



# Management of altered mental status and delirium in cancer patients

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**Abstract:** Delirium is a syndrome characterized by acute onset of changes in awareness and cognition, which fluctuate in severity during the episode. Altered mental status (AMS) and delirium have a high incidence rate among patients with cancer and this increases dramatically towards the end of life. Delirium is multifactorial, as cancer patients have an array of predisposing and precipitating factors: metabolic disturbances, structural lesions, in addition to medications and infection. The complex nature of delirium in cancer patients and the high variability of its presentation make its diagnosis and management challenging and frequently missed. Management of delirium requires identifying and correcting the precipitating cause if feasible. Diagnosis of delirium requires a high index of suspicion, and a systematic assessment to confirm the diagnosis and identify the possible cause. This includes detailed history and comprehensive physical examination together with the use of diagnostic tools, for example: Confusion Assessment Method (CAM) tool. Given the considerable distress cancer patients suffer from, clinicians must assure safety of patients with delirium and safety of the medical team caring for the patient. Family members should be provided with counseling and support.

**Keywords:** Altered mental status (AMS); cancer; delirium; diagnosis; management

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## Introduction

Patients with cancer are well known for the numerous complications associated with their disease and/or with the rigorous treatment modalities they receive (1). Two frequently misdiagnosed and potentially fatal neuropsychiatric complications are altered mental status (AMS) and delirium (2,3). The diagnosis and treatment of AMS and delirium have long puzzled clinicians (4,5), especially in patients with oncological diseases. Patients with cancer very frequently present with AMS and/or delirium especially in the end of life stage (2). Consequently, the evaluation of these conditions in terms of diagnosis and

management becomes more challenging, particularly in the era where patient's quality of life is a medical priority (6).

## Definitions

- ❖ AMS: a broad term that encompasses all manifestations of brain dysfunction including confusion, clouding of consciousness, disorientation, inattention, altered behavior, or drowsiness (7,8).
- ❖ Delirium: a more specific term commonly used to describe an acute state of confusion resulting from organic brain dysfunction. Delirium is characterized by a sudden onset of fluctuating level of consciousness.

Despite being a common presentation, delirium has been described vaguely throughout the years. With increased awareness of researchers, there has risen a pressing urge to construct various assessment and diagnostic tools that aid physicians in managing delirious patients (9-13). A general physician can easily miss a case of delirium, and this undoubtedly has profound drastic consequences on patient outcomes (13,14).

## Epidemiology

AMS and delirium are of the most prevalent neurological presentations of patients with cancer (15,16). These conditions are commonly found in hospitalized patients, even in the absence of cancer. Siddiqi *et al.* conducted a systematic review of 46 cohorts and found that the prevalence of delirium in newly admitted patients is 20% and the incidence per admission ranges from 3% to 29% (17). Nonetheless, delirium is even more prevalent among patients with advanced cancer. It comes just after adjustment disorders in neuropsychiatric diagnoses among cancer patients (18). Delirium is more commonly observed in the older cancer patient age groups and is equally prevalent in both genders (2,19,20). Studies show that 22–44% of patients with cancer experience delirium and that the incidence rises to 87% in the final days of life (21-24). Han *et al.* found that delirium was missed 76% of the time in the emergency department, suggesting that the incidence might even be higher (13). Additionally, evidence shows that hospitalized cancer patients with no signs of delirium on admission are highly prone to developing delirium during their admission. In a prospective cohort study of patients with terminal cancer, Gagnon *et al.* found that 20% presented with delirium on admission, in comparison to 31% of patients who were free of delirium on admission but became so during their admission (25). Similarly, Lawlor *et al.* studied a cohort of 113 patients with advanced cancer and reported delirium in 42% of admitted patients. Of the remaining, 45% developed delirium after admission (19).

