ProCare **HospiceCare** *November/December Edition 2015*

On-Demand Clinical News

Serotonin Syndrome in Hospice Patients

Sheri Irvine, PharmD

Serotonin syndrome is a symptom of over stimulation of serotonin receptors caused by using a drug that affects serotonin or more commonly, as a result of drug interactions. The syndrome is categorized as a combination of mental status changes, neuromuscular hyperactivity, and autonomic hyperactivity. Hospice patients are at an increased risk of serotonin syndrome because of changes in drug metabolism due to factors such as age and renal or hepatic function. They are also a population more likely to use combinations of drugs that influence serotonin.

The following is a list of commonly used medications in hospice patients that can impact serotonin:

- **Antidepressants/Anxiolytics:**
  Bupropion, trazodone, mirtazapine, buspirone
  Serotonin-Norepinephrine Reuptake inhibitors (SNRI):
  duloxetine, venlafaxine, desvenlafaxine,
  Selective Serotonin Reuptake Inhibitors (SSRI): sertraline,
  citalopram, escitalopram, fluoxetine,
  fluvoxamine, paroxetine
  *Tricyclic Antidepressants (TCA)***:** amitriptyline,
  clomipramine, desipramine, doxepin, imipramine,
  nortriptyline
- **Antiemetics:** promethazine, ondansetron
- **Antihistamine/OTC cold products:** chlorpheniramine, dextromethorphan
- **Opiates**: meperidine, oxycodone, tramadol, fentanyl
- **Parkinson's drug:** L-dopa
- **Triptans:** sumatriptan, frovatriptan, rizatriptan, etc.
- **Mood stabilizer:** lithium
- **Prokinetic agents:** Metoclopramide
- **Monoamine oxidase inhibitors (MAOI's)** *(not commonly prescribed anymore*): Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline
- **Drugs with MAOI activity**: linezolid and Procarbazine

Continued on page 2

Antipsychotics for Dementia: Under Control or Over-Prescribed?

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Dementia is a chronic and progressively worsening disease marked by memory disorders, personality changes and impaired reasoning. As the disease process continues, many patients develop worsening neuropsychiatric symptoms of agitation, depression, insomnia, delusions and psychosis. These symptoms can be distressing to patients, caregivers and especially family members. Recently, the use of antipsychotics for such symptoms has been met with some controversy and conflicting information can make the difficult task of selecting an appropriate therapy an even greater challenge.

Because there is no cure for most cases of dementia, the primary goal of treatment is to delay the progression of symptoms while preserving the patient's day-to-day function and quality of life. While no treatment has yet been shown to slow the physical degeneration of neurons in the brain, several therapies can help to alleviate symptoms by 'boosting' the function of the remaining neurons. Cholinesterase inhibitors such as donepezil or galantamine work by slowing the degradation of acetylcholine from surviving pre-synaptic nerve terminals. NMDA receptor antagonists, such as memantine, serve to block the over-stimulated glutamate receptors postulated to occur in Alzheimer's Dementia. Both of these mechanisms can be beneficial in the early stages of the disease but become progressively less effective as the patient enters the later stages of dementia.

Continued on page 3

Serotonin Syndrome in Hospice Patients continued from page 1

Some combinations of medications have a higher incidence of serotonin syndrome. Fifty percent of patients taking a MAOI + SSRI/TCA develop severe symptoms with >60% accounts of death due to serotonin syndrome. Linezolid + SSRI have a greater risk of mild symptoms that can be rapidly reversed. Serotonin syndrome also occurs with about 0.03% of patients on Triptans + SSRI.[3]

