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 = .48; 95% CI, .36- .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 Dopheide 1996), and 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 antide-

From the Departments of Psychiatry and Neurology (KA), Comprehensive Epilepsy Center, New York University School of Medicine, New York, New York; Northwest Clinical Research Center (KAS, AK), Bellevue; Department of Psychology (RLK), Eastern Washington University, Cheney, Washington; Department of Psychiatry and Behavioral Sciences (AK), Duke University Medical Center, Durham, North Carolina.

Address reprint requests to Kenneth Alper, M.D., New York University Comprehensive Epilepsy Center, 403 East 34th Street, 4th Floor, EPC, New York, NY 10016; E-mail: kra1@nyu.edu.

Received July 27, 2006; revised September 8, 2006; accepted September 25, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.09.023

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 (Clinckers *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

Table 1. Incidence of Seizures during Phase II–III Clinical Trials of Psychotropic Drugs Approved between 1985 and 2004, Rank-Ordered by Incidence of Seizures Unadjusted for PEY

	Incidence of Seizures in Patients Assigned to Drug				Incidence of Seizures in Patients Assigned to Placebo			
Indication Category	*n*	# of Seizures	%	PEY	*n*	# of Seizures	%	PEY
Antidepressant								
(Group I)								
Bupropion IR	4419	26	.6	NR	NR	NR	NR	NR
(Group II)								
Citalopram	4168	12	.3	1333.3	691	4	.6	200
Fluoxetine	6000	12	.2	NR	NR	NR	NR	NR
Venlafaxine	2181	3	.1	897.0	451	NR	NR	100.0
Bupropion SR	3094	3	.1	NR	NR	NR	NR	NR
Paroxetine	2963	2	.07	NR	554	NR	NR	NR
Nefazodone	2256	1	.04	NR	672	0	.0	NR
Mirtazapine	2796	1	.04	671.1	605	NR	NR	71.4
Escitalopram	715	0	.0	NR	592	NR	NR	NR
Duloxetine	2314	0	.0	754	NR	NR	NR	NR
Sertraline	2979	0	.0	NR	1285	NR	NR	NR
Anti-anxiety								
(Group I)								
Alprazolam - 1983	1723	46	2.7	NR	NR	NR	NR	NR
(Group II)								
Alprazolam - 1990	1698	7	.4	NR	1237	0	.0	NR
Buspirone	3558	3	.08	NR	209	NR	NR	NR
Antipsychotic								
(Group I)								
Clozapine	1742	61	3.5	NR	NR	NR	NR	NR
(Group II)								
Olanzapine	2500	23	.9	1122.2	236	0	.0	27.1
Quetiapine	2387	18	.8	1103.2	206	0	.0	14.6
Ziprasidone - 1997	2588	12	.5	NR	366	NR	NR	51.0
Aripiprazole	4710	18	.4	2656.3	928	1	.1	85.8
Ziprasidone - 2000	3834	15	.4	NR	605	NR	NR	91.8
Risperidone	2607	7	.3	858.0	195	NR	NR	15.0
OCD								
Clomipramine	3519	25	.7	NR	719	0	.0	NR
Fluoxetine	773	2	.3	471.1	89	NR	NR	22.5
Sertraline	1289	4	.3	NR	NR	NR	NR	NR
Fluvoxamine	2737	6	.2	940.0	1055	1	.09	133.0
Bulimia								
Fluoxetine	579	0	.0	175.0	267	NR	NR	NR
Total	70,129	307	.4	10,981.2	5,744	6	.1	460.5

NR, Information not provided in SBA reports; PEY, person exposure years; OCD, obsessive compulsive disorder.

