

Review Article

Delirium in Palliative Medicine: A Review

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Abstract

Delirium is a devastating complication of general medical and surgical populations but of particular importance in palliative medicine. It is a clinical syndrome that is often not recognized and, therefore, not treated appropriately. The presence of delirium is a predictor of increased morbidity and mortality, longer hospitalization, and more likely discharge to a nursing facility. This article reviews the pathophysiology, etiology, diagnosis, and treatment of delirium in the palliative medicine population. J Pain Symptom Manage 2012;44:583–594. © 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Delirium, palliative medicine, antipsychotic

Introduction

Delirium is a neuropsychiatric diagnosis that is very common in general medical and surgical populations. It is of particular importance in palliative medicine as the incidence ranges from 28% to 88% depending on the stage of illness, with the higher number occurring at end of life.^{1–4} Delirium is a clinical syndrome with myriad presentations often divided into motoric subtypes—hypoactive, hyperactive, and mixed.^{5–7} It is underdiagnosed, particularly

the hypoactive subgroup, which may be more common in the palliative medicine population.^{8,9} The *Diagnostic and Statistical Manual of Mental Disorders* defines delirium related to a medical condition as “1) a disturbance in consciousness with reduced ability to focus, sustain, or shift attention, 2) a change in cognition that is not better accounted for by a preexisting, established, or evolving dementia, 3) the disturbance that develops over a short period (hours to days) and tends to fluctuate during the course of the day, 4) the evidence that the disturbance is caused by the direct physiological consequences of a general medical condition.”¹⁰ Additional symptoms include alteration in sleep-wake cycle, short- and long-term memory deficits, delusions, hallucinations, and emotional lability.¹¹ The presence of delirium is a predictor of increased morbidity and mortality, longer hospitalization, and more likely discharge to a nursing facility.^{11–14} This article reviews the pathophysiology, etiology, diagnosis, and treatment of delirium in the palliative medicine population.

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Pathophysiology

There has been research trying to find the one common pathway that would explain all deliriums. There are numerous theories, all with some evidence to support them. It is likely that the symptoms of delirium are the expression of many different abnormalities that impact neurotransmitters and neurons in different areas of the brain. Theories include 1) decreased oxidative metabolism with an impact on neurotransmitter systems leading to cerebral dysfunction; 2) direct effects on neurotransmitters such as decreased acetylcholine and increased dopamine; changes also have been documented to norepinephrine, gamma-aminobutyric acid, glutamate, and serotonin; 3) neurotransmitter changes in normal aging making the elderly more at risk; 4) increased inflammatory cytokines that impact neurotransmitter systems; 5) stress reactions leading to blood-brain barrier changes, and hypothalamic-pituitary-adrenal axis increases leading to neurotransmitter synthesis changes; and 6) changes in intraneuronal signal transduction affecting neurotransmitter synthesis and release.¹⁵

The leading theory is decreased cholinergic activity accompanied by dopaminergic increase.^{16–18} Anticholinergic medications have been shown to cause inattention, which is one of the cardinal symptoms in delirium. This neurotransmitter also is involved in arousal, learning and memory, rapid eye movement sleep, behavior, mood, thought, perception, and orientation.¹⁶ Anticholinergic medications can cause slowing of the electroencephalogram, a common finding in delirium. Serum anticholinergic levels correlate with severity of delirium and decrease as symptoms improve.¹⁸ Dopaminergic excess causes a decrease in cholinergic activity.¹⁷ Dopaminergic agonist medications such as L-dopa, bupropion, and cocaine can cause delirium. Dopamine antagonists are used therapeutically.

Etiology

There are several studies defining risk factors for the development of delirium in a general medical population, with varying results.^{19,21,22} An early study in the elderly identified urinary tract infection, low serum albumin, elevated white count, and proteinuria

as risk factors.²⁰ In a later study, factors were age, visual impairment, severe illness, cognitive impairment, and dehydration (increased BUN/creatinine ratio).²² Groups were categorized as low (zero risk factors), intermediate (one to two risks), or high risk (three to four risks) and developed delirium 3%, 16%, and 23%, respectively. Additional studies have identified advanced age, cognitive impairment, preexisting severe chronic illness, and functional impairment.²¹ Five precipitating factors were identified in a general medical geriatric population: 1) the use of physical restraints, 2) malnutrition (serum albumin <3.0 mg/dL), 3) the addition of more than three medications, 4) the use of bladder catheterization, and 5) iatrogenic events.²²

