First Do No Harm . . . Terminal Restlessness or Drug-Induced Delirium

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ABSTRACT

Terminal restlessness is a term frequently used to refer to a clinical spectrum of unsettled behaviors in the last few days of life. Because there are many similarities between the clinical pictures observed in terminal restlessness and delirium, we postulate that at times what is referred to as terminal restlessness may actually be an acute delirium sometimes caused by medication used for symptom control. It is important therefore to consider the causes for this distressing clinical entity, treat it appropriately, and ensure the treatment provided does not increase its severity. This brief review aims to consider the medications that are commonly used toward the end of life that may result in a picture of delirium (or terminal restlessness). These include opioids, antisecretory agents, anxiolytics, antidepressants, antipsychotics, antiepileptics, steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). This review also aims to raise awareness regarding the recognition and diagnosis of delirium and to highlight the fact that delirium may be reversible in up to half of all cases. Good management of delirium has the potential to significantly improve patient care at the end of life.

INTRODUCTION

Terminal restlessness is a term frequently used to refer to a clinical spectrum of unsettled behaviors in the last few days of life. Many other terms including terminal anguish, terminal agitation, and predeath restlessness have been used to describe this clinical state. The symptoms of terminal restlessness include irritability, anxiety, unease, distress, inattention, hallucinations, and paranoia. The signs include restlessness, fidgeting, purposeless yet coordinated movements, tossing and turning, trying to get out of bed, moaning, grimacing, jerking, twitching, myoclonus, confusion, picking at sheets, cognitive impairment and aggression. In one study the prevalence of terminal restlessness was 42% in the last 48 hours of life.1

Delirium is a condition with specific diagnostic criteria, characterized by acute onset, altered level of consciousness, fluctuating course and disturbances in orientation, memory, thought, and behavior.2 Delirium is associated with increased levels of mortality,2,3 with papers quoting mortality rates ranging from 10% to 65%.4 Table 1 outlines the criteria used for diagnosing delirium according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).3,5,6 Delirium is often underrecognized or misdiagnosed as other psychiatric conditions and therefore undertreated.5,7 Although the earliest symptoms of delirium are neuropsychiatric, other nonspecific symp-

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Toms should raise concern that delirium is present—the frail elderly may manifest decreased food intake and decreased activity. Because there are many similarities between the clinical pictures observed in terminal restlessness and delirium, we postulate that at times what is referred to as terminal restlessness and considered to be a common, if unwanted, part of the dying process, may actually be a potentially reversible acute delirium.

Lawlor et al. studied the occurrence, precipitating factors, and reversibility of delirium in patients with advanced cancer. The study found that delirium was reversible in 49% of episodes and that terminal delirium occurred in 88% of deaths. In univariate analysis, psychoactive medications, predominately opioids, and dehydration were associated with reversibility. In multivariate analysis, psychoactive medications, hypoxic encephalopathy, and nonrespiratory infection had independent associations. Lawlor et al. concluded that despite its terminal presentation in most patients, delirium is reversible in approximately 50% of episodes, and delirium precipitated by opioids and other psychoactive medications is frequently reversible with changes in opioid, dose reduction, or discontinuation of unnecessary psychoactive medications.

It is important therefore to consider the causes for this distressing clinical entity, treat it appropriately, and ensure the treatment provided does not increase its severity. Many of the drugs used when approaching the terminal phase are reported to cause delirium. There is little written about drug-induced causes of delirium in palliative literature. Much of the published material has come from geriatric, anesthetic, and psychiatric settings and can be applied in the palliative setting. This brief review aims to consider the medications that are commonly used towards the end of life that may result in a picture of delirium (or terminal restlessness).

**TABLE 1. CRITERIA FOR DIAGNOsing DELIRIUM (DSM-IV)**

1. Disturbed consciousness with reduced ability to focus, sustain or shift attention
2. Change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a new perceptual disturbance
3. Acute onset (usually hours to days) and a fluctuating course.
4. Evidence of a physical (organic) cause.

Delirium is not a homogeneous syndrome and has different subtypes. The most commonly used classification of delirium subtypes is that proposed by Lipowski. He described three different subtypes based on psychomotor activity or alertness: hyperactive–hyperalert (or agitated), hypoactive–hypoalert (somnolent), and a mixed delirium.