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 2 x 2. 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,

Table 2. Fisher's Exact Test Probabilities (Two Tailed) for Incidence of Seizures in Patients Assigned to Drug versus Placebo, for Data Reported as Unadjusted for PEY and Data Reported as Adjusted for PEY

	Unadjusted for PEY			Adjusted for PEY		
	Sample Size	# Seizures (%)	Fisher's Exact *p*	PEY	# Seizures (per PEY)	Fisher's Exact *p*
Antidepressant						
Drug	33,885	60 (.2)	.315	3,655.4	16 (.004)	.019[a]
Placebo	1,363	4 (.3)		200	4 (.020)	
Anti-anxiety						
Drug	6,979	56 (.8)	<.001[a]	NR	NA	NA
Placebo	1,237	0 (.0)				
Antipsychotic						
Drug	20,368	154 (.8)	<.001[a]	5,739.7	66 (.012)	.798
Placebo	1,370	1 (.1)		127.5	1 (.008)	
OCD						
Drug	8,318	37 (.4)	.010[a]	1,411.1	8 (.006)	.557
Placebo	1,774	1 (.1)		133.0	1 (.008)	
Bulimia						
Drug	579	0 (.0)	NA	175.0	0	NA
Placebo	267	NR		NR	NR	

NR, Information not included in the SBA report; NA, Not applicable; OCD, obsessive compulsive disorder; PEY, person exposure years.
[a]Significant at level of $p \leq .05$.

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 $p = .050$), with no statistically significant differences between the remaining sequential antidepressants. We designated

Table 3. Standardized Incidence Ratio (SIR) for Seizure Incidence in Active Drug Arm Relative to Placebo, for Antidepressant, Antipsychotic, and OCD Indication Categories

Indication Category	Number of Patients, Active Drug Arm	Average Trial Duration[b] Years (days) Active Drug Arm	Placebo Seizure Rate (per 100,000 PEY)	Observed Number of Seizures	Expected Number of Seizures[c]	SIR	95% CI
Antidepressant							
All	33,885	0.319 (116 days)	1166.7	60	126.1	.48[a]	(0.36-0.61)
All, excluding bupropion IR	29,466			34	109.6	.31[a]	(0.21-0.43)
Bupropion IR only	4,419			26	16.4	1.58[a]	(1.03-2.32)
Antipsychotic							
All	20,368	0.470 (172 days)	784.3	154	75.1	2.05[a]	(1.74-2.40)
All, excluding clozapine	18,626			93	68.7	1.35[a]	(1.09-1.66)
All, excluding clozapine and olanzapine	16,126			70	59.5	1.18	(0.92-1.49)
All, excluding clozapine, olanzapine, and quetiapine	13,739			52	50.7	1.03	(0.77-1.35)
Clozapine only	1,742			61	6.4	9.50[a]	(7.27-12.20)
Olanzapine only	2,500			23	9.2	2.50[a]	(1.58-3.74)
Quetiapine only	2,387			18	8.8	2.05[a]	(1.21-3.23)
OCD							
All	8,318	0.402 (146 days)	433.4	37	14.5	2.55[a]	(1.80-3.52)
All, excluding clomipramine	4,799			12	8.4	1.44	(.74-2.51)
Clomipramine only	3,519			25	6.1	4.08[a]	(2.64-6.02)

PEY, person exposure years; OCD, obsessive compulsive disorder; SIR, standardized incidence ratio.
[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).

bupropion IR as "group I", and the remaining antidepressants as "group II". Seizure incidence was significantly greater with bupropion IR than bupropion SR (Fisher's exact $p < .001$).

The difference between clozapine and olanzapine was significant (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 classified 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 trials (Fisher's exact $p < .001$). Seizure incidence 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 antidepressant (60/33,885; .2%), anti-anxiety (56/6,979; .8%), antipsychotic (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, antipsychotic, OCD, and bulimia agents (Fisher-Freeman-Halton exact $p < .001$), indicating that differences between drug indication 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 indications, we noted a higher rate of seizures in patients treated with sertraline for the indication of OCD (4/1,289; .3 %) 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 psychopharmacological 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. Proconvulsant effects of psychotropic drugs tend to occur relatively more often with drug introduction and dosage increases, resulting in a tendency for seizures to occur relatively early in treatment (Mendez *et al.* 1986; Pacia and Devinsky 1994; Skowron and Stimmel 1992). A proconvulsant effect would be expected 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 antidepressant 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 antidepressant placebo arm in Table 2 yielded an antidepressant placebo arm seizure incidence of (4/342.9 PEY) = 1166.7 per 100,000 PEY.

