



## Hostility Events Dog Small Minority of SSRI Users

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### MedPage Today Action Points

- Explain to patients that in a small number of patients the antidepressants in the selective serotonin reuptake inhibitor (SSRI) class, such as Paxil (paroxetine), Prozac (Fluoxetine), and Zoloft (sertraline) have been associated with an increased risk of violence toward others or suicidal thoughts and actions.
- Explain that the risk of aggression or suicide among patients on SSRIs appears to be greatest during the first few months of therapy, and that patients should be carefully monitored during the early phase of treatment for changes in mood.

### Review

BANGOR, Wales, Sept. 12 -- Selective serotonin reuptake inhibitors (SSRI) can have a rare paradoxical effect, sparking aggressive or violent behaviors in otherwise placid patients.

So reported three researchers here who concluded from an odd mix of studies and reports on the antidepressants, including e-mail responses to a TV documentary, that Paxil (paroxetine) and other SSRIs can trigger what they called "hostility events."

The three study authors have all served as expert witnesses in legal cases revolving around antidepressants and violence or suicide. Their findings have legal implications, they reported in the September issue of the online journal *PLoS Medicine*, because "many jurisdictions appear not to have considered the possibility that a prescription drug may induce violence."

"Our main finding is that unselected sets of placebo-controlled trials of antidepressants show evidence for an increased relative risk of aggressive behaviors on treatment, although such outcomes apply to only a small subset of patients," wrote psychologist David Healy, Ph.D., of Cardiff University here, and colleagues.

The investigators reviewed data on the SSRIs Paxil, Prozac (fluoxetine), and Zoloft (sertraline), looking at controlled trials and other sources. They found in a pooled analysis of studies of children and adults treated with Paxil, 0.65% had a "hostility event," versus 0.31% of patients on placebo (odds ratio [OR]: 2.10; 95% confidence interval [CI]: 1.37-3.48).

They cautioned that in criminal or civil cases involving a suspected influence of antidepressants on behavior, the relative rarity of the documented events should be taken in consideration.

"When violence is a suspected outcome, every case has to be considered carefully, on the principle that individuals are responsible for their conduct, unless there is clear evidence of compromised function that cannot be otherwise explained," they wrote.

They focused their attention on Paxil because of the availability of data from legal cases in which the drug was implicated, as well as data sets provided to British regulators by GlaxoSmithKline, makers of Paxil.

In their study, Dr. Healy and David B. Menkes, Ph.D., also at Cardiff University, and Andrew Herxheimer,

Ph.D., a clinical pharmacologist at the United Kingdom Cochrane Center in Oxford, reviewed data presented to the United Kingdom's Committee on Safety of Medicines Expert Working group on placebo controlled trials of Paxil in adults and children, as well as placebo-controlled studies of Zoloft in children.

They also reviewed data from United Kingdom Drug Safety Research Unit prescription-event monitoring studies on Paxil and Prozac.

In addition, the authors considered e-mails from 1,374 patients who responded to a BBC program on Paxil broadcast in 2002.

They found that in clinical trials of Paxil, regulatory agencies lumped aggression and violence together under the heading "hostility," using clinical codes that include homicide, homicidal acts, and homicidal ideation as well as aggressive events and conduct disorders.

In a pooled analysis of hostile events occurring in both children and adults, both on therapy and during a 30-day drug-free phase after patients were tapered off the drug, 60 of 9,219 patients (0.65%) overall had hostile events. In contrast, there were 20 hostile events among 6,455 patients (0.31%) on placebo.

"In these trials, hostile events are found to excess in both adults and children on paroxetine compared with placebo, and are found across indications, and both on therapy and during withdrawal," the authors wrote. However, although the difference in the pooled analysis in adult and pediatric placebo-controlled trials was significant, the odds ratios for individual conditions (depression, obsessive compulsive disorder, anxiety and premenstrual dysphoria disorder) were not in the combined analysis.

The highest rates occurred in children with obsessive-compulsive disorder, who had a nearly 17-fold greater risk for a hostile event (CI: 2.22-130.0) compared with those on placebo.

Additionally, the authors found that in studies of Paxil in healthy volunteers, hostile events occurred in 1.1% of those on the active drug, compared with none on placebo.

"Although not statistically significant, this finding is striking because hostile events are unusual in healthy volunteer trials," they wrote.

In prescription-event monitoring studies of Paxil and Prozac, there were 18 reports of aggression among 13,741 patients (0.13%) during the first six month of treatment with Paxil, compared with 20 of 12,692 patients (0.16%) among patients on Prozac. There was one reported murder, committed by a patient on Paxil.

Additionally, data submitted by Pfizer on two clinical trials of Zoloft in children with depression showed that aggression was most common cause of discontinuation.

"When discontinuations for any manifestation of treatment-induced activation (suicidal ideation or attempts, aggression, agitation, hyperkinesis, or aggravated depression) were considered, there were 15 discontinuations on sertraline compared with two on placebo, a relative risk of 7.3 (95% CI, 1.70-31.5,  $P=0.0015$ )," the authors noted.

In a review of nearly 1,400 responses to a BBC program on Paxil, Dr. Healy found that people who had taken the drug frequently reported severe mood changes associated with dosing changes in the first week of treatment, later dosage increases, dosage decreases, and drug withdrawal.

The legal implications of their findings, the authors wrote, are that "if antidepressants can in principle trigger violence, a need will always remain to establish whether such a general possibility might have been realized in an individual case. The principles involved in making such assessments will involve a consideration of the timing of the events in relation to treatment, the merits of competing explanations, and the existence of evidence in a particular case for a mechanism through which treatment may have led to violence."

**Primary source:** PLoS Medicine

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Healy D et al. "Antidepressants and Violence: Problems at the Interface of Medicine and Law." *PLoS Med* 3(9): e372. DOI: 10.1371/journal.pmed.0030372

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