ProCare **HospiceCare** *March/April Edition 2016*

On-Demand Clinical News

Terminal Restlessness and Delirium in the Dying

Priya Narula, PharmD, CGP

Common neuropsychiatric symptoms that patients may present at the end of life include delirium, agitation and terminal restlessness. Delirium is an altered state of consciousness or an acute change in the level of arousal caused by toxic, structural and/or metabolic disorders. It includes symptoms like agitation, anxiety, restlessness, apathy, withdrawal, disturbance of memory and attention, altered sleep/wake cycle, confusion, mumbling speech, and perceptual disturbances with delusions and hallucinations. It is transient, has an abrupt onset, and a fluctuating course differentiating it from dementia, which is a progressive and chronic mental syndrome. As hospice clinicians, we can typically identify specific causes of delirium, which can be reversible. This is usually not the case with dementia.

There are several available screening tools for delirium that are validated in palliative care patients.

Agitation is a state of restlessness and increased psychomotor activity, and is often a behavioral manifestation of multiple conditions, like delirium, dementia, pain, depression, anxiety, or end of life symptoms like fear, anger, interpersonal or spiritual conflict. Terminal delirium or restlessness is delirium in a patient in the final days or weeks of life, where treatment of the underlying cause may not be possible, practical, or consistent with the goals of care.

It is estimated that the prevalence of delirium and cognitive disturbances in the end of life ranges from 25-85% and as an illness progresses, becomes more common. Prevalence also increases with age and results in higher mortality rates.

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Pharmacogenomics: The Future of Patient Specific Care

Nathaniel Hedrick, PharmD

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. Many medications that are currently available are designed using a "one size fits all" model. However, it can be difficult to predict who will benefit from a medication, who will experience negative side effects, and who may not respond to a drug at all. Researchers are starting to learn how inherited differences in genes may affect the body's response to medications. These genetic differences can be used to design new medications, predict whether a medication will be effective for a particular person, or to help prevent adverse drug reactions.

Deoxyribonucleic Acid (DNA) is the foundation on which all life is built. This sequence of nucleic acid bases codes for everything that makes up an individual. The Human Genome Project was launched by the National Institute of Health in 1990 with the goal of mapping the more than 3 billion nucleic acid base pairs that make up our DNA. Researchers took genetic code from more than 100 individuals to create an "average" human genome. What they discovered is that genetically, each human is about 99.6% the same. That last fraction of a percent is what makes an individual unique in appearance, personality, and biochemistry.
So far, these variations in genetic makeup have been mapped to code for more than 1,800 different diseases and over 2,000 human conditions.

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In a palliative care setting, 13-42% of patients can have delirium on admission and 26-62% can have delirium during an inpatient stay. In an attempt to manage delirium, it is important to identify possible underlying causes, especially those that are potentially treatable. The common causes of delirium are listed in the graphic below:

Overall, the management of delirium requires a stepwise approach. In order to identify a cause, it is first necessary to do a thorough patient assessment and utilize screening tools. It is important to get a complete medical, medication and family history, as well as to conduct a physical and neurologic exam, and draw appropriate labs if needed. There are several available screening tools for delirium that are validated in palliative care patients. These include the Memorial Delirium Assessment Scale (MDAS), Confusion Assessment Method (CAM) and Bedside Confusion Scale (BCS). It is also important to focus on delirium prevention by routinely reviewing new medications and avoiding or minimizing delirium-inducing medications whenever possible and using the lowest effective dose when they are needed.

If treatment is needed, both non-pharmacologic and pharmacologic management should be considered. Non-pharmacological interventions include maintaining a calm and comfortable environment for the patient, a quiet well-lit room, using music, aromatherapy, maintaining consistency in caregiving and involving family members. If medications are to be used for management, antipsychotics (such as haloperidol, chlorpromazine, risperidone or quetiapine), while not FDA approved for the management of delirium, are the primary treatment of choice. Clinicians recommend haloperidol as a first line agent, which is effective at lower doses of 1-3 mg, however up to 20mg/day can be used. Haloperidol can be given via multiple routes of administration including by mouth, sublingually or rectally. It is not recommend for use in movement disorders like Parkinson's disease (quetiapine is the preferred agent in movement disorders). Benzodiazepines are not recommended for delirium management because they can increase paradoxical reactions. It is best to think of benzodiazepines as *sedatives* and *anxiolytics* but not as therapy for underlying delirium.