In the hyperactive–hyperalert variant, patients may range from being fidgety or restless to being verbally and physically aggressive. Hallucinations and delusions are most common in hyperactive delirium. In the hypoactive–hypoalert variant patients range from being lethargic and quiet to stuporous, in which they can only be aroused by vigorous and repeated stimuli. In the mixed variant many patients alternate unpredictably between a hyperactive–hyperalert and a hypoactive–hypoalert pattern of delirium, either during a single day or over the course of a few days and changes of this type may be interpreted as a major change in the underlying clinical condition.

**PREDISPOsing AND PRECIPITATING FACTORS**

Delirium, especially in older patients, is usually multifactorial in origin. There is an inverse relationship between the severity of the insult necessary to precipitate delirium and the preexisting vulnerability of the patient. Risk factors for delirium can therefore be categorized according to whether they are predisposing or precipitating factors.

One predisposing factor is age. There is a significant increase in the prevalence of delirium with increasing age: 0.4% in those over 18 years old, 1.1% of those over the age of 55, and 13.6% in those over 85. Other predisposing factors (baseline patient characteristics) include male gender, visual impairment, previous dementia (especially if severe), depression, functional dependence, immobility, hip fracture, dehydration, alcoholism, severity of physical illness, stroke and metabolic abnormalities.

Precipitating factors include infection, metabolic disturbances, hypoxaemia, anaemia, urinary retention, bladder catheterization, fecal impaction, alcohol withdrawal, surgery, psychosocial factors, and drugs. Nearly any drug can...
cause cognitive impairment in susceptible individuals; however, certain classes such as opioids, anticholinergics, and benzodiazepines are commonly implicated.4

Many patients approaching the end of life therefore have multiple predisposing factors to delirium, and it is important to minimize the precipitating factors whenever possible.

**PATHOPHYSIOLOGY**

Insight into the mechanism by which some medications contribute to delirium can be gained by understanding the etiology of delirium. Delirium is marked by a global cerebral dysfunction resulting in a generalized reduction in cerebral oxidative metabolism and an imbalance of several neurotransmitters.4,11,12 Any drug that interferes with neurotransmitter function or with the supply or use of substrates for metabolism can cause delirium.12

Neurotransmitter pathways act and interact at many areas throughout the brain, and none of the clinical characteristics of delirium can be solely attributable to the disturbance of a single pathway.9 However, many lines of evidence support the hypothesis that delirium is mediated in part by a failure in central cholinergic transmission, a major system that regulates arousal, attention and memory process.4 Data from animal and clinical studies support the hypothesis that acetylcholine is one of the critical neurotransmitters in the pathogenesis of delirium, and it may be that acetylcholine serves as the final common neurotransmitter pathway.13 The administration of anticholinergic substances to both experimental animals and humans results in the characteristic manifestations of delirium including specific electroencephalogram (EEG) changes.14 This may be an oversimplification, however, because other neurotransmitters, including serotonin, norepinephrine, dopamine and gamma-aminobutyric (GABA) have also been implicated in the pathogenesis of delirium.12 Flacker and Lipsitz14 proposed that there is probably no final common pathway to delirium, but that delirium should be thought of as the final common symptom of a variety of situation-specific neurotransmitter abnormalities.

There is additional evidence to support a role for cholinergic deficiency in delirium. First, risk factors for delirium include metabolic and structural brain abnormalities associated with decreased acetylcholine activity. Second, high serum anticholinergic activity is associated with the severity of the delirium. Third, there is anecdotal evidence to suggest that anticholinesterase drugs used in the treatment of Alzheimer’s disease may also be of good benefit in treating the symptoms of delirium.5 The impact of acetylcholine is also supported by studies that show that acetylcholine neurotransmission decreases with age, which supports that increasing age is a consistent risk factor for delirium.13 The centrally acting cholinomimetic agent physostigmine salicylate has been used to treat anticholinergic delirium since the mid-1800s, and conversely hyoscine hydrobromide, a powerful anticholinergic drug, has been used to induce and study these confusional states experimentally.15 A study in Finland demonstrated that cerebrospinal fluid (CSF) acetylcholinesterase levels measured in acute delirium correlated with the length of life after delirium suggesting that cholinergic dysfunction may also have prognostic significance in these patients.16

Neuroimaging studies suggest that disruption to the frontal cortex, anteromedial thalamus, right basal ganglia, right posterior parietal cortex and mesial-basal temporooccipital cortex is particularly important. This is consistent with models of delirium that involve disruption of attentional systems in the brain, including those responsible for arousal.17

