Information for Healthcare Professionals

Selective Serotonin Reuptake Inhibitors (SSRIs)

FDA ALERT [07/2006]: Increased Risk of Neonatal Persistent Pulmonary Hypertension

A recently published case-control study has shown that infants born to mothers who took selective serotonin reuptake inhibitors (SSRIs) after the 20th week of pregnancy were 6 times more likely to have persistent pulmonary hypertension (PPHN) than infants born to mothers who did not take antidepressants during pregnancy (see SSRI drug names at the bottom of this sheet). The background risk of a woman giving birth to an infant affected by PPHN in the general population is estimated to be about 1 to 2 infants per 1000 live births. Neonatal PPHN is associated with significant morbidity and mortality. The FDA is updating the prescribing information for all SSRIs with this new information. The FDA is also accruing data from additional sources pertaining to the potential association between SSRIs and neonatal PPHN. The FDA will provide additional information when it becomes available. In the interim, the FDA recommends that physicians carefully consider and discuss with patients the potential risks and benefits of SSRI treatment throughout pregnancy, including late pregnancy.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report serious adverse events associated with the use of these drugs, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations

Physicians should consider the benefits and risks of treating pregnant women with SSRIs, alternative treatments, or no treatment late in pregnancy.

Data Summary

A retrospective case-control study published on February 9, 2006, in the New England Journal of Medicine assessed the risk for persistent pulmonary hypertension of the newborn (PPHN) following exposure to SSRIs during pregnancy. 377 women whose infants were born with PPHN and 836 women whose infants were healthy were enrolled in the study in four United States metropolitan areas between 1998 and 2003. The study showed that infants born to mothers who took SSRIs after the completion of the 20th week of gestation were 6 times more likely to have PPHN than infants who were not exposed to antidepressants during pregnancy. 14 infants with PPHN and 6 healthy control infants had been exposed to an SSRI after the 20th week of gestation. There were too few cases of PPHN with each individual SSRI to compare risks for

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PPHN with individual SSRIs. The study did not find an association between exposure to SSRIs during the first 20 weeks of gestation and PPHN.

Exposure to non-SSRI antidepressants did not appear to be associated with an increased risk of PPHN, although the number of infants with exposure to non-SSRI antidepressants was too small to permit a reliable risk estimate or comparison with the risk observed for SSRIs.

In weighing the risks and benefits of treatment with SSRIs and other antidepressants during pregnancy for individual patients, physicians should also note the recent publication of a prospective longitudinal study of 201 pregnant women with a history of major depression in the February 1, 2006, issue of JAMA. In this study, women who discontinued antidepressant medication during pregnancy had a higher risk of relapse of major depression during pregnancy (68%) than women who maintained antidepressant medication throughout pregnancy (26%).

SSRI Drug Names and a Combination Drug Containing and SSRI

Celexa (citalopram)
Fluvoxamine
Lexapro (escitalopram)
Paxil (paroxetine)
Prozac (fluoxetine)
Symbyax (olanzapine/fluoxetine)
Zoloft (sertraline)

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Selective Serotonin Reuptake Inhibitors (SSRIs)
Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
5-Hydroxytryptamine Receptor Agonists (Triptans)

FDA ALERT [07/2006]: Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications

There is the potential for life-threatening serotonin syndrome (a syndrome of changes in mental status, autonomic instability, neuromuscular abnormalities, and gastrointestinal symptoms) in patients taking 5-hydroxytryptamine receptor agonists (triptans) and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly (see drug names at the bottom of this sheet). This information is based on reports of serotonin syndrome occurring in patients treated with triptans and SSRIs/SNRIs, and the biological plausibility of such a reaction in persons receiving two serotonergic medications. The FDA recommends that patients treated concomitantly with a triptan and an SSRI/SNRI be informed of the possibility of serotonin syndrome (which may be more likely to occur when starting or increasing the dose of an SSRI, SNRI, or triptan) and be carefully followed.

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Considerations

- Weigh the potential risk of concomitant SSRI/SNRI and triptan use with the benefit expected from using each drug, prior to prescribing these drugs together.

- When prescribing an SSRI or a triptan, physicians should discuss the possibility of serotonin syndrome with patients if an SSRI and a triptan will be used concomitantly. Healthcare providers should keep in mind that triptans are often used intermittently, and that the SSRI, SNRI, or triptan may be prescribed by a different healthcare provider.

- Healthcare providers should be alert to the highly variable signs and symptoms of serotonin syndrome. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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Selective Serotonin Reuptake Inhibitors (SSRIs)
Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
5-Hydroxytryptamine Receptor Agonists (Triptans)

- If concomitant treatment with an SSRI or SNRI and triptan is clinically warranted, the patient should be carefully observed, particularly during treatment initiation and dose increases.

Data Summary

The FDA has reviewed 27 reports of serotonin syndrome reported in association with concomitant SSRI or SNRI and triptan use. Two reports described life-threatening events and 13 reports stated that the patients required hospitalization. Some of the cases occurred in patients who had previously used concomitant SSRIs or SNRIs and triptans without experiencing serotonin syndrome. The reported signs and symptoms of serotonin syndrome were highly variable and included respiratory failure, coma, mania, hallucinations, confusion, dizziness, hyperthermia, hypertension, sweating, trembling, weakness, and ataxia. In 8 cases, recent dose increases or addition of another serotonergic drug to an SSRI/triptan or SNRI/triptan combination were temporally related to symptom onset. The median time to onset subsequent to the addition of another serotonergic drug or dose increase of a serotonergic drug was 1 day, with a range of 10 minutes to 6 days.

Serotonin syndrome following concomitant SSRI or SNRI and triptan use is biologically plausible. SSRIs, SNRIs, and triptans independently increase serotonin levels. Therefore, it is expected that concomitant use of SSRIs or SNRIs and triptans would result in higher serotonin levels than the serotonin levels observed with the use of SSRIs, SNRIs, or triptans alone, potentially leading to serotonin syndrome.

Drug Names

SSRIs & a Combination Drug containing an SSRI	SNRIs	Triptans
Celexa (citalopram)	Cymbalta (duloxetine)	Amerge (naratriptan)
Fluvoxamine	Effexor (venlafaxine)	Axert (almotriptan)
Lexapro (escitalopram)		Frova (frovatriptan)
Paxil (paroxetine)		Imitrex (sumatriptan)
Prozac (fluoxetine)		Maxalt and Maxalt-MLT (rizatriptan)
Symbyax (olanzapine/ fluoxetine)		Relpax (eletriptan)
Zoloft (sertraline)		Zomig and Zomig-ZMT (zolmitriptan)