Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports

Kenneth Alper, Kelly A. Schwartz, Russell L. Kolts, and Arif Khan

Background: Clinical trial data provide an approach to the investigation of the effects of psychopharmacological agents, and psychiatric disorders themselves, on seizure threshold.

Methods: We accessed public domain data from Food and Drug Administration (FDA) Phase II and III clinical trials as Summary Basis of Approval (SBA) reports that noted seizure incidence in trials of psychotropic drugs approved in the United States between 1985 and 2004, involving a total of 75,873 patients. We compared seizure incidence among active drug and placebo groups in psychopharmacological clinical trials and the published rates of unprovoked seizures in the general population.

Results: Increased seizure incidence was observed with antipsychotics that was accounted for by clozapine and olanzapine, and with drugs indicated for the treatment of OCD that was accounted for by clomipramine. Alprazolam, bupropion immediate release (IR) form, and quetiapine were also associated with higher seizure incidence. The incidence of seizures was significantly lower among patients assigned to antidepressants compared to placebo (standardized incidence ratio = 0.48; 95% CI, 0.36–0.61). In patients assigned to placebo, seizure incidence was greater than the published incidence of unprovoked seizures in community nonpatient samples.

Conclusions: Proconvulsant effects are associated with a subgroup of psychotropic drugs. Second-generation antidepressants other than bupropion have an apparent anticonvulsant effect. Depression, psychotic disorders, and OCD are associated with reduced seizure threshold.

Key Words: Antidepressant, antipsychotic, anxiety disorder, clinical trial, depression, epilepsy, mood disorder, obsessive-compulsive disorder, psychotic disorder, seizure

Seizures are a serious adverse event that can occur with psychopharmacological treatment, although concern regarding seizure threshold can also result in the undertreatment of psychiatric disorders. To a great extent, such concern is based on case reports involving tricyclic antidepressants at supratherapeutic levels (Dailey and Naritoku 1996; Jobe and Browning 2005; Preskorn and Fast 1992). This is particularly unfortunate with regard to epilepsy, in which depression tends to be undertreated despite markedly elevated rates of depression and suicide (Jones et al. 2003; Kanner 2003; Swinkels et al. 2005), and depression is reportedly an even stronger determinant of quality of life than seizure control (Boylan et al. 2004; Gilliam et al. 2003). There is also a substantial excess incidence of psychosis in epilepsy in the form of acute postictal or chronic interictal psychoses (Alper et al. 2001; Hyde and Weinberger 1997; Logsdail and Toone 1988; Qin et al. 2005; Sachdev 1998; Stefansson et al. 1998).

Proconvulsant effects are evident in a subset of psychotropic drugs. The association of clozapine with increased seizure risk, even at therapeutic serum levels, is well established (Devinsky et al. 1991; Gunther et al. 1993; Hedges et al. 2003; Pacia and Devinsky 1994; Sajatovic and Ramirez 1995; Stimmel and Dopheid 1996). Clozapine is the only psychotropic drug to have received a Food and Drug Administration (FDA) black box warning regarding seizures. The prescribing information for clomipramine, alprazolam, and bupropion provides warnings and statements regarding seizure risk specific to each compound. For the remaining atypical antipsychotics and second-generation antidepressants, the prescribing information includes a generic statement regarding caution in patients with epilepsy or otherwise at risk for seizures. These generic statements are applied equally to agents that might differ with respect to their effects on seizure incidence, for example olanzapine versus the serotonin reuptake inhibitor (SRI) antidepressants. Olanzapine, which is structurally similar to clozapine, has been reported to be associated with electroencephalogram (EEG) slowing or epileptiform abnormalities (Amann et al. 2003; Centorrino et al. 2002; Lee et al. 2003; Pillmann et al. 2000; Woolley and Smith 2001) and is viewed by some authors as being associated with higher seizure risk (Camacho et al. 2005; Lee et al. 1999; Lee et al. 2003; Woolley and Smith 2001). On the other hand, fluoxetine (Favale et al. 1995) and citalopram (Favale et al. 2003; Specchio et al. 2004) have been reported to produce antiepileptic effects in open label studies of nondepressed epileptic patients, which is also consistent with research utilizing animal models indicating an anticonvulsant effect of SRI antidepressants (Borowicz et al. 2006; Dailey et al. 1992; Kabuto et al. 1994; Kecskemeti et al. 2005; Leander 1992; Pasini et al. 1992; Pericic et al. 2005; Pisani et al. 1999; Prendiville and Gale 1993; Sparks and Buckholtz 1985; Ugale et al. 2004; Wada et al. 1999).

Epidemiological studies looking retrospectively at depression in patients with incident unprovoked seizures suggest that depression or attempted suicide are themselves risk factors for seizures (Forsgren and Nystrom 1990; Hesdorffer et al. 2000, 2006). Improved seizure control has also been observed in epileptic patients treated for psychiatric disorders with antid-
pressants (Fromm et al. 1978; Hurst 1986; Ojemann et al. 1983, 1987; Sakakihara et al. 1995; Specchio et al. 2004). Greater severity of depression has been correlated with poorer seizure control (Cramer et al. 2003), including a recent study which found evidence for a bidirectional causal association utilizing a modification of path analysis (Thapar et al. 2005).

