Wyoming Drug Utilization Review

Preventing Serotonin Syndrome

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Disease Description

Serotonin Syndrome (SS) is an iatrogenic toxic condition, hence it is preventable.[1] Clinical guidelines for the prevention of SS do not yet exist.[2] Recommendations for preventing it are based on case reports. A particularly challenging aspect of diagnosing SS is differentiating it from the expected effects of serotonin augmenting agents.[1]

Serotonin (5HT) activation and SS have similar signs and symptoms.[1] Serotonin activation is an expected result of taking a serotonergic drug and includes: gastrointestinal problems, dry mouth, headaches, nervousness, agitation, insomnia, night-time tremor, sexual difficulties, and diaphoresis.[1] Serious side effects of selective serotonin re-uptake inhibitors (SSRIs) include increased suicidal ideation, manic behavior and hyponatremia, that are not due to serotonin toxicity.[1]

SS is caused by serotonergic hyper-stimulation.[2] Patients with SS typically display a triad of symptoms: 1) change in mental status, 2) autonomic hyperactivity, and 3) neuromuscular hyperactivity.[1,3] Signs and symptoms include: agitation (restlessness), diaphoresis, diarrhea, hyperreflexia, incoordination (ataxia), confusion, hypomania, myoclonus, shivering, and tremor.[2] Sternbach's diagnostic criteria indicate serotonergic hyper-stimulation when the patient exhibits at least three of these 12 signs and symptoms.[2] Hallmarks of serotonin toxicity are clonus and tremors.[3]

Some patients may not exhibit the complete triad of symptoms, yet they have SS. This may result in cases of serotonin toxicity being missed by practitioners.[1] This article aims to describe the potential risk of developing SS among various types of serotoninergic agents; as well as offer prescribing, education and risk mitigation strategies, in order to to reduce the risk of developing SS. A list of serotonergic drugs and their relative risk for SS is found in Table 1 on page 3.

What is the risk?

Serotonergic drugs increase 5HT in the body through six different mechanisms: increased serotonin 5HT production, inhibition of 5HT reuptake, inhibition of 5HT metabolism, increased 5HT release, stimulation of 5HT receptors, and decreased elimination of the serotonergic drug.[3] Serotonergic drugs may use multiple mechanisms to exert their effects.[3] Decreased elimination of serotonergic drugs may occur when the cytochrome enzyme needed to process that the drug is inhibited.[3]

Risk Mitigation

Number of agents – When two or more serotonergic drugs are prescribed to a patient, the risk for SS increases.[3] Use caution when prescribing two or more serotonergic medications and try to avoid any unnecessary serotonergic drug combinations.[3] Remember to allow sufficient time between drugs when switching from agents with a long half-life, such as fluoxetine or MAOIs.[3]

Serotonergic effect – Medications that affect 5HT have variable serotonergic effects.[3] Although toxicological data is limited to case studies, some classes of serotonergic drugs have been estimated as high risk

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P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on November 14, 2013.

Highlights of this meeting include:

Kapvay will be limited to those aged 4 and older with an ADHD diagnosis in addition to existing clinical criteria.

Approval of Xyrem will require diagnosis of cataplexy and/or excessive daytime sleepiness associated with narcolepsy, confirmed by a sleep study performed by a sleep specialist. Trial and failure of modafanil and methylphenidate or dextroamphetamine at maximum recommended dose is required.

The TOBI podhaler and Bethkis will require prior authorization.

Patients currently taking clonazepam will be grandfathered and allowed to continue use. Existing criteria will be applied to new patients.

Adempas will be approved for patients with pulmonary arterial hypertension confirmed by right-heart catheterization.

The Committee reviewed the draft 2014 Preferred Drug List. The PDL will be posted on the DUR website for review and comment.

All proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to December 20, 2013.

The next P&T Committee meeting will be held on Wednesday, February 12, 2014 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Preventing Serotonin Syndrome continued

for SS: MAOI's, SSRI's and SNRI's.[3] Fluoxetine has a very long half-life and providers should wait up to 5-6 weeks after discontinuation before starting another serotonergic drug.[2,3]

Patient history – Because patients have variable responses to drugs in general, there is no way to predict which patient will develop serotonin toxicity.[3] A patient's medication response may indicate whether development of SS is likely to occur. Counsel the patient on how to recognize signs and symptoms of SS.[3] Educate staff on potential drug combinations that could lead to SS.[3]

Newness of the drug – If a drug is relatively new; there are fewer cases to report regarding SS and consequently, less data is available to estimate the risk of serotonin toxicity. Consider the newness of the drug when using it in combination with other serotonergic agents.

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Serotonergic Agents Table

*Compiled results[2-9]

Drug	Risk +	Mechanism of Toxicity/ Clinical Pearls
SSRIs	High	Inhibits 5HT reuptake
Demerol	High	Inhibits 5HT reuptake/ Associated with severe SS when used with MAOI's
Fentanyl	Undefined	Direct serotonin agonist
TCAs: Clomipramine, Imipramine, Amitriptyline	Undefined	Inhibits 5HT reuptake/ Amitriptyline inhibits reuptake to a lesser degree
Triptans	Low	5HT receptor stimulation
Chlorpheniramine	Undefined	Inhibits 5HT reuptake
St John's Wort	Undefined	Inhibits 5HT reuptake
Methylene Blue	Undefined	Inhibits serotonin metabolism
Linezolid	Undefined	Inhibits serotonin metabolism
MAOIs – Selegiline, Tranylcypromine, Phenelzine, Isocarboxazid	High	Inhibits serotonin metabolism/ Allow up to 1 weeks after MAOI discontinuation before starting another serotonergic drug
l-tryptophan	Undefined	Increased 5HT production, because it is a 5HT precursor
SNRIs	High	Inhibits 5HT reuptake
Buspirone	Undefined	5HT receptor stimulation, Direct 5HT agonist
LSD, MDMA, Cocaine	Undefined	Inhibits 5HT reuptake
Lithium	Undefined	5HT receptor stimulation
Atypical Antidepressants - Bupropion	Undefined	Inhibits 5HT reuptake
Dihydroergotamine	Undefined	5HT receptor stimulation
Serotonin Modulators - Nefazodone, Trazodone Vilazodone	Undefined	Inhibits 5HT reuptake/ Nefazodone inhibits CYP3A4 as well; Trazodone antagonizes 5HT at low doses, and agonizes at high doses
Lorcaserin	Undefined	Inhibits CYP1C9/ CYP inhibition especially problematic with patients taking dextromethorphan
Ritonavir	Undefined	Inhibits serotonin metabolism
Synthetic Phenylpiperidine Opioids – Methadone, Dextromethorphan, Tramadol, Pentazocine	Low	Inhibit 5HT reuptake/ Switch methadone users to buprenorphine; Dextromethorphan associated with severe SS when used with MAOI's
Cyclobenzaprine	Undefined	Inhibits 5HT reuptake
Levodopa, Carbidopa- Levodopa	Undefined	Indirectly causes release of 5HT

+ When used in combination with other agents

2014 P & T Committee Meeting Dates

Wednesday, February 12; Thursday, May 8; Thursday, August 14; Thursday, November 13

Meetings are held in Cheyenne at Laramie County Community College, 10 am - 1 pm.

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