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Identifying baseline characteristics of placebo responders *versus* nonresponders in randomized double-blind trials of refractory partial-onset seizures

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ABSTRACT – In add-on studies of partial-onset seizures, the placebo response, defined as a 50% decrease from baseline in seizure frequency, ranges from 0-19%. Reasons for this significant difference between placebo groups in different trials are not given in the literature. This exploratory analysis was undertaken to compare the baseline characteristics of placebo responders and nonresponders, in an attempt to identify common features. The pooled statistical analysis was performed on the database for three pivotal studies of levetiracetam (n = 904). Using the 50% response definition, we found that 45.6% of placebo nonresponders were on one antiepileptic drug at baseline, compared with 69% of placebo responders. The difference in number of baseline antiepileptic drugs was almost statistically significant (p = 0.056). Placebo nonresponders also tended to have epilepsy for longer than responders. The mean age at onset of epilepsy was consistently different between placebo nonresponders and responders (15.2 *versus* 20.8 years, respectively; p = 0.019). These findings suggest that the placebo response is higher in patients with partial-onset seizures who are taking only one antiepileptic drug at baseline and have later onset and shorter duration of epilepsy than in patients on more than one antiepileptic drug at baseline with earlier onset and longer duration of epilepsy.

Key words: partial-onset seizures, epilepsy, placebo response, clinical trial methodology, antiepileptics

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When developing a new antiepileptic drug (AED), the initial clinical studies are commonly conducted in refractory patients with partial-onset seizures. These patients have seizures despite taking one or more AED and so require additional treatment. It is considered ethical to study this patient population in randomized placebo-controlled trials because in the pla-

cebo group, the add-on treatment is only postponed, not withheld. In this refractory patient population, the frequency of partial-onset seizures is such that it allows for a reasonable study duration during which the treatment effect can be detected, making the treatment period manageable for both the patient and investigator.

While reviewing the published literature on add-on studies of refractory partial-onset seizures, we noticed that the placebo response, defined as a 50% decrease from baseline in seizure frequency, varied from 0% (Ben-Menachem and Henriksen 1996) to 19% (French *et al.* 1996). The treatment effect size (the difference between placebo and the highest dose of active medication) varied considerably as well, from 8% (Kalviainen *et al.* 1998) to 47% (Dean *et al.* 1999) and 51% (French *et al.* 2003). We found it rather intriguing that the placebo response in one study was as much as four times that in another study. After comparing the key clinical trials of new AEDs, Cramer *et al.* (1999) concluded that the efficacy data demonstrate differences in overall improvement rates among five AEDs and placebo. They found as well that the rates of response on placebo differed significantly among trials ($p = 0.01$). They were of the opinion that these significant differences among control groups, as well as other differences, make comparisons between trials problematic.

A search of the literature for explanations of these significant differences among placebo groups in different trials was disappointing. We were unable to identify a publication that dealt with the baseline characteristics of patients in epilepsy trials, with the special emphasis on the characteristics of patients who responded to placebo. This is in sharp contrast to the abundance of literature on the predictors of placebo response in psychopharmacological studies (Downing and Rickels 1973, Quitkin *et al.* 1984, Fairchild *et al.* 1986, Brown *et al.* 1988, Khan *et al.* 1989, Zammit *et al.* 1988, Khan *et al.* 1991, Khan and Brown 1991, Brown *et al.* 1992, Wilcox *et al.* 1992, Ribeiro *et al.* 1993, Kleijnen *et al.* 1994, Woodman *et al.* 1994, Volz *et al.* 1995, Shear *et al.* 1995, Nierenberg 2003, Storossum *et al.* 2004).

The placebo response in add-on studies of refractory partial-onset seizures represents a nonspecific therapeutic effect and is composed of very diverse elements (Thompson 2000). Just being in a study makes the patient alert to the correct medication intake, increasing compliance with baseline AEDs. Further, patients' and investigators' expectations, the special patient - investigator relationship, and the attention of study personnel contribute to the improvement of seizures on placebo treatment.