Approaches to estimating the comparative effect of psychotropic drugs on seizure threshold include in vitro assays and animal models (Clinekers et al. 2004a; Krijzer et al. 1984; Luchins et al. 1984; Pisani et al. 1999; Trimble et al. 1977), reports on the incidence of seizures in overdoses (Balit et al. 2003a, 2003b; Buckley et al. 1994; Kelly et al. 2004; Shepherd et al. 2004; Wedin et al. 1986; Whyte et al. 2003), post marketing reports (Jick et al. 1992), and clinical trials. Among these alternatives, clinical trials may provide the most clinically relevant data from which to formulate an estimate effect on seizure threshold, with advantageous methodological features including prospective evaluation, large sample sizes, systematic recording and evaluation of reports of seizures as adverse events, the exclusion of potentially confounding medical risk factors for seizures, and the use of standardized methods of psychiatric diagnosis and assessment (Rosenstein et al. 1993).

In addition to proconvulsant effects associated with a subset of psychotropic drugs, the available clinical and experimental evidence appears to support the hypotheses that psychiatric disorders themselves are associated with lowered seizure threshold, and that antidepressants may diminish the incidence of new onset seizures in clinical trials. The focus of this study is the analysis of FDA clinical trial data documenting the incidence of seizures in active drug and placebo groups in studies of antipsychotic, antidepressant, and anti-anxiety compounds. One aim of this study is to investigate the incidence of seizures relative to placebo in clinical trials of psychiatric drugs. Another aim is to examine the data for evidence regarding psychiatric disorders as risk factors for seizures, as evidenced by the incidence of seizures in the placebo group in phase II and III trials compared to the reported incidence of unprovoked seizures in the general population.

Methods and Materials

Summary Basis of Approval (SBA) Reports

An SBA report is a review of the pre-clinical and clinical data from the New Drug Application (NDA) for a new drug or new drug indication. The FDA staff includes physicians, pharmacologists, and toxicologists, who prepare reviews of the NDA research data that are then compiled into an SBA report. After the senior FDA staff physician signs off on the completed SBA report, it is made available to the public under the Freedom of Information Act (US Department of Justice 1996), and a subset of the information is incorporated into the product labeling.

The voluntary participants involved in an NDA for a psychotropic drug are termed “intent-to-treat” when randomized to an assigned treatment in a clinical trial. The data on these intent-to-treat patients are compiled into separate efficacy and safety sections of the SBA report. The safety section typically ranges from approximately 30 to 60 pages in length and summarizes the occurrence of adverse events, including seizures. In this analysis, we focused on the safety sections of the SBA reports, which summarize safety data from clinical trials conducted to establish proof of efficacy for either approved or not yet approved indications, as well as studies specifically conducted for the purpose of evaluating safety.

If a seizure is reported during a clinical trial, the principal investigator (PI), a physician at the sponsoring pharmaceutical company, an FDA staff physician, and their neurological consultants determine the clinical likelihood that the reported event was a seizure, as well as its possible relationship to the study drug. During the double blind placebo controlled trials, both the PI and physician from the pharmaceutical company are blinded to the treatment assignment (placebo vs. drug) of the patient. The FDA staff physician makes the ultimate determination regarding whether a reported event was a seizure, and the possible etiological role of the study drug. In this study, events were included which the SBA report indicated were likely to have been seizures, and judged to not have been provoked by an identifiable factor such as acute traumatic brain injury or alcohol withdrawal.

Under the Freedom of Information Act, we gathered all available public domain data in the form of SBA reports which provided information regarding seizure incidence in phase II and phase III clinical trials involving a total of 75,873 patients, for the following psychotropic drugs approved in the United States between 1985 and 2004: alprazolam, aripiprazole, bupropion (immediate release; IR), bupropion (sustained release; SR), buspirone, citalopram, clomipramine, clozapine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, olanzapine, paroxetine,quetiapine, risperidone, sertraline, venlafaxine, and ziprasidone. The data set included all of the second-generation antidepressants and atypical antipsychotics. The data did not include any first generation antipsychotics, or first generation antidepressants except for clomipramine, due to the absence of systematic reporting on seizure incidence in clinical trials for psychotropic drugs approved prior to 1985. The procedures for obtaining the clinical trial information from the FDA were very similar to those used in prior publications (Khan et al. 2000, 2001, 2002, 2003).

In Table 1, we recorded available numbers of patients assigned to drug or to placebo and the total number of reported seizures in the drug and placebo treated groups. We also recorded total person exposure years (PEY; the cumulative time in years that a patient is exposed to a drug or placebo). In the case of citalopram, the SBA report provided a rate for PEY rather than the actual number of PEY, therefore, we calculated the PEY using the number of reported seizures (number of seizures divided by reported rate).