Multiple precipitating factors have been identified in cancer and palliative medicine patients (Table 1). In a study of delirium in this population, a median of three precipitating factors was identified, with a range of one to six.^{2,4} Psychoactive medications, metabolic disturbances,

Table 1
Etiologies of Delirium

Metabolic disturbance
Hypercalcemia
Hyponatremia
Hypernatremia
Dehydration
Glycemic derangements
Organ failure
Renal failure
Liver failure
Respiratory failure
Medications
Opioids
Benzodiazepines
Anticholinergic agents
Steroids
Sepsis
Pneumonia
Urinary tract infection
Brain pathology
Primary brain tumor
Brain metastases
Leptomeningeal disease
Nonconvulsive status epilepticus
Hypoxia
Withdrawal
Alcohol
Benzodiazepines
Hematologic
Disseminated intravascular coagulation
Anemia

dehydration, nonrespiratory infection, hypoxic encephalopathy, and intracranial causes were among the factors noted. In other studies, medications, brain pathology, and dehydration were the most common precipitating events.^{4,12} A study specifically looking at psychoactive medications in a cancer population identified exposure to benzodiazepines, corticosteroids, and opioids as etiologic factors.²³ Surprisingly, the involvement of common anticholinergic medications was not noted, although they have been identified as risk factors in other studies. Benzodiazepines and opioids are listed as potentially anticholinergic on the anticholinergic drug scale.²⁵ Underappreciated causes include alcohol withdrawal and iatrogenic benzodiazepine withdrawal.^{25,26}

A study of cognitive function in cancer patients found that one-third had possible or definite cognitive dysfunction that was related to opioid dose (400 mg of morphine equivalents a day), older age, low Karnofsky Performance Status, lung cancer, short time since diagnosis, and no breakthrough pain.²⁷

Diagnosis

Delirium is often underrecognized or misdiagnosed.^{12,28–30} A key factor in diagnosis is a high index of suspicion. In addition, a baseline assessment at admission is important, especially if medication changes are planned. Information from multiple sources, particularly family, is critical. After admission, nursing impressions can be quite helpful, given the fluctuating course of delirium. In the palliative medicine setting, hypoactive delirium is more common and more likely to be misdiagnosed as depression.²⁹

There are numerous diagnostic tools both for identification and severity assessment. Many of these, such as the Memorial Delirium Assessment Scale (MDAS) and the Delirium Rating Scale (DRS and DRS-98-R), are useful for diagnosis and severity rating and most commonly used for research assessment. They have been used and tested with psychiatric consultants.^{31–34} The MDAS has been evaluated with palliative care professionals using simulated patients.³⁵ One of the more common tools used is the Mini-Mental State Examination (MMSE), although this only diagnoses cognitive impairment

and is not discriminatory for delirium; therefore, the MMSE should not be the only tool used.^{3,36} A nursing tool for continuous evaluation, the Nursing Delirium Screening Scale, also has been validated although not in a palliative medicine population.³⁷

In the clinical setting, a test that determines either the presence or absence of delirium quickly may be more practical. The most researched and convenient is felt to be the Confusion Assessment Method (CAM), which has been validated in the palliative care population and takes approximately five minutes to complete.^{38,39} This tool reflects the *Diagnostic and Statistical Manual of Mental Disorders* criteria with the exception that altered consciousness is not required in the CAM (Table 2). It requires the presence of both an acute onset and fluctuating course and the presence of inattention, then either disorganized thinking or altered level of consciousness. Various tools have been used to assess disorganized thinking including the MMSE, the Bedside Confusion Scale (months of the year backward), and the clock drawing test.^{4,40} There is an entity of subsyndromal delirium described in which a patient has one or more of the core symptoms but does not have delirium according to CAM.^{41,42} This may reflect either a prodrome to delirium, a syndrome of its own, or evidence of persistent delirium. This is associated with longer hospitalization and increased mortality but not as high as seen in full blown delirium. Treatment for this entity has not been described and its manifestations are not fully defined.