## Etiology

### *Structural and non-structural causes*

AMS and delirium can occur as a result of structural and/or nonstructural causes (3). Nonstructural causes of delirium are more common among patients with cancer and are

typically related to drug intoxication and withdrawal or other metabolic imbalances (3,26). Doriath *et al.* found that toxic or metabolic encephalopathy was the main cause of delirium in 57% of confused cancer patients, with structural brain lesions coming in second at 36% (27).

Evidence suggests that delirium is a multifactorial condition. Doriath *et al.* reported that 61% of patients with toxic or metabolic encephalopathy had more than one contributing factor. The most common contributing factors were electrolyte abnormalities, renal insufficiency, liver dysfunction, anti-cancer drugs, infections and use of opiates (27). Tuma and DeAngelis studied 140 confused patients with non-central nervous system cancer, 50% of whom had disseminated systemic metastasis. The authors reported that only 33% of patients had a single cause for AMS, whereas multiple causes were identified for 67% of patients. Among the AMS cases, 54% were opioid-related and 64% were caused by metabolic abnormalities such as hypoxia, hyponatremia and renal failure. Infections and recent surgeries were also found to be common causes of delirium (2).

On another hand, structural causes of AMS are related to pathological processes within the brain, such as ischemic or hemorrhagic stroke, hydrocephalus, intracranial tumors, and mass effect producing lesions (28). Tuma and DeAngelis reported structural lesions as a cause of AMS in 36% of cases, with 26% being caused by metastatic lesions to the brain (2). Doriath *et al.* obtained similar findings, with AMS being associated with structural causes in 34% of cases, almost all of which were caused by metastatic disease (27).

### *Predisposing and precipitating factors*

It is believed that delirium is caused by a precipitating factor in a patient predisposed to having the problem. This concept was first introduced by Inouye in 2006 (29). *Predisposing factors* for delirium include advanced cancer, visual impairment, advanced disease, baseline cognitive impairment and dementia (29). *Precipitating factors*, on the other hand, are those that trigger delirium such as toxins, metabolic disturbances, brain insults, dehydration, physical restraints, urinary catheters and multidrug regimens (6,29). Laurila *et al.* found that both predisposing factors and precipitating factors are directly correlated to the patient's susceptibility to delirium. The authors reported an average of 3 precipitating factors and an average of 5 predisposing factors per patient, which supports a multi-factorial etiology of delirium (30). This is further supported by Magny *et al.*,

who studied a sample of 208 geriatric patients presenting with dementia from the community and reported that 80% of patients had a predisposing cognitive or neurologic disorder. Additionally, they noted that infections, followed by drugs and dehydration, were the most common precipitating factors (31). In a similar study conducted on cancer patients, Sagawa *et al.* noted that the most frequent precipitating factor is the use of opioids, with inflammation and electrolyte abnormalities also being common causes (28).

Other overlooked but increasingly important factors are loneliness and unfamiliar environments, which also add to the psychological stress afflicting the cancer patient (32). Given the complex nature of delirium and its multifactorial etiologies, it is difficult to contain delirium under one heading. Instead, delirium would be better described as a spectrum of disorders with numerous and often compounding causative factors. As a result, cancer patients form a subgroup that is highly prone to such a dire neuropsychiatric complication.

### Pathophysiology

Multiple theories have been proposed to explain the pathogenesis of delirium. Most of these theories, reviewed by Maldonado, center on the roles of neurotransmitters, inflammatory cytokines, and blood-brain barrier integrity in the development of delirium. The *neurotransmitter hypothesis* builds upon the role of neurotransmitter changes in the development and treatment of delirium and AMS (33). This theory was originally devised following observations of delirium in patients using neurotransmitter-altering medications or substances such as opioids (34). This theory suggests that delirium can be the result of a decrease in acetylcholine levels and an increase in dopamine levels, with alterations in glutamate and gamma-aminobutyric acid (GABA) (33). Knowing that the cholinergic system is involved in regulating selective attention and memory, any disruption in cholinergic transmission is postulated to be a potential cause of delirium (35,36). This theory is supported by multiple studies showing that delirium can be induced by anti-cholinergic drugs and reversed by administration of cholinergic agonists (33). Opioid use is known to be associated with an anticholinergic effect (37) and is also well known to play a role in producing delirium (26). Patients with cancer are at a high risk, as they rely on highly potent opioids for pain control, such as morphine (26). There is also evidence suggesting that low levels of acetylcholine are found in delirious patients not using anticholinergic

medication. This suggests that endogenous anticholinergic substances may be produced during acute illness (38,39).