Statistical Analysis

Statistical analysis was performed utilizing StatsDirect statistical software, version 2.5.6 (StatsDirect Ltd., Cheshire, United Kingdom). We summarized seizure rates for drugs from among five indication categories: antidepressant, anti-anxiety, antipsychotic, obsessive-compulsive disorder (OCD), and bulimia. For some drugs, the FDA reported multiple clinical data sets by indication, for example, separate reports of seizure incidence with fluoxetine for the indications of depression, OCD, or bulimia. We recorded the occurrence of seizures separately by indication in view of potential differences in seizure rates with the same drug for different psychiatric indications. The FDA reported seizure incidence separately based on the year of evaluation for the same drug in several studies as indicated in Table 1.

To evaluate differences within each drug indication category, drugs were listed by rank order of seizure incidence and compared to the adjacent preceding and succeeding drug using the Fisher’s exact test two-tailed probability. For example, in the...
antidepressant indication category, we compared bupropion to citalopram, citalopram to fluoxetine, and so on. We designated the resulting subcategories as “group I” and “group II” to denote higher and lower seizure incidence respectively. The Fisher-Freeman-Halton (generalized Fisher exact) test (Mehta and Patel 1983) was used for comparisons among drug indication categories that involved contingency tables larger than 2x2. As indicated in Table 2, Fisher’s exact test probabilities were computed to evaluate the significance of differences in the incidence of seizures in the placebo versus active drug arms for each indication category separately for data reported as unadjusted for PEY, and for data reported as adjusted for PEY.

We calculated the standardized incidence ratio (SIR) (Armitage and Berry 1994; StatsDirect 2006) for seizure incidence in the active treatment arm as indicated in Table 3. The SIR is used in this study to calculate probability based on the null hypothesis that the observed seizure incidence in patients receiving active drug is equal to the seizure incidence expected with placebo, i.e. that the SIR = 1. The SIR allows correction for differences in trial duration, which is important due to the frequent occurrence of disparities regarding trial length in the active drug versus placebo arms in clinical trials of psychopharmacological agents. Its standardization of seizure incidence in the common metric of relative probability is useful for comparisons among psychotropic agents. The SIR uses the Poisson distribution to generate the limits of the confidence interval, which adapts it to analysis of infrequent events.

For the purpose of calculating the SIR, the expected number of seizures is the rate of seizures in the placebo arm, multiplied by the product of the number of patients and the average trial duration in the active drug arm. Average trial durations were computed separately by indication category and arm, as the total number of PEY divided by the number of subjects in those trials which provided information on PEY. Placebo seizure rates were calculated for the antidepressant, antipsychotic, and OCD indication categories based on the studies that provided data on seizure incidence adjusted for PEY in the placebo arm. Additionally, for one antidepressant, nefazodone, and one OCD agent, NR, Information not provided in SBA reports; PEY, person exposure years; OCD, obsessive compulsive disorder.

<table>
<thead>
<tr>
<th>Indication Category</th>
<th>Incidence of Seizures in Patients Assigned to Drug</th>
<th>Incidence of Seizures in Patients Assigned to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td># of Seizures</td>
</tr>
<tr>
<td>Antidepressant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Group I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion IR</td>
<td>4419</td>
<td>26</td>
</tr>
<tr>
<td>(Group II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>4168</td>
<td>12</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6000</td>
<td>12</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2181</td>
<td>3</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>3094</td>
<td>3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2963</td>
<td>2</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>2256</td>
<td>1</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>2796</td>
<td>1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>715</td>
<td>0</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>2314</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>2979</td>
<td>0</td>
</tr>
<tr>
<td>Anti-anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Group I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam - 1983</td>
<td>1723</td>
<td>46</td>
</tr>
<tr>
<td>(Group II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam - 1990</td>
<td>1698</td>
<td>7</td>
</tr>
<tr>
<td>Buspironine</td>
<td>3558</td>
<td>3</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Group I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>1742</td>
<td>61</td>
</tr>
<tr>
<td>(Group II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2500</td>
<td>23</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2387</td>
<td>18</td>
</tr>
<tr>
<td>Ziprasidone - 1997</td>
<td>2588</td>
<td>12</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>4710</td>
<td>18</td>
</tr>
<tr>
<td>Ziprasidone - 2000</td>
<td>3834</td>
<td>15</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2607</td>
<td>7</td>
</tr>
<tr>
<td>OCD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>3519</td>
<td>25</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>773</td>
<td>2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1289</td>
<td>4</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2737</td>
<td>6</td>
</tr>
<tr>
<td>Bulimia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>579</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>70,129</td>
<td>307</td>
</tr>
</tbody>
</table>

NR, Information not provided in SBA reports; PEY, person exposure years; OCD, obsessive compulsive disorder.
clomipramine, seizure incidence in the placebo group was reported with unadjusted data, and these trials were included by estimating the placebo arm PEY as the product of the number of placebo patients multiplied by the average placebo trial duration. The level of the SIR confidence interval (CI) was set at 95%.

## Results

In Table 1, we rank ordered all of the active compounds based on total seizure incidence unadjusted for PEY for each diagnostic category, and included corresponding PEY and placebo data where it was available.

