



Indiana Medicaid Drug Utilization Review Board Newsletter

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Indiana Medicaid DUR Board

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Center, South

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Serotonin Syndrome Risk in

Patients on Multiple Proserotonergic Therapies

Serotonin syndrome has been identified increasingly in animals and humans since the 1960s.¹ The term is used to describe a group of symptoms observed with the administration of medications that elevate serotonin concentrations and is characterized by a triad of mental, autonomic, and neurological disorders.^{1,2} Serotonin syndrome is a toxic condition, which requires heightened clinical awareness in order to prevent, recognize, and treat the condition promptly. Given that an estimated 85% of prescribers are unfamiliar with this syndrome as a diagnosis, the exact incidence is unknown.⁷ The principle differential diagnosis for serotonin syndrome is neuroleptic malignant syndrome because of its similar symptoms and clinical presentation.²⁻⁴

Serotonin syndrome is characterized by the following symptoms: mental (confusion, delirium, hallucinations, elevated mood, coma, agitation, and insomnia); autonomic (fever, hyperhidrosis, lacrimation, shivering, tachycardia, tachypnea, dyspnea, diarrhea, and blood pressure fluctuation); and neurological (nystagmus, myoclonus, tremors, chills, rigidity, hyperreflexia, impaired coordination, mydriasis, akathisia, seizures, and rhabdomyolysis).^{2,5,6} Serotonin syndrome is most often reported in patients taking 2 or more medications that increase serotonin concentrations in the central nervous system by different mechanisms. Serotonin syndrome usually develops after a dose increase of a serotonergic medication or the addition of another sero-

tonergic medication. The symptom onset typically occurs within 2 hours of a change.⁶ Meperidine and dextromethorphan are potent inhibitors of serotonin uptake and have been implicated in the precipitation of serotonin syndrome, primarily in patients taking monoamine oxidase inhibitors (MAOIs). In general, health care professionals should avoid prescribing concomitant medications with serotonergic activity.

Causative agents associated with serotonin syndrome include those with the following mechanisms: increase serotonin synthesis (e.g., L-tryptophan); decrease serotonin metabolism (e.g., MAOIs); increase serotonin release (e.g., amphetamines); inhibit serotonin uptake (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants); direct stimulation of serotonin receptors (e.g., buspirone); and nonspecific increase in serotonin activity (e.g., lithium).^{2,6} Although antidepressants are most commonly associated with serotonin syndrome, amphetamines, dopamine agonists, and 5-HT₁ receptor agonists are also capable of contributing to serotonin syndrome.

In most patients, serotonin syndrome can be managed with the following 4 principles: provision of supportive care, acute discontinuation of all serotonergic medications, potential use of antiserotonergic medications, and appropriate alterations in the patient's treatment regimen before re-initiating serotonergic medications. Mild to moderate cases of serotonin syndrome usually resolve in 24 to 72 hours when the

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offending medication is discontinued. Although most cases can be treated and resolve within a week, some patients are acutely ill at presentation and require hospitalization. In severe cases of serotonin syndrome, admission to the intensive care unit and mechanical ventilation may be required, and deaths have been attributed to this syndrome.

The remaining challenge prescribers face is the appropriate pharmacologic therapy following a patient’s recovery from serotonin syndrome. Patients who experience serotonin syndrome are likely at an increased risk of developing signs and symptoms of the syndrome in the future. The use of serotonergic medications in these patients should be minimized, and the benefit should clearly outweigh the risk of developing serotonin syndrome. See Table 1 for serotonergic medications, which should be used with caution when prescribed concomitantly in patients.