The placebo response also is high and variable in many central nervous system (CNS) disorders (Muntaner *et al.* 1989, Lichtigfeld and Gillman 1989, Lipman *et al.* 1990, Rapaport *et al.* 2000, Bigal *et al.* 2001, Cabarrocas 2001, Goetz *et al.* 2002, Hackett *et al.* 2003, Pollo *et al.* 2003, Benedetti *et al.* 2004). In double-blind placebo-controlled clinical trials of depression, it varies from 12.5-51.8%, and there appears to be a trend for increasing placebo response over the years (Walsh *et al.* 2002, Ackerman and Greenland 2002, Khan *et al.* 2002, Stolk *et al.* 2003). Extensive research has been done in psychiatry and some neurological disorders (depression, anxiety, pain, etc.) with the aim to identify patients who do and do not respond to placebo. The most extensive research has been done in the field of depression (Quitkin *et al.* 1984, Fairchild *et al.* 1986, Nelson *et al.* 1990, Wilcox *et al.* 1992, Ribeiro *et al.* 1993, Burns *et al.* 1995, Volz *et al.* 1995, Stewart *et al.* 1998, Niklson and Reimitz 2002, Khan *et al.* 2003), where several studies identified different baseline characteristics in placebo responders; however, many of these results could not be replicated in other databases with different sets of patients. The only rather constant finding was that patients with a mild form of disease responded more favorably to placebo than did patients with a more severe form of disease (Stewart *et al.* 1983, Brown *et al.* 1992, Angst *et al.* 1993, Stassen *et al.* 1994, Bialik *et al.* 1995, Oosterbaan *et al.* 2001, Khan *et al.* 2002).

Although the 50% reduction in disease severity end point is arbitrary, this criterion is widely used in the field of depression. Discussions are ongoing whether it is a good clinical measure, as patients who experience a reduction of 50% from baseline may still be markedly depressed. The same argument may not be applicable for the epilepsy population with refractory partial-onset seizures. There appears to be a consensus that a 50% decrease in seizure frequency from baseline represents a clinically relevant outcome.

Theoretically, in a randomized, placebo-controlled trial, recruiting patients who are less likely to respond to placebo and more likely to respond to active treatment can increase the treatment effect size. This has further consequences on the sample size calculation. The placebo response and the response to active medication have a different impact on sample size. When working with continuous variables (e.g., seizure frequency per week or percent change from baseline in seizure frequency), the sample size is dependent only on the treatment effect judged clinically relevant and the common standard deviation. In this case, the placebo value has no impact on sample size. When working with continuous variables and expressing the difference between two treatments as relative, it is necessary to convert back this relative difference into absolute to make the sample size calculation. Because of this transformation, the placebo value has an impact on the sample size. When working with percentages of improved subjects (e.g., responder rate), the treatment effect size and sample size are dependent on the magnitude of the placebo response.

One way to understand the factors that can contribute to the placebo response is to conduct an exploratory analysis of existing databases and identify common elements that might be responsible for patients' improvement on pla-

cebo. The aim of this post hoc analysis was to compare the baseline characteristics of patients who did and did not respond to placebo, and try to identify common characteristics. For this purpose, we used pooled data from the AED levetiracetam (Keppra®). The database consisted of three independent, placebo-controlled clinical studies. Response was defined as a 50% decrease in seizure frequency from baseline. An analysis also was performed defining response as a 25% reduction in seizure frequency from baseline, in order to compare the number of patients that qualified for the 50% and the 25% response criteria and check the consistency of the data. We compared the demographic characteristics, history and etiology of epilepsy, medical history, seizure frequency at baseline, AEDs at baseline, incidence of pretreatment adverse events, and laboratory data during baseline.

Material and methods

A pooled statistical analysis was performed on three pivotal levetiracetam studies (Ben-Menachem and Falter 2000, Cereghino *et al.* 2000, Shorvon *et al.* 2000). A total of 904 patients with individual data were included.