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 incidence 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 category relative to placebo (SIR = 2.55; 95% C.I, 1.80-3.52), but not after the data on clomipramine 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. For

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 (Olafsson *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; Keele 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 buproprion 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-

mission involving the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in both depression (Brambilla *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 (Banasr *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 Dopheide 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 proconvulsive 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 (Browne 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;

Skowron and Stimmel 1992; Spigset et al 1997; Stimmel and Dopheide 1996). Information regarding the clinical trial should also include the medical, psychiatric, and neurological exclusion/inclusion criteria, and trial length/PEY among the various trial arms. Information regarding subjects should include gender, age, significant comorbid medical conditions, and possible seizure risk factors including the patient's family history of neurological and psychiatric disorders.

Some conclusions appear to be supported by this study. Reduced seizure threshold appears to be associated with a limited subgroup of psychotropic agents. We found that seizure incidence was less than placebo in patients treated with some antidepressants, indicating a possible anticonvulsant effect. Reported seizure incidence in the placebo groups in reports reviewed in this study was greater than the reported rates of unprovoked seizures in nonpatient populations, indicating a possible effect on seizure threshold due to psychiatric illness itself. These findings are of interest with regard to the problem of undertreatment of psychiatric disorders, particularly depression, in patients at risk for epilepsy and seizures. From a neurobiological perspective, these findings are of interest in the context of evidence for pathophysiological commonality in epilepsy and psychiatric disorders.

We declare we have no conflict of interest.

Alper K, Devinsky O, Westbrook L, Luciano D, Pacia S, Perrine K, Vazquez B (2001): Premorbid psychiatric risk factors for postictal psychosis. *J Neuropsychiatry Clin Neurosci* 13:492–499.

Amann BL, Pogarell O, Mergl R, Juckel G, Grunze H, Mulert C, Hegerl U (2003): EEG abnormalities associated with antipsychotics: A comparison of quetiapine, olanzapine, haloperidol and healthy subjects. *Hum Psychopharmacol* 18:641–646.

Annegers JF, Hauser WA, Coan SP, Rocca WA (1998): A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 338:20–24.

Armitage P, Berry G (1994): *Statistical Methods in Medical Research*: Blackwell.

Balit CR, Isbister GK, Hackett LP, Whyte IM (2003a): Quetiapine poisoning: A case series. *Ann Emerg Med* 42:751–758.

Balit CR, Lynch CN, Isbister GK (2003b): Bupropion poisoning: A case series. *Med J Aust* 178:61–63.

Banasr M, Soumier A, Hery M, Mocaer E, Daszuta A (2006): Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. *Biol Psychiatry* 59:1087–1096.

Bausch SB (2005): Axonal sprouting of GABAergic interneurons in temporal lobe epilepsy. *Epilepsy Behav* 7:390–400.

Borowicz KK, Stepien K, Czuczwar SJ (2006): Fluoxetine enhances the anticonvulsant effects of conventional antiepileptic drugs in maximal electroshock seizures in mice. *Pharmacol Rep* 58:83–90.

Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O (2004): Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 62:258–261.

Brambilla P, Perez J, Barale F, Schettini G, Soares JC (2003): GABAergic dysfunction in mood disorders. *Mol Psychiatry* 8:721–737, 715.

Brodkin ES, McDougle CJ, Naylor ST, Cohen DJ, Price LH (1997): Clomipramine in adults with pervasive developmental disorders: A prospective open-label investigation. *J Child Adolesc Psychopharmacol* 7:109–121.

Browne JL, Hauge KJ (1986): A review of alprazolam withdrawal. *Drug Intell Clin Pharm* 20:837–841.

Buckley NA, Dawson AH, Whyte IM, Henry DA (1994): Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 343:159–162.

Camacho A, Garcia-Navarro M, Martinez B, Villarejo A, Pomares E (2005): Olanzapine-induced myoclonic status. *Clin Neuropharmacol* 28:145–147.