### Differences within Drug Indication Categories

Within each drug category (as shown in Table 1), we compared the frequency of seizures for each adjacent drug. For the antidepressants, the IR form of bupropion and citalopram differed (Fisher’s exact \( p = 0.001 \)), with no statistically significant differences between the remaining sequential antidepressants. We designated

<table>
<thead>
<tr>
<th>Indication Category</th>
<th>Number of Patients, Active Drug Arm</th>
<th>Average Trial Duration (^b) Years Active Drug Arm</th>
<th>Placebo Seizure Rate (per 100,000 PEY)</th>
<th>Observed Number of Seizures</th>
<th>Expected Number of Seizures (^c)</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>33,885</td>
<td>0.319 (116 days)</td>
<td>1166.7</td>
<td>60</td>
<td>126.1</td>
<td>.48 (^a)</td>
<td>(0.36-0.61)</td>
</tr>
<tr>
<td>All, excluding bupropion IR</td>
<td>29,466</td>
<td>0.333 (109 days)</td>
<td>1096.6</td>
<td>34</td>
<td>109.6</td>
<td>.31 (^a)</td>
<td>(0.21-0.43)</td>
</tr>
<tr>
<td>Bupropion IR only</td>
<td>4,419</td>
<td>.267 (57 days)</td>
<td>75.1</td>
<td>26</td>
<td>16.4</td>
<td>1.58 (^a)</td>
<td>(1.03-2.32)</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>20,368</td>
<td>0.470 (172 days)</td>
<td>784.3</td>
<td>154</td>
<td>75.1</td>
<td>2.05 (^a)</td>
<td>(1.74-2.40)</td>
</tr>
<tr>
<td>All, excluding clozapine</td>
<td>18,626</td>
<td>0.467 (166 days)</td>
<td>714.3</td>
<td>93</td>
<td>68.7</td>
<td>1.35 (^a)</td>
<td>(1.09-1.66)</td>
</tr>
<tr>
<td>All, excluding clozapine and olanzapine</td>
<td>16,126</td>
<td>0.450 (189 days)</td>
<td>753.7</td>
<td>70</td>
<td>59.5</td>
<td>1.18 (^a)</td>
<td>(0.92-1.49)</td>
</tr>
<tr>
<td>All, excluding clozapine, olanzapine, and quetiapine</td>
<td>13,739</td>
<td>0.470 (172 days)</td>
<td>784.3</td>
<td>154</td>
<td>75.1</td>
<td>2.05 (^a)</td>
<td>(1.74-2.40)</td>
</tr>
<tr>
<td>Clozapine only</td>
<td>1,742</td>
<td>0.367 (121 days)</td>
<td>124.9</td>
<td>61</td>
<td>6.4</td>
<td>9.50 (^a)</td>
<td>(7.27-12.20)</td>
</tr>
<tr>
<td>Olanzapine only</td>
<td>2,500</td>
<td>0.470 (172 days)</td>
<td>784.3</td>
<td>93</td>
<td>68.7</td>
<td>1.35 (^a)</td>
<td>(1.09-1.66)</td>
</tr>
<tr>
<td>Quetiapine only</td>
<td>2,387</td>
<td>0.470 (172 days)</td>
<td>784.3</td>
<td>18</td>
<td>8.8</td>
<td>2.05 (^a)</td>
<td>(1.21-3.23)</td>
</tr>
<tr>
<td>OCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>8,318</td>
<td>0.402 (146 days)</td>
<td>433.4</td>
<td>37</td>
<td>14.5</td>
<td>2.55 (^a)</td>
<td>(1.80-3.52)</td>
</tr>
<tr>
<td>All, excluding clomipramine</td>
<td>4,799</td>
<td>0.402 (146 days)</td>
<td>433.4</td>
<td>12</td>
<td>8.4</td>
<td>1.44 (^a)</td>
<td>(0.74-2.51)</td>
</tr>
<tr>
<td>Clomipramine only</td>
<td>3,519</td>
<td>0.402 (146 days)</td>
<td>433.4</td>
<td>25</td>
<td>6.1</td>
<td>4.08 (^a)</td>
<td>(2.64-6.02)</td>
</tr>
</tbody>
</table>

\(^a\) Significant at level of \( p < .05 \).

\(^b\) Average trial duration = (total number of PEY)/(number of subjects), for those trials which provided information on PEY.

\(^c\) Expected number of seizures = (number of patients, active drug arm) × (average trial duration, active drug arm) × (placebo seizure rate).

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bupropion IR as “group I”, and the remaining antidepressants as
“group II”. Seizure incidence was significantly greater with bupro-
pin IR than bupropion SR (Fisher’s exact p < .001).

The difference between clozapine and olanzapine was signif-
ificant (Fisher’s exact p < .001), and clozapine was classified as a
 group I drug with no statistically significant differences between
the remaining sequential antipsychotics, which were then clas-
sified as group II. Significant differences were seen within the set
of group II antipsychotic drugs (Fisher-Freeman-Halton exact
p = .008), but not after the removal of olanzapine (Fisher-
Freeman-Halton exact p = .129).