Patient population

Men and women aged 16-70 years with clinically observed partial-onset seizures for at least 1 year before study entry, and at least two complex-partial seizures per 4 weeks during baseline despite treatment with one to three AEDs, were eligible for study enrollment. Patients were maintained on their baseline AEDs at a stable dose from randomization throughout the study. Seizures were classified according to the International League Against Epilepsy's Commission on Classification and Terminology criteria (Commission 1981). Women of childbearing age were allowed to participate only if they were surgically sterile or using a medically accepted form of contraception. All patients were required to provide written informed consent before study entry, and the studies were approved by Ethics Committees at all investigational sites.

Patients were excluded if they had a history of: status epilepticus or a seizure pattern characterized by clusters during the previous 5 years and the 12-week baseline period; progressive cerebral disease, cerebrovascular accident, or severe cardiovascular disease; chronic treatment with digitalis, glucosides, or coumarins; significant disturbance of hemostasis; insulin-dependent diabetes mellitus; unstable hyperthyroidism; impaired hepatic or renal function; poor compliance; drug or alcohol abuse within the previous 2 years; or suicidal tendency or other psychiatric disorder. Patients should not have participated in any other clinical trial within 4 weeks preceding study entry and were excluded if they had participated in any previous levetiracetam trial. The use of barbiturates, benzodiazepines, and other medications that influence the CNS (e.g., neuroleptics, antidepressants, anxiolytics, psychostimulants, anticholinergics, tranquilizers, hypnotics, or narcoleptic analgesics) was prohibited. Other compounds with intrinsic CNS activity were allowed only when administered at a constant dosage throughout the study.

Statistical analysis

Subjects were classified as responders or nonresponders (at the 25% and 50% level) after computation of the percent reduction from baseline in seizure frequency per week (for all seizure types) over the entire treatment period (including up-titration). The following baseline characteristics were thus compared between responders and nonresponders using descriptive statistics: demographics, history of epilepsy, medical history, baseline seizure frequency, number of AEDs taken at baseline, incidence of pretreatment adverse events, and laboratory data. For those factors appearing descriptively as possibly different between responder groups, a two-sided p value was computed using an ANOVA model, with responder status as factor for continuous variables and Fisher exact test for categorical variables. The two-sided level of significance for inferential analysis was fixed at 5%.

Results

Of the 904 patients randomized, 312 were assigned to placebo, including two patients having a missing responder status (at 25% and 50%). Thus, 310 patients assigned to placebo were included in all of the analyses described below.

50% response criterion

Using the 50% responder rate, 281 patients were placebo nonresponders and 29 were placebo responders. Demographic characteristics of both groups are presented in *tables 1* and 2. The effect of gender on responder status was not statistically significant at the 5% level (two-sided Fisher exact test, p = 0.336). The mean duration of epilepsy was 22 years among nonresponders and 19.8 among responders (*table 2*) (two-sided ANOVA, p = 0.321). The mean age at onset of epilepsy was 15.2 *versus* 20.8 years, respectively (p = 0.019). There were no statistically significant differences between groups in terms of seizure frequency per week at baseline, regardless of seizure subtype. Among nonresponders, 45.6% had one baseline AED, compared with 69% of responders (*table 3*). When comparing the number of baseline AEDs (one to four or more), the two-sided Fisher exact test was almost significant at the 5% level (p = 0.056).

25% response criterion

Using the 25% reduction in seizure frequency, the number of placebo responders increased to 82; 54.9% were women, 45.1% men. The numerical difference between men and women remained and was not statistically sig-

Table 1. Baseline demographic characteristics: 50% response rate.

	Placebo nonresponders (n = 281)	Placebo responders (n = 29)
Age (y)		
Mean (SD)	36.7 (11.6)	40.1 (12.3)
Median	36	38
Gender		
Women, n (%)	137 (48.8)	17 (58.6)
Men, n (%)	144 (51.2)	12 (41.4)
BMI (kg/m^2)[a]		
Mean (SD)	25.4 (5.1)	25.7 (4.5)
Median	24.6	24.2

[a] Body mass index (BMI) summary statistics for placebo nonresponders are based on 280 patients, because one patient had missing data.