On another note, the presence of inflammatory factors/cytokines resulting from malignancies may also increase the propensity of cancer patients to develop delirium. This is explained by the *neuro-inflammatory hypothesis*, which implies that peripheral inflammation results in the activation of CNS parenchymal cells, which in turn produce inflammatory cytokines that alter the normal functioning of neuronal synapses (40). This hypothesis could explain the “sickness behavior” seen in patients with inflammation or infections. In fact, most of these patients develop non-specific symptoms such as fever, fatigue, malaise and anorexia as well as behavioral symptoms such as depressed mood, anhedonia and cognitive changes. This could also be a potential explanation for the cognitive and behavioral changes seen in delirium (33).

The association between delirium and peripheral inflammation is also addressed by the *Oxidative Stress Hypothesis*. Pathologic processes, such as hypoxia, infections and malignancies, can produce oxidative stress and also compromise the body's redox systems which play a role in neutralizing this condition (41). This theory suggests that this state of oxidative stress is capable of causing cerebral damage and is therefore a potential cause for the delirium in patients with peripheral pathologies (33,42).

### Presentation

Delirium can affect cancer patients of all ages and can have myriad presentations; however, it is believed to be more common in the elderly cancer patients. Additionally, symptoms tend to fluctuate during the episode and are usually worse during the nighttime (11,22,43). The diversity of symptoms and the fluctuation of symptom severity are challenging that physicians face in diagnosing this condition particularly in the hypoactive subtype (44). In fact, delirium does not have pathognomonic features that can be readily seen; a physician must therefore maintain a high index of suspicion, take a detailed history and use proper assessment tools to detect these conditions (45).

There are three well-recognized clinical subtypes of delirium, separated according to the patient's psychomotor activity and level of arousal. These subtypes include the hyperactive subtype, hypoactive subtype and mixed subtype (46). The hyperactive subtype displays features similar to those seen in psychosis or mania: restlessness, hallucinations, delusions and hypervigilance (47). Centeno

*et al.* describes patients that fall under this subtype as disinhibited, uncomfortable or agitated. The patient may fidget around the room, attempt to pull out lines, or repeat movements, names, etc. (18). Contrarily, delirium in patients with the hypoactive subtype usually manifests with withdrawal, psychomotor retardation or lack of movement, lack of orientation, paucity of speech and unresponsiveness. This type of delirium may mimic a depressed mood (47). The hypoactive subtype is more likely to be missed, given the absence of positive symptoms (48). Patients with mixed subtype delirium usually present with features of both. Patients more commonly present with the hypoactive or mixed symptom subtypes (48,49).

AMS and delirium can cause significant stress on patients who are already enduring difficult times in their struggle with cancer. Patients have recalled their experience in great detail and have described it as being severely stressful at times (22,23). This also applies to the patients' families, who are significantly affected by the delirium. Families of delirious patients suffer from considerable stress, struggle to understand the etiology of delirium, and fear its recurrence (50,51).

## Diagnosis

Effectively diagnosing delirium is a recurring discussion among researchers, especially that many delirium cases go undetected (13). The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the gold standard for diagnosing delirium (52). One study at The University of Texas MD Anderson Cancer Center showed that 41% of delirium cases remained undetected by clinicians, even after they were trained on how to assess and diagnose it (24). Similar results were reported in the emergency department of another tertiary academic medical center, where 76% of delirium cases were missed (13).

These results are unfortunate, as studies show that delirium has more favorable outcomes when detected early (53). However, early detection can be troublesome, as some patients may appear cognitively normal with good orientation. The fluctuating pattern of the symptoms also makes the diagnosis difficult (43). This further solidifies the need for a thorough understanding of proper detection and management strategies for this psychiatric disorder, both in the general population and in the cancer patient population.