For the anti-anxiety compounds, the incidence of seizures in
the 1983-alprazolam trials was significantly greater than in the
1990-alprazolam trials was in turn significantly greater than
buspirone (Fisher’s exact p = .017). No significant differences
were found between sequential agents in the OCD indication
category, which were all classified as group II.

Differences Between Drug Indication Categories

Significant differences in the incidence of seizures were
observed among patients receiving the active drug among anti-
depressant (60/33,885; 2%), anti-anxiety (56/6,979; 8%), anti-
psychotic (154/20,368; 8%), OCD (37/8,318; 4%), and bulimia
(0/579; 0%) indication categories (Fisher-Freeman-Halton exact
p < .001). Significant differences were found among group I
antidepressant (bupropion IR), anti-anxiety (alprazolam 1983),
and antipsychotic (clozapine) agents (Fisher-Freeman-Halton
exact p < .001). Similarly, significant differences were found
observed among the group II antidepressant, anti-anxiety, anti-
psychotic, OCD, and bulimia agents (Fisher-Freeman-Halton
exact p < .001), indicating that differences between drug indi-
cation categories were not accounted for exclusively by the
group I agents. We found no significant differences among
the placebo groups for either the unadjusted data (Fisher-Freeman-
Halton exact p = .112) or the data adjusted for PEY (Fisher-
Freeman-Halton exact p = .669).

When examining psychotropic drugs used for multiple indi-
cations, we noted a higher rate of seizures in patients treated with
sertraline for the indication of OCD (4/1,289; 33%) compared to
depression (0/2,979; 0%) (Fisher’s exact p = .008). The SBA
reports did not provide data to evaluate a possible difference in
the dosage of sertraline used to treat the two indications. The
data on fluoxetine revealed no significant differences in seizure
incidence among the antidepressant (12/6,000; 2%), OCD (2/
773; 3%), and bulimia (0/579; 0%) indication categories (Fisher-
Freeman-Halton exact p = .662).

Active Drug Versus Placebo Trial Length and PEY Unadjusted
and Adjusted Data

For all trials and indication categories combined for which
data was available, the mean trial length of the active drug arm
was .402 years (147 days), versus .150 years (55 days) in
the placebo arm (paired t test: t = 5.50, df = 20, p < .001). The
longer active drug arm length is a common feature of psycho-
pharmacological trials due to active drug continuation phases
and ethical reservations regarding the use of placebo in major
psychiatric disorders. Consistent with the observation noted
above of a difference in the duration of active drug versus
placebo trial arms, the data in Table 2 also suggest a possible
systematic effect of the disparity in drug versus placebo trial
length on the sensitivity to detect a pro- or anticonvulsant
effect.

Table 2 presents seizure incidence in drug versus placebo
arms for data reported as unadjusted or adjusted for PEY.
Increased seizure incidence was observed with antipsychotic and
OCD data unadjusted for PEY, and decreased seizure incidence
with antidepressant data adjusted for PEY. These disparities are
in the direction that would be expected due to the effect of a
greater length of the active drug relative to the placebo. Procon-
vulsant effects of psychotropic drugs tend to occur relatively
more often with drug introduction and dosage increases, result-
ing in a tendency for seizures to occur relatively early in
treatment (Mendez et al. 1986; Pacia and Devinsky 1994; Skow-
ron and Stimmel 1992). A proconvulsant effect would be ex-
pected to be more evident in the unadjusted data because the
adjustment for PEY incorporates time points later in the trial
when seizure incidence in the treatment arm is relatively lower.
On the other hand, the PEY adjustment increases sensitivity to
detect an apparent anticonvulsant effect relative to unadjusted
data by correcting for the greater duration of the active drug arm
that would otherwise tend to obscure the distinction from the
placebo.

Standardized Incidence Ratios

The results of the SIR analysis are presented in Table 3.
Antidepressant treatment appears to be associated with lower
seizure incidence relative to placebo (SIR = 48; 95% CI, 36-61),
an effect that appears to be accounted for broadly across the
entire set of group II antidepressants. Seizure incidence was
increased with bupropion IR relative to placebo (SIR = 1.58; 95%
CI, 1.03-2.32). The mean clinical trial length for the antidepres-
sant trials was .319 years (116.4 days) for active drug and .213
years (78 days) for placebo. For nefazodone, seizure incidence
in the placebo group was reported with unadjusted data. We
estimated PEY as the mean antidepressant placebo arm trial
length multiplied by the number of patients (672), which equaled
142.9 PEY, which combined with the 200 PEY in the antidepres-
sant placebo arm in Table 2 yielded an antidepressant placebo
arm seizure incidence of (4/342.9 PEY) = 1166.7 per 100,000

