipsychotics [22, 73]
Olanzapine
Risperidone
Quetiapine
Aripiprazole
Emerging drugs[a]
Methylphenidate hydrochloride [74]
Modafinil [75]
Melatonin [76]
Cholinesterase inhibitors [68, 69]
Cholinomimetics [77]
Valproate [78]
Dexmedetomidine [79]
Ondansetron [80]

[a]None of these medications are currently recommended for the routine management of delirium. At present, they are being investigated in the clinical setting.

peridol reduces the risk for EPSs. However, there is marked variation in patient sensitivity to EPS development. In comparison with parkinsonism, neuroleptic-induced parkinsonism consists of the triad of bradykinesia, tremor, and rigidity, with a predilection for the upper limbs, and with gait change being mild [85].

Clinical guidelines recommend starting haloperidol doses of 0.5–2 mg, with varying frequency and routes of administration [86, 87]. Most studies to date report dose ranges of 2–10 mg/day [52, 88, 89]. Some authors also suggest using regular low-dose haloperidol for the management of hypoactive delirium [47, 90]. However, further research in the form of randomized, double-blind, placebo-controlled trials is needed in the advanced cancer population to determine appropriate dosing schedules for all delirium subtypes.

More recently, atypical antipsychotics, such as olanzapine, risperidone, quetiapine, and aripiprazole, have been used in the management of delirium in patients with cancer [20, 21, 91–93]. The reduced frequency of EPSs with this class of antipsychotics is a result of 5-HT_{2A} receptor antagonism and muscarinic M_1 receptor antagonism mitigating D2 receptor blockade [73]. EPSs can still occur with atypical antipsychotics at higher doses, especially risperidone at doses >6 mg/day [22].

Olanzapine has a common side effect of sedation, which may be potentially beneficial in a hyperalert, hyperaroused patient with delirium. In addition, metabolic syndrome can occur with olanzapine [94], but the significance of this is unclear when used short term, as in the management of delirium. In an open, prospective trial of oral olanzapine for the treatment of delirium in 79 hospitalized cancer patients, Breitbart et al. [21] found that patients >70 years of age, with hypoactive delirium, delirium of "severe" intensity (defined in their study as an MDAS score >23 of 30), and a history of dementia, cerebral metastatic disease, and hypoxia had a poorer response to treatment. The parenteral olanzapine preparation for i.m. injection has been well tolerated, with no injection site toxicity when administered by the s.c. route in some units [95].

A higher risk for cerebrovascular events in elderly dementia patients has been reported with atypical antipsychotics, especially risperidone [96]. In a 2006 meta-analysis assessing the adverse events associated with the use of atypical antipsychotics in the management of behavioral disturbances in patients with Alzheimer disease or other dementia [96], the duration of the 15 identified randomized, placebo-controlled trials was in the range of 6–26 weeks. This is as opposed to the usual short-term use of antipsychotics in the management of delirium. The use of atypical and typical antipsychotics in the elderly has also been associated with a higher risk for mortality [97, 98]. U.S. Food and Drug Administration (FDA) alerts have been issued for both classes of neuroleptics [99, 100].

In addition to EPSs, other adverse effects have been reported with neuroleptics. QTc interval prolongation can occur, with the risk for sudden cardiac death, including with atypical antipsychotics [84, 101]. If the QTc interval is >450 msec, or increases >25% from baseline, then the dose of haloperidol and any other contributory medications should be reduced or ceased [86]. In 2007, the FDA recommended electrocardiogram monitoring when i.v. haloperidol is given [102]. Most reported cases of neuroleptic malignant syndrome have occurred in patients receiving parenteral haloperidol, although it may also occur with other neuroleptics, including atypical antipsychotics [103].

Nonpharmacological Management

Simple environmental measures may help in the management of patients with delirium [104]. Education should be provided to the family and bedside nurse on the nature and prognosis of delirium, and on measures required to minimize patient stimulation (Table 5).

