BRAC UNIVERSITY
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PHARMA HIGHLIGHTS

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Tizanidine and Ciprofloxacin- Serious Drug Interaction

Tizanidine, a centrally acting skeletal muscle relaxant, is metabolized mainly by cytochrome P450 (CYP) 1A2 and has a low oral bioavailability. The fluoroquinolone antibiotic ciprofloxacin is only a moderately potent inhibitor of CYP1A2. In a double-blind, randomized, 2-phase crossover study, 10 healthy volunteers ingested 500 mg ciprofloxacin or placebo twice daily for 3 days. On day 3, a single dose of 4 mg tizanidine was ingested 1 hour after the morning dose of ciprofloxacin. Plasma concentrations of tizanidine and ciprofloxacin and pharmacodynamic variables were measured. A caffeine test was used as a marker for CYP1A2 activity. It was found that Ciprofloxacin increased the area under the plasma concentration-time curve from time 0 to infinity [AUC(0-infinity)] of tizanidine by 10-fold (range, 6-fold to 24-fold; P < .001) and its peak concentration by 7-fold (range, 4-fold to 21-fold; P < .001), whereas its elimination half-life was only prolonged from 1.5 to 1.8 hours (P = .007). The pharmacodynamic effects of tizanidine were much stronger during the ciprofloxacin phase than during the placebo phase with regard to changes in systolic blood pressure (-35 mm Hg versus -15 mm Hg, P = .001), diastolic blood pressure (-24 mm Hg versus -11 mm Hg, P < .001), Digit Symbol Substitution Test (P = .02), subjective drug effect (P = .002), and subjective drowsiness (P = .009). The AUC(0-infinity) of tizanidine and its change correlated (P < .01) with the caffeine/paraxanthine ratio and its change. Ciprofloxacin greatly elevates plasma concentrations of tizanidine and dangerously potentiates its hypotensive and sedative effects, mainly by inhibiting its CYP1A2-mediated metabolism, at least when administered 1 hour before tizanidine. Tizanidine seems to be a useful probe drug for measuring presystemic metabolism by CYP1A2. Care should be exercised when tizanidine is used concomitantly with ciprofloxacin.

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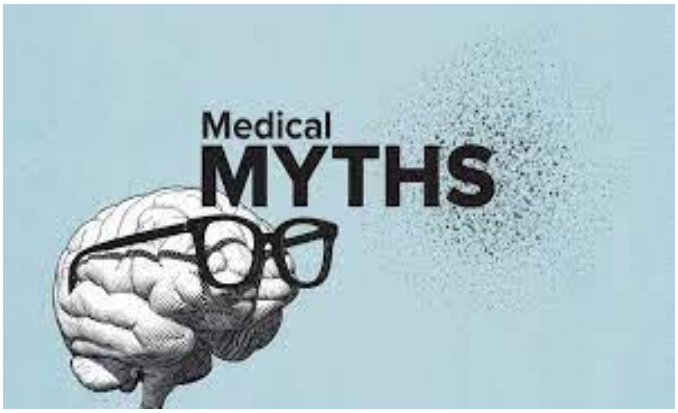
Serotonin Syndrome-Myths and Misconceptions



Serotonin is a neurotransmitter (a naturally occurring brain chemical) that helps regulate mood and behavior, and increasing serotonin is one way of treating depression. But if you're taking antidepressant medication that increases serotonin too much, you could be at risk for a dangerous drug reaction called serotonin syndrome.Serotonin syndrome (SS) was one of the first serious drug interactions ever described, with the first cases reported more than 50 years ago. SS is caused largely by drug—drug interactions, although occasional cases have been reported following the use of single serotonergic drugs. Unfortunately, there is still some confusion and controversy about SS.

Early reports of serotonin overload occurred in the 1950s with antidepressants called monoamine oxidase inhibitors (MAOIs). When new drugs called selective serotonin reuptake inhibitors (SSRIs) became widely used to fight depression, reports of serotonin syndrome increased.

A large number of cases of SS have been reported in the literature and to the FDA over the past few decades. Unfortunately, many of these cases probably do not represent actual SS. More than 20 years ago, psychiatrist Harvey Sternbach proposed a set of diagnostic features of SS known as Sternbach's criteria. While useful and sometimes still used today, these criteria included some relatively nonspecific symptoms, such as agitation, confusion, diarrhea, fever, and sweating. This resulted in misdiagnosis of SS in many patients and sometimes, paradoxically, failure to identify mild forms of the

disorder. There is now general agreement that the Hunter criteria—which focus more on the neuromuscular findings of clonus, muscle rigidity, tremor, and hyperreflexia—are more reliable for diagnosing SS.