The set of all antipsychotics were associated with significantly
increased seizure incidence (SIR = 2.05; 95% CI, 1.74-2.40),
which remained significant after the removal of the group I drug
clozapine (SIR = 1.35; 95% CI, 1.09-1.66), but not after the
removal of both clozapine and olanzapine (SIR = 1.18; 95% CI,
.92-1.49), indicating that the observed increase in seizure inci-
dence in the antipsychotic category was accounted for by both
clozapine and olanzapine. Quetiapine was also associated with
increased seizure incidence (SIR = 2.05; 95% CI, 1.21-3.23)
relative to placebo. The remaining group II antipsychotics, i.e.
ziprasidone, aripiprazole and risperidone showed no significant
effect on seizure incidence (SIR = 1.03; 95% CI, .77-1.35). The
mean clinical trial length for the antipsychotic trials was .470
years (172 days) for active drug and .113 years (41 days) for
placebo. The antipsychotic placebo arm seizure incidence was
(1/127.5 PEY) = 784.3 per 100,000 PEY.

Seizure incidence was increased in the OCD indication cate-
gory relative to placebo (SIR = 2.55; 95% CI, 1.80-3.52), but not
after the data on clo mipramine was removed from the analysis
(SIR = 1.44; 95% CI, .74-2.51). Clomipramine appeared to
account for the increased seizure incidence in the OCD category,
and by itself was associated with increased seizure incidence
relative to placebo (SIR = 4.08; 95% CI, 2.64-6.02). The mean
clinical trial length for the OCD category was .402 years (146
days) for active drug and .136 years (50 days) for placebo.
clomipramine, seizure incidence in the placebo group was reported with unadjusted data, and we estimated PEY as the mean OCD placebo arm trial length (above) multiplied by the number of patients (719), which equaled 97.7 PEY, which combined with the OCD placebo arm total of 133.0 PEY in Table 2 yielded an overall OCD placebo arm seizure incidence of (1/230.7 PEY) = 433.4 per 100,000 PEY. The SIR was not computed for the anxiety and eating disorder categories due to zero cells and/or missing seizure incidence data.

**Discussion**

The synthesis and extraction of relevant conclusions from this data set involves recognition of its limitations, evaluation of analyses within indication categories and between active treatment and placebo arms, and interpretation of the results in the context of existing clinical, experimental, and epidemiological evidence.

The clinical trial data reviewed in this study indicated that a relatively high rate of seizures occurred in patients assigned to placebo, which suggests that psychiatric disorders themselves may be associated with seizure risk. There is a significant consensus among published estimates of the incidence of unprovoked seizures in community nonpatient populations. A widely cited study utilizing a medical record-linkage system in Rochester, New York, reported an age-adjusted incidence of unprovoked seizures of 61 per 100,000 PEY (Hauser et al. 1993), and a recent study utilizing a national surveillance system in Iceland estimated the mean annual incidence of unprovoked seizures at 56.8 per 100,000 PEY (Olausson et al. 2005). A systematic meta-analysis of 40 studies found a median incidence of unprovoked seizures of 56 per 100,000 PEY (Kotsopoulos et al. 2002).

Both retrospective case control and prospective cohort evidence indicate an effect of lowering of the seizure threshold that is apparently due to depression itself. Assuming from the above discussion that the incidence of unprovoked seizures in the general population is 60 per 100,000 PEY, the reported incidence of seizures of 1,166.7 per 100,000 PEY in patients treated with placebo in the antidepressant clinical trials reviewed in this study, represents approximately 19 times the rate seen in the general population. Three epidemiological community-based studies have examined depression as a risk factor for seizures by assessing depression retrospectively in incident cases of unprovoked seizures, and reported the following odds ratios for the occurrence of unprovoked seizures in depression: 1.7 (5.1 for suicide attempts) (Hesdorffer et al. 2006); 3.7 (Hesdorffer et al. 2000); and 7.0, which was increased to 17.2 in the subset of patients with “localized onset” (i.e., partial) seizures (Forsgren and Nystrom 1990). The analysis of clinical trial data may provide some methodological advantages relative to the above retrospective epidemiological studies, including prospective evaluation of depressed patients (as opposed to the retrospective evaluation of depression in patients presenting with unprovoked seizures), much larger numbers of depressed patients, and the systematic use of standardized methods of psychiatric diagnosis and assessment.

Unlike depression, we were unable to find published epidemiological studies of psychotic disorders or OCD in patients with incident unprovoked seizures. Nonetheless, in the placebo arms of antipsychotic and OCD clinical trials in this study, the incidence of seizures was respectively 784.3 and 433.4 per 100,000 PEY, approximately 13- and 7-times greater than the reported rate of unprovoked seizures in the general population. The neuropsychiatric literature strongly supports an association of epilepsy with increased risk for psychiatric disorders (Gaitatzis et al. 2004; Swinkels et al. 2005), including mood, psychotic (Hyde and Weinberger 1997; Qin et al. 2005; Sachdev 2001) and obsessive-compulsive (Monaco et al. 2005) disorders. This association has been interpreted as evidence for the hypothesis of a common neurobiological substrate conferring risk to both epilepsy and psychiatric disorders (Jobe 2003; Kanner 2006; Kelle 2005).