Up to 75% of patients recall their own symptoms after delirium resolution [11]. Patients require reassurance to help reduce their significant associated distress, with hypo-

Table 5. Summary of nonpharmacological management

Environment
Physically safe for patient, and also for staff and family
Minimize noise, excessive light, and excessive darkness
Streamline the patient's environment
• Call bell and other essential items visible and within reach
Simple, clear, and concise communication
• Glasses, hearing aid, dentures where needed
• Explain each intervention prior to instituting care
Orient patient frequently
• Provide a clock and calendar that are visible from the bed
• Name of nurse also visible from the bed
• Presence of familiar objects
Enlist the family to assist with reorientation
Education
Family
Bedside nurse
Other health care providers
Counseling
Family
Patient, after delirium resolution

active delirium being just as distressing to patients as hyperactive delirium [9, 11].

Family caregivers observe patient behaviors and experience distress more frequently than health care professionals [9, 11], and require ongoing education (especially regarding patient disinhibition) and psychosocial support from the interprofessional team [10, 105]. Expressive supportive therapy [106] is often helpful in reducing family member distress.

Refractory Agitated Delirium

This often necessitates the use of more sedative drugs for patient comfort and symptomatic relief [107]. Palliative sedation (PS) has been defined as the monitored use of proportionate sedative medication to reduce the patient's awareness of intractable and refractory symptoms near the end of life when other interventions have failed to control them [108]. Refractory agitated delirium is the most common indication for PS. Other indications for PS include severe dyspnea or respiratory distress, pain, hemorrhage, severe seizures, and uncontrolled myoclonus. Appropriately titrated PS in the dying is an ethically and legally accepted intervention, with the aim of relieving suffering and not hastening death. Medications that have been used for PS include midazolam, lorazepam, phenobarbitol (phenobarbitone), propofol, and methotrimeprazine (levomepromazine) (not available in the U.S.) [109–112]. Consultation with a palliative care specialist is strongly recommended before initiating PS [108].

Clinical Course and Prognosis

Although approximately 50% of delirium episodes are reversible, episodes are significantly more reversible if the precipitating factor is opioids and other psychoactive drugs and hypercalcemia [7, 25]. Opioid rotation and discontinuation of other drugs results in resolution of approximately 75%–80% of episodes of drug-induced delirium. Delirium is less likely to improve in patients with underlying dementia [3] or if the delirium is related to hypoxic or global metabolic encephalopathy, or disseminated intravascular coagulation [7, 25].

The presence of delirium is an independent factor in predicting short-term survival of patients with advanced cancer [14, 113]. Similarly, delirium is associated with greater mortality in medical inpatients [12, 86]. In 121 palliative care inpatients with delirium, Leonard et al. [114] found that patients with more advanced age, greater cognitive impairment, and organ failure had significantly shorter survival. In patients >50 years old, persistent delirium is frequent and associated with poorer outcomes, including greater mortality [115].

Future Directions

Studies are required on delirium predictors that are specific to patients with advanced cancer and on the efficacy of multimodal preventative interventions in this patient population, as compared with trials that have been conducted in the elderly [3]. There remains limited information from pharmacological randomized controlled trials to guide practice in evidence-based neuroleptic administration to cancer and palliative care patients. Further research is needed to determine efficacious and safe neuroleptic dosing schedules according to the different delirium subtypes and etiologies, and also on the role of nonpharmacological and environment management strategies to improve the comprehensive multifaceted management of this distressing syndrome.

Summary

In advanced cancer patients, the high frequency of delirium accompanied by the frequent underdiagnosis of this syndrome strongly suggests that regular screening for delirium should be conducted using validated tools in order to reach an earlier diagnosis. Although delirium in this population is often associated with a poor prognosis, 50% of patients can improve with

appropriate management of contributing etiologies, especially if opioids and other psychoactive drugs are precipitating factors, and involvement of the interprofessional team. Patients, family, and staff require ongoing support to reduce the impact of this potentially devastating condition.

Acknowledgments

The authors would like to thank Kathy R. King for her secretarial assistance in the preparation of this manuscript. Eduardo Bruera is supported in part by National Institutes of Health Grant numbers: RO1NR010162-01A1, RO1CA122292-01, and RO1CA124481-01.

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