Table 2
The Confusion Assessment Method Diagnostic Algorithm³⁹

Feature 1: Acute onset and fluctuating course
Obtained from family member or nurse. Is there an acute change in mental status from baseline? Does it fluctuate during the day?
Feature 2: Inattention
Is the patient easily distractible or having difficulty keeping track of what is being said?
Feature 3: Disorganized thinking
Was the patient's thinking disorganized or incoherent? Rambling or irrelevant conversation, illogical or unclear flow of ideas, unpredictable switching from subject to subject
Feature 4: Altered level of consciousness
Anything other than alert

One of the key differential diagnoses is dementia vs. delirium. Complicating this differential is delirium in the setting of preexisting dementia.⁴³ Because cognitive impairment and advanced age are predisposing factors for delirium, its presence in hospitalized patients with dementia is not surprising. Given our aging population and the increasing incidence of dementia, a corresponding increase in delirium can be expected.^{30,31} Delirium has a sudden onset and fluctuating course, whereas dementia has a slow progressive decline, the history of which can be obtained from family. Both diagnoses will have cognitive impairment, but dementia may have more severe cognitive impairment and more severe impairment in level of consciousness.⁴³ An acute behavioral change is the most consistent with delirium even in the setting of preexisting dementia.

The differential of depression from delirium also depends on the time course. Hypoactive delirious patients may have depressed mood and psychomotor retardation, but cognitive impairment is not typically seen in depression. Depression cannot be diagnosed in the setting of acute delirium.³⁰

Impact

As noted, delirium is associated with prolonged hospitalization, increased mortality, and more likely discharge to a long-term care facility. The mortality impact has been examined in an advanced cancer population.¹ A median survival of 21 days in delirious patients was compared with a median survival of 39 days in non-delirious patients. Delirium can have a prolonged impact on function, with symptoms continuing more than three months after diagnosis in up to 25–45%.^{44–47} This is relevant to palliative medicine populations as they may not fully recover during their life expectancy.^{44,45} The long-term abnormal cognitive function or the development of dementia that has been seen up to five years after delirium may be of less concern.⁴⁷ Depression and anxiety symptoms including post-traumatic stress disorder also have been seen in recovered delirious patients.⁴⁸ In a study of suicidal patients, 20% were found to have delirium.⁴⁹

Subtypes of delirium have been associated with varying symptoms. The hyperactive subtype

is more readily diagnosed, given its interference in care. Increased falls were seen in this population as they did not remember they were supposed to stay in bed or ask for assistance.⁵⁰ In the hypoactive subtype, the one most often overlooked, there was an increase in bedsores and infection. This is most likely related to the patients' relative immobility. There was an increase in mortality for the hypoactive subtype once admitted to a postacute care unit.⁵¹

Three studies have looked at the distress caused by delirium on palliative medicine patients, families, and caregivers. In the first study, patients who had recovered from their delirium were questioned regarding their recall.⁵² The more severe the delirium, the less likely they were to remember it. In those who did, patients had mean distress levels of 3.2 on a four-point scale. The mean level was 3.75 for their families and 3.09 for nurses. Of note, those with hypoactive delirium were just as distressed as those with the hyperactive subtype. In a qualitative study, only two of 34 patients did not remember the experience.⁵³ Distress was found in "most" patients and their caregivers. Those who were told in advance of the risk of delirium were less distressed. Many families felt that the cause was the pain medication. A third study replicated the work of the first, addressing recall and distress in advanced cancer patients, caregivers, and nurses.⁵⁴ Moderate-to-severe distress was noted in patients and caregivers but not in nurses.

The presence of delirium can interfere in the assessment of symptoms.^{55,56} In one study, patients were on stable doses of narcotics before their delirium and resumed these doses after the episode resolved, suggesting adequate pain control.⁵⁵ Increased use of clinician bolus doses during the period of delirium was found, and it was felt that moaning was interpreted as pain. Families also were in conflict with the team, feeling their loved ones were in uncontrolled pain. After resolution of the delirium, pain medication use returned to pre-delirium levels.