Mechanistically, serotonin syndrome occurs when there is inhibition of serotonin uptake, decreased serotonin metabolism, increased serotonin synthesis or release, and the activation of serotonergic receptors. It can also involve the inhibition of cytochrome P450 (CYP450) enzymes by SSRI's or other medications that affect these enzymes. The sum of these interactions results in an excess of serotonin. Studies do not demonstrate a specific receptor responsible for the development of serotonin syndrome. There is some evidence that the 5HT-2A receptors play a large role in this syndrome because they are found both centrally and peripherally. Increased stimulation of central receptors affects wakefulness, attention, behavior, thermoregulation, appetite, motor control, migraines, emesis, pain, and aggression. Peripheral receptors affect vasoconstriction, bronchoconstriction, GI motility and platelet aggregation. Using these agents alone or in combination with each other, increases the risk of serotonin syndrome.[2]

Serotonin syndrome normally occurs within 6-24 hours of initiating the offending agents. It is typically diagnosed by exclusion, ruling out other causes like infection, substance abuse, or withdrawal. Management starts with discontinuing the offending agent(s). Improvements normally occur within 24 hours but may be longer depending on the half-life of the drugs. Supportive care may include use of a benzodiazepine. For more severe symptoms cyproheptadine and chlorpromazine can be initiated. Table one demonstrates the different symptoms a patient with serotonin syndrome may experience and ways to manage them.

Table 1. Mild, Moderate and Severe Symptoms Associated with Serotonin Syndrome and Ways to Manage them.[4]

	Symptom	Management
Mild	Mild hypertension, tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, hyperreflexia	-Discontinue the offending agent/agents -Support by stabilizing vital signs, cooling measures -Benzodiazepines
Moderate	Above symptoms, plus temperature of at least 40.8^{0}C, hyperactive bowel sounds, ocular clonus, agitation, hypervigilance, pressured speech	-All of the above plus, -Severe agitation and hyperthermia: 5HT-antagonist (cyproheptadine) -Admission to hospital for cardiac monitoring/observation
Severe	Above symptoms, plus temperature greater than 41.18^{0}C, dramatic swings in heart rate and blood pressure, delirium, muscle rigidity	-All of the above plus, -Severe hypertension/tachycardia: esmolol or nitroprusside -Sedation and paralysis with a non-depolarizing agent and intubation/ventilation -Admission to the intensive care unit

Hospice patients are at risk for serotonin syndrome and it often goes unrecognized. This is because many of the symptoms like agitation, anxiety, restlessness, increased temperature, tremors, etc. are attributed to disease progression. This can significantly decrease a patient's quality of life by increasing undesirable side effects. Recognition, selecting appropriate medications and removal of offending agents is the key to reducing the risk of serotonin syndrome.

References:

1. Brown, C. (2010). Drug-Induced Serotonin Syndrome. US Pharmacist, 1-8.
2. Cushing, Tracy et al. (2014). Selective Serotonin Reuptake Inhibitor Toxicity. Medscape, 1-5.
3. Evans RW. The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and triptans: and analysis of the 29 case reports. October 01, 2015 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2100123/?tool=pubmed. Accessed January 26, 2010.
4. Lexi-Comp Drug Database. Available by subscription only from: online.lexi.com

Antipsychotics for Dementia continued from page 1

Psychosis, hallucinations and agitation can develop at any stage of dementia but are particularly prominent in end-stage patients. These symptoms impair quality of life, are distressing to patients and to caregivers, and are commonly a major contributor to the decision to move a family member with dementia into a nursing home. Antipsychotics remain the major pharmacological treatment for these symptoms. Multiple reputable studies have found consistent improvement in aggression, agitation, psychosis and behavioral disturbances when an antipsychotic was compared to placebo. However, large-scale meta-analyses of clinical trials have also demonstrated a 1.5–1.7 times increased risk of mortality when antipsychotics were used to treat dementia. These analyses have also linked a two to three-fold higher risk of cerebrovascular events.

In light of this data, the FDA has issued a black box warning for *all* antipsychotics about this risk and none have an approved indication for the treatment of any neuropsychiatric symptoms of dementia. Furthermore, in 2010, the Center for Medicare and Medicaid Services (CMS) found that 39.4% of nursing home residents nationwide who had cognitive impairment and behavioral issues but no diagnosis of psychosis or related conditions received antipsychotic medications. As a result, CMS launched an initiative to reduce the amount of antipsychotics used in nursing homes and long term care facilities by 25% by the end of 2015, and a further 30% reduction by the close of 2016.