Independent samples provide some support for the validity of the SIR and placebo arm seizure rates calculated in this study. In an entirely independent postmarketing sample of 1,986 patients receiving bupropion IR in a 56 day trial (304.7 PEY), 8 seizures occurred (Johnston et al. 1991). This agrees with the predicted incidence of 5.6 seizures calculated for the same PEY using the SIR for bupropion IR and the antidepressant placebo seizure rate reported in this study (SIR = 1.42; 95% CI .61-2.81). The SIR for all antidepressants in this study indicates a reduction of seizure incidence of 52%, which appears to be a similar order of effect size to that which has been reported in open label trials of SRIs in patients with epilepsy. Trials of citalopram have reported overall reductions in seizure frequency of 37% (Specchio et al. 2004) and 64% (Favale et al. 2003), and in another study with fluoxetine, 6 of 17 (35%) patients became seizure free with the remainder having 30% reductions in seizure frequency (Favale et al. 1995).

The finding of lower seizure incidence relative to placebo for antidepressants agrees with evidence of anticonvulsant effects in preclinical studies (Borowicz et al. 2006; Clinckers et al. 2004a; Dailey et al. 1992; Kabuto et al. 1994; Kecskemeti et al. 2005; Leander 1992; Pasini et al. 1992, 1996; Pericic et al. 2005; Pisani et al. 1999; Prendiville and Gale 1993; Sparks and Buckholtz 1985; Trimble et al. 1977; Ugale et al. 2004; Wada et al. 1995; Wada et al. 1999), open label studies of antidepressant drugs indicating an antiepileptic effect in nondepressed epilepsy patients (Favale et al. 1995, 2003), as well as additional studies reporting no worsening (Gross et al. 2000; Harmant et al. 1990; Hovorka et al. 2000; Kanner et al. 2000; Kuhn et al. 2003; Munchau et al. 2005), or even improvement (Fromm et al. 1978; Hurst 1986; Ojemann et al. 1983, 1987; Sakakihara et al. 1995; Specchio et al. 2004) of seizure control in depressed patients with epilepsy being treated with antidepressants. An apparent anticonvulsant effect of antidepressants at therapeutic dosages may be reconcilable with the proconvulsant effect observed with overdoses (Cuenca et al. 2004; Isbister et al. 2004; Kelly et al. 2004; Lee et al. 2003; Pisani et al. 2002; Stimmel and Dopheide 1996). A proconvulsant effect has been observed with very large increases in extracellular monoamine levels in brain tissue (Clinckers et al. 2004b; Clinckers et al. 2005). The apparent anticonvulsant effect of some antidepressants at conventional dosages may be associated with a relatively moderate increase in extracellular serotonin, with a tendency towards a proconvulsant effect at the much higher concentrations of extracellular serotonin that may be associated with supratherapeutic dosage or rapid increases in blood level of antidepressant (Clinckers et al. 2004a, 2004b, 2005; Pisani et al. 1999).

The findings of apparent association of depression and seizure risk, and a possible antiepileptic effect of antidepressant medication, are of interest in view of evidence relating depression and epilepsy on the basis of a common attribute of increased neuronal excitability (Kanner 2006; Post 2004). A substantial literature reports evidence of alteration of neurotrans-

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mission involving the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in both depression (Brannhill et al. 2003; Sanacora et al. 2004) and epilepsy (Cossart et al. 2005). Postictal psychosis, a correlate of more severe refractory epilepsy, is reportedly associated with increased prevalence of a family history of mood disorder (Alper et al. 2001). Postmortem neuropathological examination of depressed patients has indicated hippocampal atrophy (Stockmeier et al. 2004), which is a classic finding in partial epilepsy, although the patterns of neuron sprouting and loss may differ between epilepsy and mood disorders (Bausch 2005; de Lanerolle and Lee 2005). Antidepressants reportedly increase hippocampal cell proliferation and neurogenesis (Banerjee et al. 2006; Malberg and Blendy 2005), which might offset the neuronal loss associated with epilepsy. Imaging studies report common deficiencies of serotonergic transmission in depression and epilepsy (Kanner 2006; Theodore 2004), and in the animal model, antidepressant drugs typically elevate extracellular serotonin in the hippocampus and cerebral cortex, which is associated with an anticonvulsant effect (Pisani et al. 1999; Pozzi et al. 1999; Yoshitake et al. 2003).

The antipsychotic drugs were associated with seizure rates exceeding those in patients treated with placebo. A higher rate of traumatic brain injury (TBI) has been reported in schizophrenia relative to mood disorders (Malaspina et al. 2001), which may interact with antipsychotic medication to reduce seizure threshold. Such an interaction of TBI with a proconvulsant insult has been observed with even mild TBI, which reportedly increases the relative risk of alcohol withdrawal seizures to an extent that appears synergistic and not merely additive (Annegers et al. 1998). A further confound in clinical trials is the possibility that patients with psychotic disorders may be relatively less reliable in disclosing a prior history of traumatic brain injury or epilepsy which might otherwise exclude them from clinical trials.