Terminal delirium is seen in at least 88% of patients.² This creates significant distress for families.^{52–54,57,58} Treatment of this symptom at end of life may involve sedation, which removes the possibility of communication with the loved one. In a series of focus groups, five themes were identified: 1) a perception

of suffering. Family members saw the delirium as a reflection of multidimensional suffering. They also felt that their loved one was fighting not to die; 2) the lack of communication. There was a significant need to communicate and the sedative medication was identified as the reason it could not occur; 3) ambivalence. Family members felt ambivalent about the use of the sedating medication. Some felt that the medication hastened death. Family members felt that staff was overly generous in their use of the medication because they knew the person was dying; 4) a need for information. Understanding of the patient's symptom, the dying process, and when the death was expected decreased confusion; and 5) sensitivity and respect. Family members were very aware of how their loved one was treated by staff. A perception that they were ignored created lasting painful memories.⁵⁷ In another study, 37% of family members felt that considerable or much improvement in professional care was needed.⁵⁸ A psychoeducational intervention explaining delirium was found to be useful.⁵⁹

Evaluation

The evaluation of delirium is similar to detective work (Table 3). One needs to question all involved parties, especially family, to get a sense of baseline function and when it

Table 3
Evaluation

Determine goals of care
Review medications
Consider the possibility of withdrawal
Identify any hematologic or metabolic abnormalities/ organ failure
Complete metabolic panel
Complete blood count
Evaluate oxygen levels
Oxygen saturation
Identify infections
Urine culture
Blood cultures
Chest x-ray
Specialized testing if appropriate
Electroencephalogram
Arterial blood gas
Tests for disseminated intravascular coagulation
Thyroid-stimulating hormone
Computed tomography scan or magnetic resonance imaging scan of the brain
Lumbar puncture

became abnormal. Then one searches for any changes, particularly medications, which may have occurred before the alteration in mental status. A previously tolerated medication can be a source of delirium if there has been a change in renal or liver function or a change in pain level, as might occur with radiation therapy. A change in dosage or a new medication should always be considered a potential cause.

How much one evaluates an episode of delirium is dependent on goals of care. In a patient clearly nearing death, it may not be reasonable to subject them to investigative procedures. It also may not be relevant to identify problems that would not be treated, for example, a magnetic resonance imaging scan to look for brain metastases in someone to whom you would not give radiation therapy. Yet, studies of outcomes of delirium identified reversibility in up to 50% of cases.^{2,60} Given this, it may be reasonable to do a search for reversible causes such as medications, hypercalcemia and other metabolic abnormalities, infection, and dehydration. Metabolic derangements such as liver or renal failure and hypoxic encephalopathy have been associated with irreversible delirium.^{2,60} An electroencephalogram might be warranted if nonconvulsive status epilepticus is suspected.^{61,62}

Treatment

The primary treatment of delirium is the management of the causative factor(s) when possible. Opioid rotation, removal of any medication that might contribute to delirium, and management of dehydration and hypercalcemia are examples. Given the paucity of placebo-controlled trials, it is difficult to know if pharmacologic treatment impacts the course rather than a response to treatment of the underlying causes. There are limited trials to evaluate the management of delirium and fewer still that compare regimens in a controlled fashion.

Treatment would be unnecessary if there were reliable preventive strategies.⁶³⁻⁶⁵ A study done in palliative care inpatients used a nurse rating system, the Confusion Rating Scale, with notification to physicians of medications with a propensity for delirium. There was routine orientation at each shift and a family

educational intervention. This was not found to decrease incidence, duration, or severity of delirium compared with usual care.⁶⁴ A multicomponent intervention has been tested in an elderly population and was found to decrease the frequency of delirium and shorten the course.⁶⁵ This intervention included an orientation protocol, cognitively stimulating activities, nonpharmacologic sleep protocol, early mobilization, obtaining vision and hearing aids, and recognition of dehydration. This has not been tested in a palliative medicine population and some aspects, such as early mobilization, might be difficult in these ill patients. Maintaining hearing and visual aids, orientation protocols, sleep protocols (quiet in the hallways and rescheduling medication and laboratory tests), and recognition of dehydration are quite doable on any unit. Addressing other risk factors such as catheters and IVs may not be as amenable to intervention because catheters can provide comfort when it is painful to get up and medication administration may often be continuous even if given subcutaneously. There also have been limited trials with pharmacologic prevention of delirium.⁶⁶ Agents that have been evaluated include haloperidol, risperidone, rivastigmine, donepezil, benzodiazepines (for sleep), and melatonin. A Cochrane review concluded that there was no evidence to suggest benefit of the cholinesterase inhibitors, rivastigmine, and donepezil.⁶⁷