Centorrino F, Price BH, Tuttle M, Bahk WM, Hennen J, Albert MJ, Baldessarini RJ (2002): EEG abnormalities during treatment with typical and atypical antipsychotics. *Am J Psychiatry* 159:109–115.

Clinckers R, Gheuens S, Smolders I, Meurs A, Ebinger G, Michotte Y (2005): In vivo modulatory action of extracellular glutamate on the anticonvulsant effects of hippocampal dopamine and serotonin. *Epilepsia* 46:828–836.

Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y (2004a): Anticonvulsant action of GBR-12909 and citalopram against acute experimentally induced limbic seizures. *Neuropharmacology* 47:1053–1061.

Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y (2004b): Anticonvulsant action of hippocampal dopamine and serotonin is independently mediated by D and 5-HT receptors. *J Neurochem* 89:834–843.

Cossart R, Bernard C, Ben-Ari Y (2005): Multiple facets of GABAergic neurons and synapses: Multiple fates of GABA signalling in epilepsies. *Trends Neurosci* 28:108–115.

Coughlin PA, Birkinshaw RI (2003): Zyban: Increasing the workload in an accident and emergency department? *Eur J Emerg Med* 10:62–63.

Cramer JA, Blum D, Reed M, Fanning K (2003): The influence of comorbid depression on quality of life for people with epilepsy. *Epilepsy Behav* 4:515–521.

Cuenca PJ, Holt KR, Hoefle JD (2004): Seizure secondary to citalopram overdose. *J Emerg Med* 26:177–181.

Dailey JW, Naritoku DK (1996): Antidepressants and seizures: Clinical anecdotes overshadow neuroscience. *Biochem Pharmacol* 52:1323–1329.

Dailey JW, Yan QS, Mishra PK, Burger RL, Jobe PC (1992): Effects of fluoxetine on convulsions and on brain serotonin as detected by microdialysis in genetically epilepsy-prone rats. *J Pharmacol Exp Ther* 260:533–540.

Davidson J (1989): Seizures and bupropion: A review. *J Clin Psychiatry* 50: 256–261.

de Lanerolle NC, Lee TS (2005): New facets of the neuropathology and molecular profile of human temporal lobe epilepsy. *Epilepsy Behav* 7:190–203.

Devinsky O, Honigfeld G, Patin J (1991): Clozapine-related seizures. *Neurology* 41:369–371.

Dogu O, Sevim S, Kaleagasi HS (2003): Seizures associated with quetiapine treatment. *Ann Pharmacother* 37:1224–1227.

Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA (1998): A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 59:366–373.

Favale E, Audenino D, Cocito L, Albano C (2003): The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis. *Seizure* 12:316–318.

Favale E, Rubino V, Mainardi P, Lunardi G, Albano C (1995): Anticonvulsant effect of fluoxetine in humans. *Neurology* 45:1926–1927.

Forsgren L, Nystrom L (1990): An incident case-referent study of epileptic seizures in adults. *Epilepsy Res* 6:66–81.

Fromm GH, Wessel HB, Glass JD, Alvin JD, Van Horn G (1978): Imipramine in absence and myoclonic-astatic seizures. *Neurology* 28:953–957.

Gaitatzis A, Trimble MR, Sander JW (2004): The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 110:207–220.

Gilliam F, Hecimovic H, Sheline Y (2003): Psychiatric comorbidity, health, and function in epilepsy. *Epilepsy Behav* 4 Suppl 4:S26–S30.

GlaxoSmithKline (2006a): Wellbutrin SR® (bupropion hydrochloride) sustained-release tablets prescribing information.

GlaxoSmithKline (2006b): Wellbutrin® (bupropion hydrochloride) tablets prescribing information.

Gross A, Devinsky O, Westbrook LE, Wharton AH, Alper K (2000): Psychotropic medication use in patients with epilepsy: Effect on seizure frequency. *J Neuropsychiatry Clin Neurosci* 12:458–464.