Table 2. Epilepsy duration, age, and seizure frequency at baseline: 50% response rate.

	Placebo nonresponders (n = 281)	Placebo responders (n = 29)
Epilepsy duration (y)		
Mean (SD)	22 (11.3)	19.8 (14)
Median	21.1	18.1
Age at onset (y)		
Mean (SD)	15.2 (12)[a]	20.8 (13.8)
Median	13	20
Seizure frequency per week, all types		
Mean (SD)	5.4 (14.7)	5.3 (12.4)
Median	1.9	1.5
Seizure frequency per week, type I		
Mean (SD)	5.4 (14.7)	5.2 (12.4)
Median	1.9	1.5
Seizure frequency per week, type IA[b]		
Mean (SD)	5.4 (17.4)	1.9 (3)
Median	1.2	0.7
Seizure frequency per week, type IB[b]		
Mean (SD)	3.7 (10.7)	4.7 (12.4)
Median	1.4	1.3
Seizure frequency per week, type IC[b]		
Mean (SD)	0.9 (1.3)	0.5 (0.7)
Median	0.5	0.1
Seizure frequency per week, type II[b]		
Mean (SD)	0.8 (0.9)	2.6[c]
Median	0.3	2.6

[a] p = 0.019 *versus* responders.

[b] For analysis of seizure subtypes, subjects having zero seizures at baseline and during treatment for the specific subtype considered were excluded from analysis. Thus, the denominators for placebo nonresponders and responders, respectively, were: IA (92; 8), IB (257; 28), IC (77; 8), and II (6; 1).

[c] Standard deviation cannot be determined: only one patient with type II seizures in this group.

Table 3. Number of antiepileptic drugs (AEDs) at baseline: 50% response rate.

AEDs	Placebo nonresponders (n = 281)	Placebo responders (n = 29)
1	128 (45.6%)	20 (69%)
2	145 (51.6%)	8 (27.6%)
3	7 (2.5%)	1 (3.4%)
≥4	1 (0.4%)	0 (0%)

nificant (p = 0.304) (*table 4*). The mean duration of epilepsy was 22.6 years among nonresponders and 19.6 among responders (two-sided ANOVA, p = 0.044) (*table 5*). The age at onset of epilepsy was 14.7 and 18.6 years, respectively (p = 0.012). Again, there were no statistically significant differences in baseline seizure frequency per week between groups, regardless of seizure subtype. Nor was there a statistically significant difference between groups in the number of baseline AEDs (*table 6*).

Discussion

In randomized controlled trials of add-on therapy for partial-onset seizures, the placebo response significantly differs among trials (Cramer *et al.* 1999). To our knowledge, this is the first attempt to study the placebo group with the intention to identify baseline characteristics of patients who respond to placebo. The most prominent finding of this post hoc analysis is that when using the 50% responder rate, placebo responders are more likely than nonresponders to be taking only one AED at baseline (69% *versus* 45.6%, p = 0.056). This difference between the two groups disappeared when the responder rate was lowered to 25%. The age of onset at epilepsy was also consistently different between placebo responders and nonresponders, with responders being older at disease onset (50% responder rate: 20.8 *versus* 15.2 years, p = 0.019; 25% responder rate: 18.6 *versus* 14.7 years, p = 0.012). A numerical difference between groups was observed for duration of epilepsy, but this difference was statistically significant (p = 0.044) only using the 25% responder rate. It should be noted that the small number of placebo responders, particularly when using the 50% criterion, limits the analyses.

Seizure frequency at baseline is another parameter that could influence the placebo response. In our dataset, however, the median seizure frequency per week was highly variable, with no statistically significant differences between responders and nonresponders, making it unlikely that this was a contributing factor. Interestingly, type 1A seizures were more common among placebo nonresponders than responders. The reasons for this are unclear. It goes against the common perception that type 1A seizures are most subject to a placebo response.