Dehydration is recognized as a cause of delirium, yet the use of fluids is controversial.^{68–72} Many hospices consider this life-prolonging therapy and routinely do not use fluid resuscitation. A classic study demonstrated that there was no suffering associated with dehydration as long as good mouth care was provided.⁷⁰ Others feel that dehydration contributes to delirium secondary to altered metabolism of medications and that treatment decreases the incidence of terminal delirium.⁷¹

Despite the fact that there is no U.S. Food and Drug Administration-approved medication for the management of delirium, antipsychotics are commonly used in all settings—intensive care units (ICUs), postoperatively, and in palliative medicine.^{73–78} The most commonly recommended and used medication is haloperidol, which is still considered the medication of choice.^{75,76} A Cochrane review stated that there are inadequate data from which to make

conclusions.⁷⁸ The first significant study was a double-blind comparison of haloperidol, chlorpromazine, and lorazepam in 30 AIDS patients with delirium.⁷⁹ There was no difference between haloperidol and chlorpromazine, but the lorazepam arm was stopped because of increased toxicity and worsening of delirium. Doses were low, with the mean haloperidol dose on Day 1 being 2.8 mg. Mean Day 1 dose for chlorpromazine was 50 mg. An hourly titration schedule was used that increased the dose of medication every hour the DRS was greater than 13 (the cutoff for diagnosis of delirium). For instance, at baseline, the dose of haloperidol was 0.25 mg. One hour later, if not improved (DRS < 12), asleep or calm, then 0.50 mg was given. One-half of the Day 1 dose was then given as maintenance, with the haloperidol average dose 1.4 mg and chlorpromazine 36 mg. Improvement was seen between Days 1 and 2, although statistically significant only for the chlorpromazine arm. There were no significant extrapyramidal side effects (EPS).

Quetiapine is the only antipsychotic that has been compared with placebo. A randomized double-blind trial was conducted with 42 medical and surgical patients.^{80,81} Quetiapine 25 mg was given as the starting dose, with a 25 mg increment daily if needed. The maximum dose was 175 mg in divided doses. Downward titration was allowed if symptoms resolved. Improvement occurred 57% faster in the quetiapine arm. The study was underpowered but still gives interesting information.⁸⁰ A second placebo-controlled randomized trial in ICU patients found a shorter time to resolution, with a median of one vs. 4.5 days.⁸¹ As-needed haloperidol was allowed and there was a nonstatistically significant difference favoring the quetiapine arm. Five episodes of sedation and one case of hypotension occurred that were felt to be secondary to the study drug. There were no cases of EPS.

Atypical antipsychotic agents have been compared with haloperidol including risperidone, olanzapine, and aripiprazole in prospective and retrospective trials.^{82–91} No statistically significant difference has been shown. Toxicity comparisons have generally shown no difference except one trial that used higher doses of haloperidol (6.5 mg on average).⁸⁹ There have been case series and open-label trials of these agents including olanzapine, risperidone,

quetiapine, aripiprazole, and ziprasidone.^{92–100} Each has shown efficacy equivalent to haloperidol, with a suggestion of fewer EPS. In one open trial of olanzapine, the medication did not seem as effective for those aged older than 70 years, or with hypoactive delirium, pre-existing dementia, hypoxic encephalopathy, cancer metastatic to the central nervous system, and severe delirium based on the MDAS.⁹⁴ The strongest predictor for poor response was age older than 70 years. In a seven-day randomized trial of risperidone vs. olanzapine, the response rates were similar but the investigators found a poorer response for the risperidone in those aged older than 70 years.⁹⁵ Both olanzapine and risperidone have been reported to cause delirium.^{101–104}

One of the disadvantages of the atypical agents is that they have been primarily available only as oral agents. Olanzapine, aripiprazole, and ziprasidone are now available as intramuscular injections but palliative medicine practitioners try to avoid this pain. One preliminary trial using olanzapine subcutaneously found no adverse skin reactions.¹⁰⁵ Ziprasidone has been used intravenously⁹⁹ in an ICU setting.