Gunther W, Baghai T, Naber D, Spatz R, Hippius H (1993): EEG alterations and seizures during treatment with clozapine. A retrospective study of 283 patients. *Pharmacopsychiatry* 26:69–74.

Harmant J, van Rijckevorsel-Harmant K, de Barsy T, Hendrickx B (1990): Fluvoxamine: An antidepressant with low (or no) epileptogenic effect. *Lancet* 336:386.

Hauser WA, Annegers JF, Kurland LT (1993): Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 34: 453–468.

Hedges D, Jeppson K, Whitehead P (2003): Antipsychotic medication and seizures: A review. *Drugs Today (Barc)* 39:551–557.

Hedges DW, Jeppson KG (2002): New-onset seizure associated with quetiapine and olanzapine. *Ann Pharmacother* 36:437–439.

Hesdorffer DC, Hauser WA, Annegers JF, Cascino G (2000): Major depression is a risk factor for seizures in older adults. *Ann Neurol* 47:246–249.

Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O (2006): Depression and suicide attempt as risk factors for incident unprovoked seizures. *Ann Neurol* 59:35–41.

Horne RL, Ferguson JM, Pope HG Jr, Hudson JI, Lineberry CG, Ascher J, Cato A (1988): Treatment of bulimia with bupropion: A multicenter controlled trial. *J Clin Psychiatry* 49:262–266.

Hovorka J, Herman E, Nemcova II (2000): Treatment of interictal depression with citalopram in patients with epilepsy. *Epilepsy Behav* 1:444–447.

Hurst DL (1986): The use of imipramine in minor motor seizures. *Pediatr Neurol* 2:13–17.

Hyde TM, Weinberger DR (1997): Seizures and schizophrenia. *Schizophr Bull* 23:611–622.

Isbister GK, Bowe SJ, Dawson A, Whyte IM (2004): Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 42:277–285.

Janicak PG, Davis JM, Preskorn SH, Ayd FJ (2001): *Principles and practice of psychopharmotherapy, third edition*. Philadelphia: Lippincott Williams and Wilkins.

Jefferson JW, Pradko JF, Muir KT (2005): Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. *Clin Ther* 27: 1685–1695.

Jick SS, Jick H, Knauss TA, Dean AD (1992): Antidepressants and convulsions. *J Clin Psychopharmacol* 12:241–245.

Jobe PC (2003): Common pathogenic mechanisms between depression and epilepsy: An experimental perspective. *Epilepsy Behav* 4 Suppl 3:S14–S24.

Jobe PC, Browning RA (2005): The serotonergic and noradrenergic effects of antidepressant drugs are anticonvulsant, not proconvulsant. *Epilepsy Behav* 7:602–619.

Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, Stark P (1991): A 102-center prospective study of seizure in association with bupropion. *J Clin Psychiatry* 52:450–456.

Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ (2003): Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav* 4 Suppl 3:S31–S38.

Kabuto H, Yokoi I, Takei M, Kurimoto T, Mori A (1994): The anticonvulsant effect of citalopram on El mice, and the levels of tryptophan and tyrosine and their metabolites in the brain. *Neurochem Res* 19:463–467.

Kanner AM (2003): Depression in epilepsy: Prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 54:388–398.

Kanner AM (2006): Epilepsy, suicidal behaviour, and depression: Do they share common pathogenic mechanisms? *Lancet Neurol* 5:107–108.

Kanner AM, Kozak AM, Frey M (2000): The use of sertraline in patients with epilepsy: Is it safe? *Epilepsy Behav* 1:100–105.

Kecskemeti V, Rusznak Z, Riba P, Pal B, Wagner R, Harasztosi C, *et al.* (2005): Norfluoxetine and fluoxetine have similar anticonvulsant and Ca2+ channel blocking potencies. *Brain Res Bull* 67:126–132.

Keele NB (2005): The role of serotonin in impulsive and aggressive behaviors associated with epilepsy-like neuronal hyperexcitability in the amygdala. *Epilepsy Behav* 7:325–335.

Kelly CA, Dhaun N, Laing WJ, Strachan FE, Good AM, Bateman DN (2004): Comparative toxicity of citalopram and the newer antidepressants after overdose. *J Toxicol Clin Toxicol* 42:67–71.