Two primary misunderstandings are responsible for the erroneous listing of various drugs as causes of SS. First, drugs capable of exerting serotonergic effects differ widely in their likelihood of causing SS. Just combining 2 serotonergic drugs does not necessarily increase the risk for SS. There are many different serotonin receptors, and only some of them appear to be involved in the etiology of SS. Second, very few drugs (mainly the monoamine oxidase inhibitors) are capable of producing severe SS, while a much greater number of drugs can cause mild to moderate SS. A good example of the confusion regarding the risk of SS with particular drug combinations is the concurrent use of triptans with selective serotonin reuptake inhibitors (SSRIs) or serotonin—norepinephrine reuptake inhibitors (SNRIs).

In July 2006, the FDA issued a warning, based on 29 cases reported to the FDA, that the combined use of triptans and SSRIs could result in life-threatening SS. In the November 2006 issue of this column, we pointed out that the evidence actually suggested that the combinations were probably safe in the vast majority of patients. Even more important, neurologist Randolph Evans obtained the details of the cases from the FDA and determined that none of the 29 cases met the Hunter criteria for SS. The issue continues to stimulate discussion, and it came up at the 2013 International Headache Congress, where Dr. Paul Rizzoli presented epidemiologic evidence suggesting that there is “no reason to believe these medications interact in such a way that would produce SS.” Yet even today, severe warnings about the concurrent use of triptans and SSRIs or SNRIs still appear in many computerized drug interaction systems, and the product information still warns about the possibility of life-threatening SS if triptans are combined with SSRIs or SNRIs. SS is a drug-induced phenomenon and usually results from the combined effects of 2 or more drugs. The diagnosis is now made primarily on the basis of adverse neuromuscular effects as found in the Hunter criteria. Many published purported cases of SS do not represent actual SS, and this has resulted in much misinformation in computerized drug interaction detection systems.

References:
Iqbal MM, Basil MJ, Kaplan J, Iqbal MT. Overview of serotonin syndrome. Ann Clin Psychiatr.
Boyer EW, Shannon M. The serotonin syndrome. New Engl J Med. 2005

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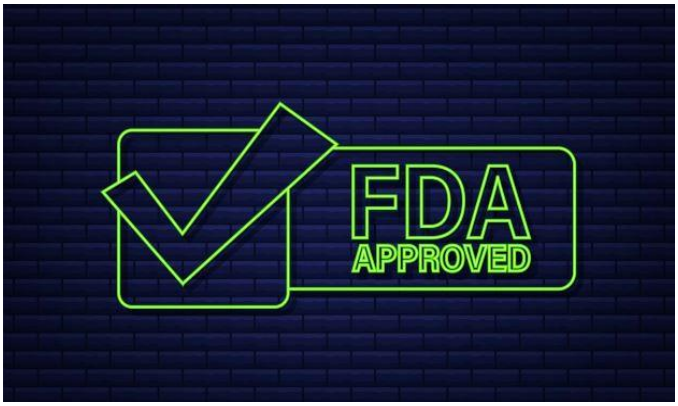
Newly Approved FDA Drugs

When it comes to the development of new drugs and therapeutic biological products, FDA’s Center for Drug Evaluation and Research (CDER) provides clarity to drug developers on the necessary study design elements and other data needed in the drug application to support a full and comprehensive assessment. To do so, CDER relies on its understanding of the science used to create new products, testing and manufacturing procedures, and the diseases and conditions that new products are designed to treat.



1. **<u>Quviviq</u> (daridorexant) Tablets**

   Company: Idorsia Ltd.

   Treatment for: Insomnia

   Quviviq (daridorexant) is a dual orexin receptor antagonist (DORA) for the treatment of insomnia

2. **Cibinqo (abrocitinib) Tablets**

   Company: Pfizer Inc.

   Treatment for: Atopic Dermatitis

   Cibinqo (abrocitinib) is a Janus kinase (JAK) 1 inhibitor for the treatment of adults with refractory, moderate-to-severe atopic dermatitis (AD).

3. **Ryaltris (mometasone furoate and lopatadine hydrochloride) Nasal Spray**

   Company: Glenmark Pharmaceuticals, Inc.

   Treatment for: Allergic Rhinitis

   Ryaltris (mometasone and olopatadine) nasal spray is a corticosteroid and antihistamine combination for the treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.

4. **Kimmtrak (tebentafusp-tebn) Injection**

   Company: Immunocore

   Treatment for: Uveal Melanoma

   Kimmtrak (tebentafusp-tebn) is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

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