The fifth edition of the DSM (52) states that for a diagnosis of delirium to be made, five criteria must be met:

(I) Alteration in attention and awareness;

- (II) Alteration in attention and awareness develops acutely (usually over a few hours to a few days), constitutes an acute change from baseline attention and awareness, with severity fluctuation throughout the day;
- (III) Alteration in cognition, which may include memory deficit, language deficit, disorientation, or changes in perception;
- (IV) Criteria 1 and 3 cannot be better explained by an established neurocognitive disorder and are not occurring in the context of a severely reduced level of arousal (coma);
- (V) Evidence from the history, physical examination, or laboratory findings that the observed changes are direct physiological consequences of another medical condition, substance intoxication, withdrawal from a substance, and/or exposure to a toxin.

## Patient history

As a first step, the clinician should look for clues within the patient's presentation, such as new-onset agitation that peaks at night or variations in sleep patterns and memory. A relatively acute onset of symptoms with a fluctuating pattern is helpful in distinguishing delirium from more chronic conditions such as dementia (11). Also, it is important to take into consideration the clinical clues given by family members or caretakers because hints as such can provide invaluable insight that the patient him/herself may not display or report. The patient's family may also provide information about their baseline cognition and attention (18). The history should also include a thorough medication history, as multiple drugs are well known to cause delirium and/or AMS. Of particular importance are any recently introduced or discontinued drugs that might have been associated with the onset of delirium (27,54). This can include steroids, opioids, anti-depressants or benzodiazepines (54-56). Moreover, the physician should assess for signs of alcohol intake/withdrawal, symptoms of infection, and any new stressors or environmental changes (11). The presence of focal nonspecific neurological signs such as tremors and asterixis may accompany AMS and the presence of focal deficits such as unilateral weakness may suggest cerebrovascular or inflammatory events. In patients with such deficits, neuro-imaging is compulsory to rule out any acute event in the brain (11).

It is important to remember that the diagnosis of

delirium in cancer patients is even more complex. Changes in mental status may result from multiple intertwining factors such as the disease itself, the medical therapy, and any comorbidities or baseline cognitive disorders (44). These patients are also under a tremendous amount of stress, and cancer diagnoses are commonly associated with a number of mental health issues, such as adjustment disorders, depression, and major depressive episodes (57,58). The physician must therefore identify and differentiate hypoactive delirium from a normal stress response or depressed mood, and hyperactive delirium from dementia or psychosis (5). Moreover, it is important to maintain suspicion to some of the less common causes of AMS that are more specific to the cancer patient population. This includes new brain lesions, paraneoplastic syndromes (usually associated with ovarian teratoma and small cell lung carcinoma), hepatic encephalopathy, renal failure, and vitamin deficiencies. Additionally, cerebrovascular events causing mental status changes may occur as a result of the increased coagulability associated with malignancies (26,44).

Delirium is considered a medical emergency and prompts investigation to rule out infections and other serious causes. The treating team should therefore ensure airway integrity, obtain blood studies, and monitor vitals while looking for underlying causes (11). However, it is also important for the care provider to balance the need for medical interventions with the patient's comfort. For example, a delirious patient who requires a scan may find it to be a disorienting and traumatic experience despite the routine nature of the procedure. This requires the treating team to be more tactful in their approach in order to minimize the patient's suffering (44).