Khan A, Khan S, Kolts R, Brown WA (2003): Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: Analysis of FDA reports. *Am J Psychiatry* 160:790–792.

Khan A, Khan SR, Leventhal RM, Brown WA (2001): Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: An analysis of the food and drug administration database. *Am J Psychiatry* 158:1449–1454.

Khan A, Leventhal RM, Khan S, Brown WA (2002): Suicide risk in patients with anxiety disorders: A meta-analysis of the FDA database. *J Affect Disord* 68:183–190.

Khan A, Warner HA, Brown WA (2000): Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the Food and Drug Administration database. *Arch Gen Psychiatry* 57:311–317.

Kotsopoulos IA, van Merode T, Kessels FG, de Krom MC, Knottnerus JA (2002): Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia* 43:1402–1409.

Krijzer F, Snelder M, Bradford D (1984): Comparison of the (pro)convulsive properties of fluvoxamine and clovoxamine with eight other antidepressants in an animal model. *Neuropsychobiology* 12:249–254.

Kuhn KU, Quednow BB, Thiel M, Falkai P, Maier W, Elger CE (2003): Antidepressive treatment in patients with temporal lobe epilepsy and major depression: A prospective study with three different antidepressants. *Epilepsy Behav* 4:674–679.

Leander JD (1992): Fluoxetine, a selective serotonin-uptake inhibitor, enhances the anticonvulsant effects of phenytoin, carbamazepine, and ameltolide (LY201116). *Epilepsia* 33:573–576.

Lee JW, Crismon ML, Dorson PG (1999): Seizure associated with olanzapine. *Ann Pharmacother* 33:554–556.

Lee KC, Finley PR, Alldredge BK (2003): Risk of seizures associated with psychotropic medications: Emphasis on new drugs and new findings. *Expert Opin Drug Saf* 2:233–247.

Logsdail SJ, Toone BK (1988): Post-ictal psychoses. A clinical and phenomenological description. *Br J Psychiatry* 152:246–252.

Luchins DJ, Oliver AP, Wyatt RJ (1984): Seizures with antidepressants: An in vitro technique to assess relative risk. *Epilepsia* 25:25–32.

Malaspina D, Goetz RR, Friedman JH, Kaufmann CA, Faraone SV, Tsuang M, *et al.* (2001): Traumatic brain injury and schizophrenia in members of schizophrenia and bipolar disorder pedigrees. *Am J Psychiatry* 158:440–446.

Malberg JE, Blendy JA (2005): Antidepressant action: To the nucleus and beyond. *Trends Pharmacol Sci* 26:631–638.

Martin A, Koenig K, Scahill L, Bregman J (1999): Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol* 9:99–107.

Mehta CR, Patel NR (1983): A network algorithm for performing Fisher's exact test in r x c contingency tables. *J Am Stat Assoc* 78:427–434.

Mendez MF, Cummings JL, Benson DF (1986): Psychotropic drugs and epilepsy. *Stress Medicine* 2:325–332.

Monaco F, Cavanna A, Magli E, Barbagli D, Collimedaglia L, Cantello R, Mula M (2005): Obsessionality, obsessive-compulsive disorder, and temporal lobe epilepsy. *Epilepsy Behav* 7:491–496.

Munchau A, Langosch JM, Gerschlager W, Rothwell JC, Orth M, Trimble MR (2005): Mirtazapine increases cortical excitability in healthy controls and epilepsy patients with major depression. *J Neurol Neurosurg Psychiatry* 76:527–533.

Nelson J, Chouinard G (1999): Guidelines for the clinical use of benzodiazepines: Pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. *Can J Clin Pharmacol* 6:69–83.

Novartis (2006): Anafranil® clomipramine hydrochloride capsules prescribing information rev. 020605.

Noyes R Jr, Perry PJ, Crowe RR, Coryell WH, Clancy J, Yamada T, Gabel J (1986): Seizures following the withdrawal of alprazolam. *J Nerv Ment Dis* 174:50–52.