If the goal of treatment is to sedate a delirious patient, a benzodiazepine may be indicated. If anxiety is a prominent part of a patient's delirium, a benzodiazepine may help. Lorazepam or alprazolam (if no liver impairment) are preferred benzodiazepines because they have relatively shorter half-lives and do not have active metabolites that can lead to accumulation, particularly in the elderly. Discussing such symptoms with a hospice clinical pharmacist can be very useful in helping to identify possible underlying causes of delirium and devising an appropriate management approach.

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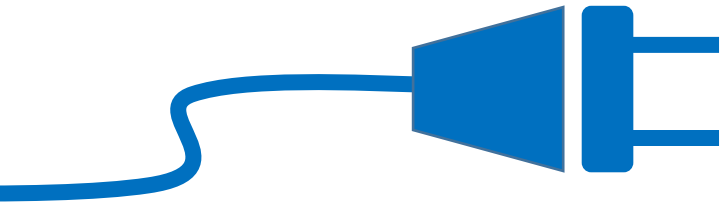
More are being discovered all the time and even slight variances in the sequence of these bases can have dramatic effects. For example, the condition known as sickle cell disease is caused by the substitution of just *one* nucleic acid in the gene that codes for hemoglobin. Realizing how these small changes can impact patients has started to change the process for medication development as well as for disease screening.

Cystic Fibrosis (CF) is an inherited life-threatening disorder that damages the lungs and digestive system. Currently it has no known cure and genetic research has discovered that there are 6 genetic mutations that can cause CF. Recently, a medication called ivacaftor has been developed that specifically targets the protein deficiency caused by one of these mutations. Patients with this specific variant that were given ivacaftor saw significant improvement in their symptoms while patients with the other 5 variants did not see any improvement when compared to placebo. Researchers hope that examples like these will lead to other targeted cures for specific variants of rare or life-threatening diseases. Targeted medications may help patients in the future but genetic research is also improving the use of older medications as well.



Pharmacogenomics is an exciting **new** field of study and its implications on **medical practice** are **changing** all the time…

Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. Researchers are trying to reduce this problem by measuring changes in drug metabolism based on genetic code. The majority of the population usually falls somewhere in the range of intermediate or extensive metabolizers when looking at how their body processes a given medication. A much smaller subset of people end up in the extremes of this spectrum as either poor or ultra-rapid metabolizers. This means that their body does not process medication in the expected way. Take for example codeine, a medication that needs to be metabolized in the body before it can become active. In the case of a poor metabolizer, their body is unable to convert enough drug into the active form to provide pain relief. Many of these patients will report that the medication they were given simply did not work. Ultra-rapid metabolizers on the other hand, may convert a lot of that drug into the active form very quickly, which can lead to overdose or adverse reactions. The hope is that as the reactions are better understood and as screening tools improve, patients could theoretically use their genetic code to ensure they are started on just the right dose the first time around.

Pharmacogenomics is an exciting new field of study and its implications on medical practice are changing all the time. Whether it be for new drug development, disease screening or in-office patient testing, it is likely that its influence will only grow in the coming years. Hopefully, through use of this information, patient care can be improved through multiple avenues.

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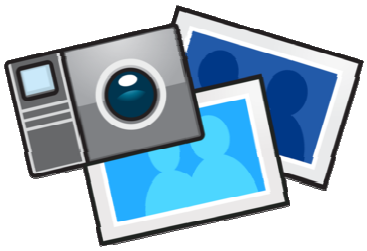

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March: "Common Symptom Medications and Associated Side Effects"
Presenter: Karen Bruestle-Wallace, PharmD, CGP
Tuesday, March 8, 2016 at 3:00pm ET; Wednesday, March 9, 2016 at 12:00pm ET

April: "Alternative Medications for Pain Management"
Presenter: Priya Narula, PharmD, CGP
Tuesday, April 12, 2016 at 3:00pm ET; Wednesday, April 13, 2016 at 12:00pm ET

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