### *Assessment and diagnostic tools*

Multiple tools have been developed in order to facilitate the detection of delirium. Wong *et al.* showed that among such tools, the Confusion Assessment Method (CAM) had the most evidence supporting its use as a bedside assessment questionnaire (59). This questionnaire has been validated for use in the general population in different settings. The Confusion Assessment Method for Intensive Care Unit (CAM-ICU) is a version of the CAM that was developed for use in the ICU and can be performed in patients who are unable to communicate verbally (60). Other tools used for delirium detection include the Delirium Observation Screening Scale, the Nursing Delirium Screening Scale, and the Mini Mental Status Examination (MMSE). However,

Bush *et al.* have noted that while the CAM and most of the other tools have been validated for the general patient population, no validation studies have been done on the cancer patient population. Additionally, the commonly used MMSE was shown to be the least favorable, although it still provides a decent assessment of baseline cognition (43,59). On another note, instruments such as the Memorial Delirium Assessment Scale and the Delirium Severity Scale provide a good assessment of delirium severity and have been validated for use in the cancer patient population and in terminally ill patients respectively (18), while the Nursing Delirium Symptom Score has been shown to be accurate in bedside screening of delirium (61).

### **Treatment**

The treatment of AMS and delirium includes both pharmacological and nonpharmacological interventions. Nonpharmacological interventions require collaborative effort from the physicians, nurses, and family/caregivers (11). They focus on preserving the patient's safety and integrity, while minimizing any unnecessary stress. The essential need for patient and staff safety must always be kept in mind. The patient should be made comfortable and unnecessary and potentially harmful devices (lines, catheters, etc.) should be removed or fixated to prevent harm to the patient/caregiver or staff. Bed exercises and ambulation are encouraged. These should be tailored to the patient's capacity. On the other hand, the use of physical restraints should be avoided as they risk exacerbating the symptoms and cause significant distress (43). Patient needs, such as bathroom access, should be addressed and promptly tended to. Although the patient with AMS or delirium needs constant monitoring, unnecessary procedures (such as excessive blood tests or pressure monitoring) should be avoided and any potentially aggravating stimuli (such as excessive light, noise, or commotion) should be minimized or removed (62). In case of any vision or hearing impairment, eyeglasses or hearing devices should be provided as needed (43). The patient must be kept calm, with every effort made to keep the patient familiar with his or her surroundings; this is done by ensuring that a familiar face or setting is near at hand (11). Family members/caregivers should be counseled as to what delirium is and its fluctuating course. The physician needs to be mindful of the fact that this is a stressful time for the family members as much as the patient (23). Educating the caregiver/family member on the efforts they can make to decrease agitation and support the patient as medical

treatment is provided will help the patient during recovery and decrease stress in an already-difficult situation (11,22).

Before pharmacological therapy is initiated, an underlying cause of delirium or multiple contributors to the delirium must be sought out and addressed. This includes discontinuing offending medications (opioids in particular), treating infections and rehydrating the patient to support the kidney in flushing out metabolites. As for the use of medications in delirium management in cancer patients, evidence is relatively scarce. Most studies are underpowered, and there is a great need for large randomized clinical trials that compare the use of different medications with non-pharmacological interventions and evaluate the effectiveness of each drug. *Table 1* presents the most typical pharmacological interventions used for delirium as well as the evidence on their uses in cancer patients. The European Society for Medical Oncology (ESMO) Guidelines Committee on delirium management in cancer patients recognize Olanzapine, Quetiapine and Aripiprazole as drugs that may be helpful in treating delirium. However, the Committee did not recommend the use of Haloperidol and Risperidone, which were proven by Agar *et al.* to be non-beneficial when compared with non-pharmacological management (43,63). Further evidence is needed in order to identify the pharmacological interventions that may help improve symptoms and outcomes in cancer patients suffering from delirium.

## Prognosis

There is an abundance of evidence suggesting that delirium is a predictor of long-term morbidity or mortality in the general population. In fact, a meta-analysis of 16 studies conducted by Zhang *et al.* reported increased risks of complications, longer hospital stays, prolonged mechanical ventilation, and increased mortality rates in patients presenting with delirium (73). Delirium has also been suggested as a risk factor for future development of dementia (74). For patients with cancer, the development of AMS is a particularly challenging complication. A study of patients with terminal cancer by Fang *et al.* compared in-hospital mortality rates among terminal cancer patients admitted to the hospital with or without delirium. The results showed a 77.6% mortality rate among in terminal

cancer patients presenting with no delirium compared with a mortality rate of 50.9% in patients admitted without delirium (75). Additionally, patients with cancer presenting with delirium also exhibit shorter survival time in comparison with cancer-free patients with delirium (24).