We identified a subgroup of “group I” agents, which were selected by comparison of adjacent agents as presented in Table 2, namely clozapine, bupropion IR, and alprazolam. Clozapine’s association with seizures is well known (Gunther et al. 1993; Hedges et al. 2003; Pacia and Devinsky 1994; Stimmel and Dopfheide 1996) and the finding that it had the highest SIR of all of the drugs evaluated in this study is not surprising. Bupropion IR was associated with increased seizure incidence, in contrast to the other antidepressants included in this study. Bupropion is contraindicated in epilepsy according to the manufacturer’s prescribing information. It appears to be relatively frequently involved in drug-related seizures presenting to emergency services (Balit et al. 2003b; Coughlin and Birkinshaw 2003; Pesola and Avasarala 2002; Shepherd et al. 2004), and in clinical trials was associated with a particularly high incidence of seizures in patients with eating disorders (Horne et al. 1988; Pope et al. 1989). The incidence of seizures with bupropion is strongly related to dosage, and is increased approximately tenfold in patients receiving 600 mg/day or more relative to patients on 450 mg/day or less (Davidson 1989). The lower rate of seizures in the clinical trials of SR versus IR forms may be due to lower peak plasma concentrations with the SR form, suggesting the importance of pharmacokinetic factors in bupropion’s proconvulsant effect (Dunner et al. 1998; Jefferson et al. 2005). However, the dosage of bupropion used in clinical trials is a potential confound because the maximum recommended dose is 400 mg/day for the SR form (GlaxoSmithKline 2006a) versus 450 mg/day for the IR form (GlaxoSmithKline 2006b). As with other antidepressants in the animal model (Pisani et al. 1999), bupropion has been associated with anticonvulsant effects at lower serum levels and proconvulsant effects at higher levels (Tutka et al. 2004).

For alprazolam, the risk of seizures is apparently due to benzodiazepine withdrawal, which is a relatively common cause of drug-related seizures (Pesola and Avasarala 2002; Shepherd et al. 2004), and a particular risk associated with alprazolam compared with other benzodiazepines due to its short half-life (Brown and Hauge 1986; Janicak et al. 2001; Nelson and Chouinard 1999; Noyes et al. 1986). The lower seizure incidence for alprazolam in the 1990 relative to the 1983 trials followed an FDA-mandated change of the labeling information regarding the clinical management of discontinuation, which the original labeling information did not address. The new labeling information advised that the daily dosage be decreased by no more than .5 mg every three days in order to reduce the risk of withdrawal seizures.

Olanzapine, quetiapine, and clomipramine also appear to mediate higher seizure incidence. Olanzapine, which is structurally similar to clozapine, has been reported to be associated with EEG slowing or epileptiform abnormalities (Amann et al. 2003; Centorrino et al. 2002; Lee et al. 2003; Pillmann et al. 2000; Woolley and Smith 2001), and is viewed as being associated with relatively higher seizure risk (Lee et al. 1999, 2003; Woolley and Smith 2001). Quetiapine has less frequently been associated with seizures or EEG changes than olanzapine (Amann et al. 2003; Centorrino et al. 2002), but has been mentioned in some case reports (Balit et al. 2003a; Dogu et al. 2003; Hedges and Jeppson 2002; Martin et al. 1999; Peuskens and Link 1997; Worthley et al. 2004). Clomipramine has been regarded as being particularly likely to provoke seizures even among the tricyclic antidepressants, with a much higher incidence of seizures at dosages greater than 300 milligrams per day (Brodkin et al. 1997; Novartis 2006; Robinson 1978; Rosenstein et al. 1993; Skowron and Stimmel 1992; Stimmel and Dopheide 1996).

An important methodological limitation of this work is the lack of information regarding the incidence of seizures in the placebo group in clinical trials, which was available for only 8 of 26 trials. Another issue is that a correction for the multiple statistical comparisons was not utilized. Notwithstanding the existing debate regarding the validity and utility of such corrections (Perneger 1998), avoiding their associated loss of sensitivity is consistent with this paper’s exploratory focus. This paper should be viewed as generating hypotheses that require confirmation by prospective independent replication.

Future clinical trials of psychotropic medications provide an excellent opportunity to independently confirm the results reported here, and to extend on these findings if the FDA would provide access to information related to seizure occurrence, patient characteristics, and trial design that is routinely gathered in clinical trials. Information regarding the occurrence of seizures should be reported separately for active drug, placebo, and active comparator, and include the clinical history and probable classification of the seizure, its time of occurrence relative to entry into the study, and dosage and blood levels of the investigational drug at the time of the occurrence of the seizure. The timing of the seizure with respect to study length is of particular importance because the cumulative incidence as a function of time is likely nonlinear over longer intervals of observation, due to the tendency for seizures to occur early in treatment in association with the introduction of the drug and upward titration of the dosage (Devinsky et al. 1991; Mendez et al. 1986; Pacia and Devinsky 1994; Sajatovic and Meltzer 1996;
We declare we have no conflict of interest.


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