**COMMONLY USED DRUGS IN PALLIATIVE CARE THAT CAUSE DELIRIUM**

A variety of drugs have been reported to induce delirium, and drug-induced delirium is common. In studies of elderly hospital patients, drugs have been reported as the cause of delirium in 11%–30% of cases.12 The relationship of drugs to delirium is most clear for anticholinergic drugs with muscarinic receptor affinity,18 and there have been over 600 drugs identified with anticholinergic effects. Anticholinergic delirium is characteristically associated with agitation behavior and florid visual hallucinations, however, signs of peripheral autonomic anticholinergic toxicity may or may not be present.12

All drugs with pure anticholinergic activity such as hyoscine hydrobromide will in suffi-
ciently high doses induce delirium, especially in susceptible individuals and are therefore considered as high risk. To this high-risk group also belong some other drugs which, with regard to the ability to induce delirium, behave like anticholinergic drugs. Other drugs, like benzodiazepines, will induce delirium, but less frequently and therefore are classed as medium risk. Some drugs are very seldom associated with delirium and constitute a low risk group.18 Central nervous system (CNS) toxicity can occur in a dose-dependent manner, often as a result of interference with neurotransmitter function. Drug-induced delirium can also occur as an idiosyncratic complication12 or as unforeseen side effects of prescribed medication, and can be contributed to by metabolites of drugs not usually thought of as having major anticholinergic effects.11 Anticholinergic drugs with less ability to cross the blood–brain barrier have a lower tendency to produce delirium.18

For a drug to be clearly implicated as a cause of delirium, its administration should precede the onset of symptoms within a short time span (usually hours to days) and withdrawal of the drug should lead to a return to baseline cognitive functioning.12

Below are discussed some drugs that are commonly used near the end of life and have been implicated in causing delirium.

**Opioids**

Opioid use was associated with delirium in 3 of 5 large prospective studies of hospitalized patients.4 Opioids will often induce delirium in aged or demented patients, with codeine and dextropropoxyphene inducing delirium a little less often than other analgesic drugs. However, the risk of delirium associated with opioids is dose related.18 Kuzuma et al.19 reported a case of a 14-year-old boy with acute toxic delirium. He had been treated for several months with transdermal fentanyl, and when the dose was increased he became delirious. They concluded that if central nervous excitatory symptoms develop in a patient treated with transdermal fentanyl, after other causes of delirium have been excluded, consideration should be given to removing the patch and opioid rotating.19

There is experimental evidence that some opioid analgesics reduce the release of acetylcholine in the cerebral cortex, and dose dependent binding to muscarinic receptors in the brain has been demonstrated with fentanyl.20 Oxycodone has also been demonstrated to have anticholinergic effects.13 Therefore changes in an opioid or an increase in a dose prior to the onset of a delirium picture should be considered as a possible cause and appropriate measures taken (Table 2).

**Antisecretory medication**

Hyoscine hydrobromide (scopolamine) and glycopyronium (Robinul) are both anticholinergic drugs that are commonly used for the treatment of terminal secretions (or death rattle). Unlike glycopyronium, hyoscine hydrobromide crosses the blood–brain barrier. It therefore has central anticholinergic effects resulting in drowsiness, hypnosis, amnesia, and occasionally coma. However, it may cause agitation, delirium, excitement and hyperpyrexia due to an absolute or relative reduction in cholinergic activity in the central nervous system (CNS), possibly due to an antagonistic effect to arousal at a hypothalamic and brainstem level.21 Hyoscine hydrobromide, even at very low doses, is commonly associated with cognitive changes, including hallucinations and overt delirium.12 Hyoscine hydrobromide can be used topically as a transdermal patch or subcutaneously by injection or syringe driver. In a case report from the anaesthetic setting, Wilden and Rapeport21 suggested reducing the use of anticholinergic premedication and advocated the increased use of glycopyrrolate which does not cross the blood brain barrier and therefore is unlikely to cause central effects. The use of glycopyronium should lead to a lower incidence of the anticholinergic problems which were often seen in anesthesia. As these drugs are commonly used in the palliative setting, it may be possible to draw a similar conclusion.

**Anxiolytics**

Although most patients become sedated after receiving benzodiazepines, it has been well documented that benzodiazepines can infrequently cause paradoxical hostility, aggressiveness, confusion, and agitation. The etiology of these paradoxical reactions is unknown, although it has been postulated that benzodiazepines alter the levels of multiple CNS neurotransmitters including catecholamines, serotonin, and acetylcholine, resulting in disinhibitory behavior in susceptible
The reversal of benzodiazepine-induced somnolence with the cholinergic-activating drug physostigmine suggests that the benzodiazepines reduce cholinergic function, which would imply a mechanism. Benzodiazepines can therefore induce delirium and all elderly seem to be more sensitive to these side effects. Benzodiazepines have varying potency to cause delirium, but all should be regarded as medium risk drugs. A study in postoperative patients found that long-acting benzodiazepines and higher dose exposure showed a trend toward a stronger correlation with delirium than did short-acting benzodiazepines, and low-dose exposures. Midazolam has repeatedly been shown to be associated with anterograde amnesia that is likely to negatively influence cognitive assessment particularly in relation to orientation in time and place. Paradoxical reactions may be dose dependent and more prevalent in stressful situations, and may occur in patients who have previously taken benzodiazepines without ill effects.