Our findings therefore suggest that the placebo response is higher in patients on only one baseline AED, with later age at onset and shorter duration of epilepsy than in patients with more than one baseline AED, earlier age at onset, and longer duration of epilepsy. These data are consistent with the basic principles found in other CNS diseases, where less severely ill patients are more prone to respond to placebo. For example, studies of the baseline characteristics of patients with major depressive disorder indicate that the placebo response is higher in patients with less severe disease as measured by the Hamilton Depression Rating Scale (Brown *et al.* 1988, Brown *et al.* 1992, Khan *et al.* 1991, Wilcox *et al.* 1992, Angst *et al.* 1993, Stassen *et al.* 1994, Bialik *et al.* 1995, Posternak *et al.* 2002, Khan *et al.*

Table 4. Baseline demographic characteristics: 25% response rate.

	Placebo nonresponders (n = 228)	Placebo responders (n = 82)
Age (y)		
Mean (SD)	36.8 (11.4)	37.7 (12.5)
Median	36	38
Gender		
Women, n (%)	109 (47.8)	45 (54.9)
Men, n (%)	119 (52.8)	37 (45.1)
BMI (kg/m^2)[a]		
Mean (SD)	25.4 (5.2)	25.5 (4.7)
Median	24.6	24.5

[a] Body mass index (BMI) summary statistics for placebo responders are based on 81 patients, because one patient had missing data.

Table 5. Epilepsy duration, age, and seizure frequency at baseline: 25% response rate.

	Placebo nonresponders (n = 228)	Placebo Responders (n = 82)
Epilepsy duration (y)		
Mean (SD)	22.6 (11.1)[a]	19.6 (12.8)
Median	22.1	17.9
Age at onset (y)		
Mean (SD)	14.7 (11.8)[b]	18.6 (13.1)
Median	12.8	17.6
Seizure frequency per week, all types		
Mean (SD)	5.8 (16.2)	4.2 (8.2)
Median	1.9	1.9
Seizure frequency per week, type I		
Mean (SD)	5.8 (16.2)	4.1 (8.2)
Median	1.9	1.8
Seizure frequency per week, type IA[c]		
Mean (SD)	5.8 (19.2)	3.3 (5.3)
Median	1.1	1.1
Seizure frequency per week, type IB[c]		
Mean (SD)	4.0 (11.9)	3.1 (7.7)
Median	1.5	1.4
Seizure frequency per week, type IC[c]		
Mean (SD)	0.9 (1.5)	0.7 (0.9)
Median	0.4	0.3
Seizure frequency per week, type II[c]		
Mean (SD)	0.8 (1.0)	1.5 (1.6)
Median	0.3	1.5

[a] p = 0.044 *versus* responders;
[b] p = 0.012 *versus* responders.
[c] For analysis of seizure subtypes, subjects having zero seizures at baseline and during treatment for the specific subtype considered were excluded from analysis. Thus, the denominators for placebo nonresponders and responders, respectively, were: IA (74; 26), IB (209; 76), IC (58; 27), and II (5; 2).

2002). Although in epilepsy there is no single measure of the severity of illness, seizure frequency, the number of failed AEDs, age at onset, duration of epilepsy, and number of baseline AEDs generally are indicators of refractoriness.

Because this analysis is post hoc and hypothesis-generating, the data have serious limitations, and no firm conclusions can be drawn. The sample size, especially for responders, is very small; an event in one patient substantially increases the percentage of that event in the group. Other databases on other AEDs used to treat refractory partial-onset seizures will have the same issue of poor balance between placebo responders and nonresponders that is inherent in add-on trials, due to the overall placebo response, which is limited to around 20% in the published literature. The issues should be explored more robustly utilizing a greater number of placebo-controlled trials of other AEDs (besides levetiracetam). A meta-analysis

Table 6. Number of antiepileptic drugs (AEDs) at baseline: 25% response rate.