Mortality risk may vary depending on the delirium subtype, as well as the potential etiological factors involved. The hypoactive subtype of delirium is associated with a higher mortality rate and a shorter mean survival time compared to the mixed and the hyperactive subtypes (75,76). In addition, patients with delirium caused by structural brain lesions display a poorer prognosis in comparison with patients with toxic or metabolic encephalopathies or infections. Moreover, shorter survival was noted in patients with more metabolic abnormalities (27).

On another hand, studies show that at least 50% of delirium cases among cancer patients are reversible, as there is usually no organic change to the brain (19). Patients who do not recover fully continue to show signs of cognitive impairment and functional decline (77). Reversibility may depend on the precipitating and predisposing factors, and can improve once these factors are addressed (78). For example, delirium resulting from medication use, electrolyte abnormalities or dehydration is usually reversible (18,43), unlike delirium caused by a hypoxic event or organ dysfunction (19).

## Conclusions

With the increasing prevalence of malignancy in the community (79), it is important for physicians and nurses to become more cautious about some of the complications that are highly prevalent to cancer patients. Delirium is a complication that is commonly missed in this population and is associated with considerable distress for both the patients and their caregivers. The onset of delirium is associated with poor prognosis in cancer patients and its treatment can be challenging due to its multifactorial etiology. Physicians and nurses involved in the care of oncology patients should therefore receive adequate training in the use of diagnostic tools for delirium and maintain a low threshold for its detection. Additionally, further studies are needed to validate the available diagnostic tools in the cancer patient subgroup.

**Table 1** Pharmacological interventions in management of delirium in patients

Class	Drug	Administration	Adverse effects	Evidence for use in patients with cancer
Typical antipsychotics	Haloperidol	• Oral	(I) Extrapyramidal symptoms. Avoid use in patients with Parkinson Disease	• RCT by Agar <i>et al.</i> (n=247) showed that Haloperidol worsens mild to moderate delirium symptoms causing distress in cancer patients in comparison with individualized management and supportive care (63);
		• Subcutaneous	(II) Prolonged QT interval (ECG monitoring needed in IV administration)	• RCT by Hui <i>et al.</i> (n=90) showed that Haloperidol is more effective in combination with Lorazepam in decreasing agitated delirium symptoms (64);
		• Intramuscular	(III) Anticholinergic effects	• Van der Vorst showed that cancer patients suffering from delirium benefit equally from Haloperidol and Olanzapine (65);
		• Intravenous Use lower doses in elderly or frail patients	(IV) Orthostatic hypotension (V) Neuroleptic malignant syndrome	• In a prospective non-randomized study, Goncalves <i>et al.</i> showed effective and safe use of a protocol combining Haloperidol and Midazolam, with subsequent Midazolam doses given if symptoms do not remit following initial combined dose (66)
	Chlorpromazine	• Oral	(I) Sedation;	No evidence for use in patients with cancer
		• Rectal	(II) Extrapyramidal symptoms (avoid use in patients with Parkinson disease);	
		• Intravenous	(III) ECG abnormalities (ECG monitoring needed in IV administration);	
		• Intramuscular	(IV) Anticholinergic effects;	
		Use with caution in patients with hepatic or renal dysfunction	(V) Orthostatic hypotension;	
		Use lower doses in elderly or frail patients	(VI) Neuroleptic malignant syndrome	
	Methotrimeprazine	• Oral;	(I) Sedation;	No evidence for use in patients with cancer
		• Subcutaneous;	(II) Extrapyramidal symptom (avoid use in patients with Parkinson disease);	
		• Intramuscular	(III) Anticholinergic effects;	
		Use lower doses in elderly or frail patients	(IV) Orthostatic hypotension;	
			(V) Neuroleptic malignant syndrome	