Ojemann LM, Baugh-Bookman C, Dudley DL (1987): Effect of psychotropic medications on seizure control in patients with epilepsy. *Neurology* 37: 1525–1527.

Ojemann LM, Friel PN, Trejo WJ, Dudley DL (1983): Effect of doxepin on seizure frequency in depressed epileptic patients. *Neurology* 33:646–648.

Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA (2005): Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: A prospective study. *Lancet Neurol* 4:627–634.

Pacia SV, Devinsky O (1994): Clozapine-related seizures: Experience with 5,629 patients. *Neurology* 44:2247–2249.

Pasini A, Tortorella A, Gale K (1992): Anticonvulsant effect of intranigral fluoxetine. *Brain Res* 593:287–290.

Pasini A, Tortorella A, Gale K (1996): The anticonvulsant action of fluoxetine in substantia nigra is dependent upon endogenous serotonin. *Brain Res* 724:84–88.

Pericic D, Lazic J, Svob Strac D (2005): Anticonvulsant effects of acute and repeated fluoxetine treatment in unstressed and stressed mice. *Brain Res* 1033:90–95.

Perneger TV (1998): What's wrong with Bonferroni adjustments. *BMJ* 316: 1236–1238.

Pesola GR, Avasarala J (2002): Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *J Emerg Med* 22:235–239.

Peuskens J, Link CG (1997): A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand* 96:265–273.

Pillmann F, Schlote K, Broich K, Marneros A (2000): Electroencephalogram alterations during treatment with olanzapine. *Psychopharmacology (Berl)* 150:216–219.

Pisani F, Oteri G, Costa C, Di Raimondo G, Di Perri R (2002): Effects of psychotropic drugs on seizure threshold. *Drug Saf* 25:91–110.

Pisani F, Spina E, Oteri G (1999): Antidepressant drugs and seizure susceptibility: From in vitro data to clinical practice. *Epilepsia* 40 Suppl 10:S48–S56.

Pope HG, Jr., McElroy SL, Keck PE, Hudson JI, Ferguson JM, Horne RL (1989): Electrophysiological abnormalities in bulimia and their implications for pharmacotherapy: A reassessment. *Internat J Eating Dis* 8:191-201.

Post RM (2004): Neurobiology of seizures and behavioral abnormalities. *Epilepsia* 45 Suppl 2:5–14.

Pozzi L, Invernizzi R, Garavaglia C, Samanin R (1999): Fluoxetine increases extracellular dopamine in the prefrontal cortex by a mechanism not dependent on serotonin: A comparison with citalopram. *J Neurochem* 73:1051–1057.

Prendiville S, Gale K (1993): Anticonvulsant effect of fluoxetine on focally evoked limbic motor seizures in rats. *Epilepsia* 34:381–384.

Preskorn SH, Fast GA (1992): Tricyclic antidepressant-induced seizures and plasma drug concentration. *J Clin Psychiatry* 53:160–162.

Qin P, Xu H, Laursen TM, Vestergaard M, Mortensen PB (2005): Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: Population based cohort study. *BMJ* 331:23.

Robinson ML (1978): Epileptic fit after clomipramine. *Br J Psychiatry* 132:525–526.

Rosenstein DL, Nelson JC, Jacobs SC (1993): Seizures associated with antidepressants: A review. *J Clin Psychiatry* 54:289–299.

Sachdev P (1998): Schizophrenia-like psychosis and epilepsy: The status of the association. *Am J Psychiatry* 155:325–336.

Sachdev P (2001): The psychoses of epilepsy. *J Neurol Neurosurg Psychiatry* 70:708–709.

Sajatovic M, Meltzer HY (1996): Clozapine-induced myoclonus and generalized seizures. *Biol Psychiatry* 39:367–370.

Sajatovic M, Ramirez L (1995): Clozapine therapy in patients with neurologic illness. *Int J Psychiatry Med* 25:331–344.

Sakakihara Y, Oka A, Kubota M, Ohashi Y (1995): Reduction of seizure frequency with clomipramine in patients with complex partial seizures. *Brain Dev* 17:291–293.

Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, *et al.* (2004): Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry* 61: 705–713.

Shepherd G, Velez LI, Keyes DC (2004): Intentional bupropion overdoses. *J Emerg Med* 27:147–151.

Skowron DM, Stimmel GL (1992): Antidepressants and the risk of seizures. *Pharmacotherapy* 12:18–22.

Sparks DL, Buckholtz NS (1985): Combined inhibition of serotonin uptake and oxidative deamination attenuates audiogenic seizures in DBA/2J mice. *Pharmacol Biochem Behav* 23:753–757.

Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, *et al.* (2004): Citalopram as treatment of depression in patients with epilepsy. *Clin Neuropharmacol* 27:133–136.

Spigset O, Hedenmalm K, Dahl ML, Wiholm BE, Dahlqvist R (1997): Seizures and myoclonus associated with antidepressant treatment: Assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. *Acta Psychiatr Scand* 96:379–384.

StatsDirect (2006): StatsDirect, 2.5.6 ed. Cheshire, UK.

Stefansson SB, Olafsson E, Hauser WA (1998): Psychiatric morbidity in epilepsy: A case controlled study of adults receiving disability benefits. *J Neurol Neurosurg Psychiatry* 64:238–241.

Stimmel GL, Dopheide JA (1996): Psychotropic drug-induced reductions in seizure threshold: Incidence and consequences. *CNS Drugs* 5:37–50.

Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, *et al.* (2004): Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiatry* 56:640–650.

Swinkels WA, Kuyk J, van Dyck R, Spinhoven P (2005): Psychiatric comorbidity in epilepsy. *Epilepsy Behav* 7:37–50.

Thapar A, Roland M, Harold G (2005): Do depression symptoms predict seizure frequency--or vice versa? *J Psychosom Res* 59:269–274.

Theodore WH (2004): Epilepsy and depression: Imaging potential common factors. *Clin EEG Neurosci* 35:38–45.

Trimble M, Anlezark G, Meldrum B (1977): Seizure activity in photosensitive baboons following antidepressant drugs and the role of serotoninergic mechanisms. *Psychopharmacology (Berl)* 51:159–164.

Tutka P, Barczynski B, Wielosz M (2004): Convulsant and anticonvulsant effects of bupropion in mice. *Eur J Pharmacol* 499:117–120.

Ugale RR, Mittal N, Hirani K, Chopde CT (2004): Essentiality of central GABAergic neuroactive steroid allopregnanolone for anticonvulsant action of fluoxetine against pentylenetetrazole-induced seizures in mice. *Brain Res* 1023:102–111.

US Department of Justice (1996): The Freedom of Information Act 5 U.S.C. § 552, As Amended By Public Law No. 104-231, 110 Stat 3048. *FOIA Update* XVII.

Wada Y, Hirao N, Shiraishi J, Nakamura M, Koshino Y (1999): Pindolol potentiates the effect of fluoxetine on hippocampal seizures in rats. *Neurosci Lett* 267:61–64.

Wada Y, Shiraishi J, Nakamura M, Hasegawa H (1995): Prolonged but not acute fluoxetine administration produces its inhibitory effect on hippocampal seizures in rats. *Psychopharmacology (Berl)* 118:305–309.

Wedin GP, Oderda GM, Klein-Schwartz W, Gorman RL (1986): Relative toxicity of cyclic antidepressants. *Ann Emerg Med* 15:797–804.

Whyte IM, Dawson AH, Buckley NA (2003): Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 96:369–374.

Woolley J, Smith S (2001): Lowered seizure threshold on olanzapine. *Br J Psychiatry* 178:85–86.

Worthley DL, Burgess N, Nigro O, Shakib S (2004): Seroquel, serzone and seizures. *Intern Med J* 34:134–135.

Yoshitake T, Reenila I, Ogren SO, Hokfelt T, Kehr J (2003): Galanin attenuates basal and antidepressant drug-induced increase of extracellular serotonin and noradrenaline levels in the rat hippocampus. *Neurosci Lett* 339: 239–242.