Despite these risks and recommendations, many scenarios exist where patients with dementia and agitation can benefit from the use of antipsychotics. In fact, numerous associations and guidelines recommend antipsychotics for neuropsychiatric symptoms of dementia when used in the hospice setting or when symptoms cannot otherwise be alleviated. However, the approach to determining these situations should be a stepwise one. Before any medication is started, potential remedial causes of behavior should first be excluded. This includes delirium (which itself may have underlying remedial causes that should be addressed prior to initiation of antipsychotic), infection, pain, environmental factors, and other medications. Every effort should be taken to alleviate these potential other causes before starting an antipsychotic. Next, the patient's ability to swallow, other current medications and symptoms and whether or not the symptoms are intermittent or continuous should be considered.

For example, if a patient has Parkinson's dementia as well as agitation, quetiapine would likely be the antipsychotic of choice as it has shown to limit movement-related side effects. Finally once an antipsychotic has been chosen, the lowest effective dose necessary to control symptoms should be used and titrated up as needed. The patient should be reassessed frequently for improvement in behaviors as well as new or worsening side effects. It is also worth noting that if the patient is a threat to themselves or others, antipsychotics can and should be started immediately to assist in controlling these symptoms.

Utilizing a stepwise approach when caring for a patient with dementia is the best way to maximize quality of life while limiting potential side effects. Contact a ProCare HospiceCare Clinical Pharmacist when starting or adjusting antipsychotic treatment to discuss potential underlying symptoms and to help develop an individualized treatment plan for your patient.

References:

1. LS Schneider, KS Dagerman, P Insel "Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized palcebo-controlled trials". JAMA, 2005
2. Kverno K, Rabins P, Blass DM, Hicks K, and Black S. "Prevalence and Treatment of Neuropsychiatric Symptoms in Hospice-Eligible Nursing Home Residents with Advanced Dementia". J Gerontol Nurs. 2008 Dec; 34(12): 8–17.
3. Mitchell S, Kiely S, Hamel MB. **"**Dying With Advanced Dementia in the Nursing Home." *Arch Intern Med.* 2004;164(3):321-326.
4. Partnership to Improve Dementia Care in Nursing Homes Antipsychotic Drug use in Nursing Homes Trend Update. Centers for Medicare and Medicaid Services. Posted 9/19/14
5. The Dementias: Hope Through Research. National Institute of Health. Published Sept 2013, Last updated: January 22, 2015
6. Rochon PA, Normand S, Gomes T, et. al. "Antipsychotic Therapy and Short-term Serious Events in Older Adults With Dementia". *Arch Intern Med.* 2008;168(10):1090-1096.
7. Lee PE, Gill SS, Freedman M, et. al. "Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review". *BMJ* 2004;329:75
8. Jeste DV, Blazer D, Casey, D, et. al. "ACNP White Paper: Update on Use of Antipsychotic Drugs in Elderly Persons with Dementia". *Neuropsychopharmacology* (2008) 33, 957–97

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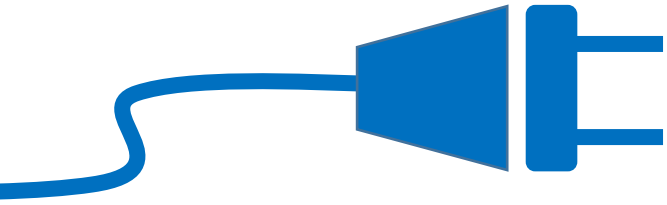

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Tuesday, November 10, 2015 at 3:00pm ET; Wednesday, November 11, 2015 at 12:00pm ET

December: "Considerations for Symptom Management in the Renal Disease Patient"
Tuesday, December 8, 2015 at 3:00pm ET; Wednesday, December 9, 2015 at 12:00pm ET

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