Interactions between medications

Problems with side effects increase considerably when a patient is given several drugs, with additive effects and prolonged half-times being common. Polypharmacy often makes it difficult to identify a single causative drug. A study by Patten et al. found that lithium, anticholinergics, and antipsychotics were all significantly associated with the occurrence of delirium, and the effects were multiplicative with no evidence of interaction between the medication exposures.

Management

A comprehensive history, physical examination, and relevant investigations are mandatory. The neurologic and mental status examination should focus on the features of delirium and any signs of focal neurologic deficits. The medication history is crucial, usually from a family member or from other medical or nursing professionals, as drug-induced delirium is generally treated conservatively by withdrawing the offending agent. The dose should at least be reduced if withdrawal is not possible. Neurologic and mental state status should be assessed. Blood investigations should assess electrolytes (hypernatremia/hyponatremia, hypercalcemia), renal function (dehydration, renal failure), white cell count (infection), and thyroid function (hypothyroidism/hyperthyroidism). Pulse oximetry may reveal hypoxia.
Prevention is better than cure, and so the general principle to minimize the occurrence of delirium is to avoid medications likely to induce it if alternative medications exist, and to use the lowest effective dose possible. If possible, low-risk drugs should be used and if drugs with a high risk of inducing delirium are used, the patient should be observed for a longer period in order to detect adverse reactions.4,18

A randomized trial,29 albeit in younger patients with acquired immune deficiency syndrome (AIDS), has confirmed that neuroleptic agents are superior to benzodiazepines for control of the symptoms of delirium because they do not impair respiratory function and are less likely than benzodiazepines to cause drowsiness or disinhibition.11 Haloperidol remains the standard treatment; it is a powerful antipsychotic that can be given orally or parenterally and has limited anticholinergic, sedative, hypotensive, or proarhythmic properties.11,28,30 Neuroleptic agents can however cause other neuropsychiatric problems such as akathisia.31 The neuroleptic agents ameliorate a range of symptoms and are effective both in patients with a hyperactive or hypoactive clinical profile.28

Physostigmine (a cholinergic agonist) is known to be helpful in the treatment of delirium caused by anticholinergic toxicity, but its use has been limited by peripheral cholinergic (parasympathetic) toxicity including excessive respiratory tract secretion, emesis, diarrhea, and cardiac dysrhythmia.14 It crosses the blood brain barrier and therefore reverses the central effects of anticholinergic drugs.12 Trials are investigating whether cholinesterase inhibitors such as donepezil may be useful in treating (or preventing) delirium.11 Serotonin antagonists such as trazodone may also be helpful.3

Benzodiazepines are the first-line treatment for delirium that is associated with seizures or withdrawal from alcohol or sedatives. They are also a useful adjuvant treatment for patients who cannot tolerate antipsychotic drugs. Benzodiazepines can therefore both protect against delirium and be a risk factor for it.28

Causes, especially those that are drug-induced, should be sought and treated when appropriate. When a patient is in the terminal phase, it is important to avoid inducing agitation by the drugs given to promote comfort. The drugs given to patients in the later phases of illness may actually cause delirium that can be misinterpreted in the palliative care setting as terminal restlessness. Therefore, if a patient does become unsettled after a potentially causative drug has been administered, a change in the medication should be considered, and the potentially causative drug should not be given again if possible. Hydration and opioid rotation should also be considered.8,30

Educational strategies in palliative care aimed at raising awareness of neuropsychiatric disorders, including delirium, should be developed. Nonrecognition and misdiagnosis of delirium appear to be common.30 It is important for optimal patient care that suspected terminal restlessness is not simply assumed to be irreversible and the patient sedated, without due consideration being given to possible causes, including the medications outlined in this paper. If the cause is found and treated, the clinical symptoms of delirium that are distressing for the patient, family members, and staff are more likely to be adequately controlled.

CONCLUSION

Terminal restlessness may be caused by an acute delirium that is a potentially reversible condition in up to half of patients who develop it.

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