The role of benzodiazepines is unclear. There is no question they are the drugs of choice for withdrawal delirium from alcohol or benzodiazepines. In the study by Breitbart et al.,⁷⁹ the lorazepam arm was stopped because all patients became worse. A systematic review of medications to avoid in high-risk patients found that benzodiazepines were associated with delirium.¹⁰⁶ The study of medications and delirium in cancer patients found benzodiazepines to be a common cause.²⁴ A Cochrane review concluded that benzodiazepines could not be recommended in the management of delirium, but this was based on very limited data.¹⁰⁷ A study of the management of delirium by different specialties still found that 21% of medical oncologists chose a benzodiazepine as primary therapy for delirium in a previously functional patient.¹⁰⁸ This compares with 3% of palliative medicine physicians, geriatricians, and psychogeriatricians.

The treatment of hypoactive delirium is controversial. Canadian guidelines do not recommend treatment,¹⁰⁹ and American Psychiatric Association guidelines do not comment specifically.⁷⁶ Many treatment studies are confined to

hyperactive or hyperactive plus mixed patients. In the studies of distress, hypoactive delirium was as distressing as hyperactive,^{52,54} arguing that intervention would be appropriate. In a study of 24 patients, 11 were hypoactive and responded well to haloperidol, with similar improvement as the hyperactive group.¹¹⁰ There have been reports on the use of methylphenidate in hypoactive delirium.^{111–113} The rationale is that the stimulant may improve arousal and the ability to concentrate. In one study of 14 patients, hypoactive delirium not explained by metabolic or drug-induced causes or one week after treatment of the underlying cause was treated with a 10 mg test dose of methylphenidate.¹¹³ Each patient was monitored for two hours after administration of the dose. Cognitive function improved to normal range on the MMSE. Psychomotor retardation improved, as did energy level. Stable doses were 20–30 mg daily.

Treatment Recommendations

Haloperidol is the most cost-effective option. It is tolerated by most patients and delirium can usually be managed with low doses, that is, under 5 mg/day. The atypical antipsychotics are no better than haloperidol, although there are suggestions of fewer EPS. They are certainly more expensive. Reasonable starting doses are haloperidol 0.5–2 mg daily, olanzapine 5 mg daily, risperidone 0.25–0.5 mg daily, and quetiapine 25 mg. Rapid titration with low doses of haloperidol has been done with hourly monitoring. Unfortunately, in a retrospective evaluation of neuroleptic doses, there was no impact on delirium recall or distress.^{85,114} This is not surprising because the symptoms are not prevented and there would be distress until response occurred. Benzodiazepines are only recommended in delirium caused by alcohol or benzodiazepine withdrawal.

Sedation

In the setting of irreversible or terminal delirium, the agitation may be so severe that sedation is required. A review of sedation is beyond the scope of this article. As noted, families are ambivalent about sedation and grieve the loss of communication.⁵⁷ Delirium is one of the more common symptoms requiring

sedation.¹¹⁵ Rates of sedation for all causes vary from 10% to 52%.^{115–121} The Edmonton group lowered their rate of sedation by monitoring cognitive function more often, looking for treatable causes and managing them when appropriate to goals of care, opioid rotation, and increased use of hydration.¹¹⁶ Midazolam and lorazepam are the most commonly mentioned medications, but methotrimeprazine and chlorpromazine also have been used.^{116,122,123} There have been no comparison trials. Cost issues also have not been addressed.

Conclusions

Delirium is a common devastating complication of advanced disease and often a result of the medications we use to treat these patients. Pathophysiology relates to various neurotransmitters with a decrease in cholinergic activity and a corresponding increase in dopaminergic activity as the leading theory. When goal appropriate, underlying causes should be sought, as 50% may be reversible.

There is significant distress experienced by patients and families, which may be decreased by educational interventions. Treatment with neuroleptics can be considered the standard of care, although there are only two placebo-controlled trials, both of which showed improved time to response. Benzodiazepines are the preferred treatment in withdrawal delirium from alcohol and benzodiazepines but are problematic in nonwithdrawal delirium. There is no drug that has been shown to be better than haloperidol but side effect profiles differ. Future research should focus on studies in the palliative medicine population with high-quality randomized controlled trials for medications, prevention trials, and ways to decrease patient and family distress.

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