References

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2. Birmes P, Coppin D, Schmitt L, Lauque D. Serotonin syndrome: a brief review. *CMAJ*. 2003;168:1439-42.
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5. Martin TG. Serotonin syndrome. *Ann Emerg Med*. 1996;28:520-6.
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5-HT1 Receptor Agonists (Triptans)	Dextromethorphan	Nefazodone	TCA's (e.g., Amitriptyline, Doxepin, Imipramine)
Amantadine	Linezolid	Phentermine	Tramadol
Amphetamines	Lithium	Selegiline	Trazodone
Bromocriptine	MAOIs (e.g., Isocarboxazid, Phenelzine, Tranylcypromine)	Sibutramine	Tryptophan
Buspirone	Meperidine	SSRIs (e.g., Fluoxetine, Sertraline, Paroxetine)	SNRIs (e.g., Venlafaxine, Duloxetine)
Cocaine/LSD/MDMA ("ecstasy")	Mirtazapine	St. John's Wort	

MAOI: monoamine oxidase inhibitor; SNRI: selective norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Correction From Previous Newsletter:

The Value of Generics Newsletter, published in January 2008, contained information regarding the ‘Anticipated Availability of First Time Generics’ on page 3. Depakote ER (Divalproex Extended Release) was incorrectly listed as having a projected date of availability of January 2008. The listed product should have been Depakote **DR** or Depakote Delayed Release Tablets. Please note that anticipated generic availability can be highly variable and depends on multiple factors including patent litigation.

Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

PDL Listing

The fee-for-service PDL listing may be found at the following Web site:
<http://www.indianapbm.com/>

Top 20 Drugs for 4Q 2007

**Top 20 Drugs 4th Quarter 2007
Ranked by Total Amount Paid**

Drug	Total Paid	Total Claims
Risperidone	\$3,681,686.72	14,745
Quetiapine Fumarate	\$3,111,328.89	13,182
Olanzapine	\$3,073,913.68	6,891
Aripiprazole	\$3,029,902.14	8,513
Antihemophilic. FVIII Plas/Alb Free	\$2,925,620.64	100
Divalproex Sodium	\$1,836,139.87	11,558
Topiramate	\$1,476,388.75	6,419
Lamotrigine	\$1,476,101.84	6913
Antihemophilic Factor, Hum Rec	\$1,347,932.25	48
Insulin	\$1,268,283.09	9,671
Oxycodone HCL	\$1,208,653.40	5,284
Ziprasidone HCL	\$1,192,202.68	4,309
Fentanyl	\$1,151,379.78	3,676
Levetiracetam	\$1,009,710.55	4,148
Fluticasone / Salmeterol	\$978,265.26	5,252
Atorvastatin Calcium	\$966,359.78	9,308
Duloxetine HCL	\$882,207.84	7,094
Oxcarbazepine	\$838,221.26	4,737
Amphet ASP/Amphthet/ D-Amphe	\$795,200.93	8,238
Pantoprazole Sodium	\$784,674.62	6,116

**Top 20 Drugs 4th Quarter 2007
Ranked by Total Claims Paid**

Drug	Total Claims	Total Paid
Hydrocodone/APAP	45,288	\$383,620.30
Aspirin	40,821	\$32,837.74
Docusate Sodium	38,762	\$79,991.01
Alprazolam	33,678	\$225,094.16
Calcium Carb/Vit D	32,427	\$66,297.47
Acetaminophen	31,982	\$82,237.83
Multivitamins	27,135	\$38,903.72
Loratadine	26,072	\$249,454.90
Clonazepam	23,257	\$115,476.69
Lorazepam	22,041	\$128,631.50
Omeprazole Magnesium	19,987	\$563,746.08
Albuterol	18,591	\$402,260.85
Multivitamins with Minerals	16,945	\$49,551.54
Risperidone	14,745	\$3,681,686.72
Levothyroxine	13,218	\$93,379.76
Quetiapine Fumarate	13,182	\$3,111,328.89
Lisinopril	12,868	\$54,702.22
Diazepam	12,704	\$253,101.01
Divalproex Sodium	11,558	\$1,836,139.87
Ferrous Sulfate	11,250	\$10,936.71