**Table 1** (continued)

Table 1 (continued)

Class	Drug	Administration	Adverse effects	Evidence for use in patients with cancer
Atypical antipsychotics*	Risperidone	Oral	(I) Extrapyramidal symptoms;	RCT by Agar <i>et al.</i> (n=247) showed that Risperidone worsens mild to moderate delirium symptoms causing distress in cancer patients in comparison with individualized management and supportive care (63)
		Use with caution in patients with severe hepatic or renal dysfunction	(II) Hyperprolactinemia;	
		Use lower doses in elderly or frail patients	(III) Increased appetite;	
			(IV) Weight gain;	
			(V) Drowsiness, dizziness;	
			(VI) 6-Headache	
	Olanzapine	• Oral;	(I) Orthostatic hypotension;	• Open-label trial by Breitbart <i>et al.</i> (n=79) showed safe and efficacious use of Olanzapine in the treatment of delirium in cancer patients in hospital (67);
		• Subcutaneous;	(II) Sedation;s	• RCT by Kim <i>et al.</i> (n=32) conducted on mostly cancer patients, showed equal effectiveness between Olanzapine and Risperidone in treatment of delirium. Olanzapine was more effective in patients above 70 years of age (68);
		• Intramuscular;	(III) Metabolic side effects;	• Prospective open-label trial by Eisayem <i>et al.</i> (n=27) showed good tolerance of subcutaneous Olanzapine in cancer patients, although further investigations were recommended to evaluate for efficacy in treating delirium (69)
		Use with caution in patients with hepatic dysfunction	(IV) 4-Extrapyramidal symptoms	
		Use lower doses in elderly or frail patients		
	Quetiapine	Oral	(I) Sedation;	Proven efficacious in treating delirium in RCT conducted by Tanimukai <i>et al.</i> (n=11) (70)
		Use with caution in patients with hepatic dysfunction.	(II) Headache;	
		Use lower doses in elderly or frail patients.	(III) Metabolic disturbances;	
			(IV) 4-Orthostatic hypotension	
	Aripiprazole	• Oral;	(I) Drowsiness;	Open-label trial by Boettger & Breitbart (n=21) showed safe and efficacious use in the treatment of delirium in cancer patients in hospital, with highest effectiveness in hypoactive subtype (71)
		• Intramuscular	(II) Sedation;	
		Use lower doses in elderly or frail patients	(III) Headache;	
			(IV) Metabolic disturbances;	
			(V) Extrapyramidal symptoms	

Table 1 (continued)



Table 1 (continued)

Class	Drug	Administration	Adverse effects	Evidence for use in patients with cancer
GABA agonists (Benzodiazepines)	Lorazepam	• Oral;	(I) Respiratory depression (use cautiously in patients with respiratory compromise);	No evidence for use as monotherapy in patients with cancer
		• Intravenous;	(II) Risk of fall, drowsiness, paradoxical agitation;	
		• Intramuscular Use lower doses when combined with an antipsychotic	(III) Hypotension	
	Midazolam	• Intravenous;	(I) Respiratory depression (use cautiously in patients with respiratory compromise);	No evidence for use as monotherapy in patients with cancer
		• Intramuscular;	(II) Risk of fall, drowsiness, paradoxical agitation;	
		• Subcutaneous Use lower doses when combined with an antipsychotic.	(III) Hypotension	
$\alpha$ 2-receptor agonists	Dexmedetomidine	Intravenous	(I) Hypotension/hypertension;	No evidence for use in patients with cancer
		Use with caution in patients with hepatic dysfunction.	(II) Bradycardia;	
			(III) Agitation	
Stimulants	Methylphenidate	Oral	(I) Insomnia;	Prospective study by Gagnon et al. (n=14) showed improvement of hypoactive delirium in cancer patients following trial of Methylphenidate (72)
			(II) Headache;	
			(III) Irritability;	
			(IV) Hypertension;	
			(V) Tachycardia;	
			(VI) Weight loss	

\*, the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Footnote

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