AEDs	Placebo nonresponders (n = 228)	Placebo responders (n = 82)
1	110 (48.2%)	38 (46.3%)
2	111 (48.7%)	42 (51.2%)
3	6 (2.6%)	2 (2.4%)
≥4	1 (0.4%)	0 (0%)

across a range of similar studies with different antiepileptic drugs is warranted. Either of these approaches would require unique cooperation between the clinical study groups responsible for the development of each AED. Nevertheless, this exploratory analysis is an important step in understanding the placebo response in this treatment-resistant epilepsy population. If our findings are confirmed, they may help investigators decide which patients to include or exclude from clinical trials at different stages of drug development. □

References

Ackerman DL, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J Clin Psychopharmacol* 2002; 22: 309-17.

Angst J, Scheidegger P, Stabl M. Efficacy of moclobemide in different patient groups. Results of new subscales of the Hamilton Depression Rating Scale. *Clin Neuropharmacol* 1993; 16: 55-62.

Benedetti F, Colloca L, Torre E, *et al.* Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat Neurosci* 2004; 7: 587-8.

Ben-Menachem E, Falter U, for the European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3,000 mg/d in patients with refractory partial seizures: a multicenter, double blind responder-selected study evaluating monotherapy. *Epilepsia* 2000; 41: 1276-83.

Ben-Menachem E, Henriksen O, Dam M, *et al.* Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996; 37: 539-43.

Bialik RJ, Ravindran AV, Bakish D, Lapierre YD. A comparison of placebo responders and nonresponders in subgroups of depressive disorder. *J Psychiatry Neurosci* 1995; 20: 265-70.

Bigal ME, Bigal JO, Bordini CA, Speciali JG. Evaluation of placebo use in migraine without aura, migraine with aura and episodic tension-type headache acute attacks. *Arq Neuropsiquiatr* 2001; 59: 552-8; [in Portuguese].

Brown WA, Dornseif BE, Wernicke JF. Placebo response in depression: a search for predictors. *Psychiatry Res* 1988; 26: 259-64.

Brown WA, Johnson MF, Chen MG. Clinical features of depressed patients who do and do not improve with placebo. *Psychiatry Res* 1992; 41: 203-14.

Burns RA, Lock T, Edwards DR, *et al.* Predictors of response to amine-specific antidepressants. *J Affect Disord* 1995; 35: 97-106.

Cabarrocas X, for the Almotriptan Study Group. Efficacy and tolerability of subcutaneous almotriptan for the treatment of acute migraine: a randomized double-blind, parallel-group, dose-finding study. *Clin Ther* 2001; 23: 1867-75.

Cereghino JJ, Biton V, Abou-Khalil B, *et al.* Levetiracetam Study Group. Levetiracetam for partial onset seizures: results of a double-blind, randomized trial. *Neurology* 2000; 55: 236-42.

Commission on the Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; 22: 489-501.

Cramer JA, Fisher R, Ben-Menachem E, French J, Mattson TH. New antiepileptic drugs: comparison of key clinical trials. *Epilepsia* 1999; 40: 590-600.

Dean C, Mosier M, Penry K. Dose-response study of vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures. *Epilepsia* 1999; 40: 74-82.

Downing RW, Rickels K. Predictors of response to amitriptyline and placebo in three outpatient treatment settings. *J Nerv Ment Dis* 1973; 156: 109-29.

Fairchild CJ, Rush AJ, Vasavada N, Giles DE, Khatami M. Which depressions respond to placebo? *Psychiatry Res* 1986; 18: 217-26.

French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. *Neurology* 2003; 60: 1631-7.

French JA, Mosier M, Walker S, Sommerwile K, Sussman N, and the Vigabatrin Protocol 024 Investigative Cohort. A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; 46: 54-61.

Goetz CG, Leurgans S, Raman R, and the Parkinson Study Group. Placebo-associated improvements in motor function: comparison of subjective and objective sections of the UPDRS in early Parkinson's disease. *Mov Disord* 2002; 17: 283-8.

Hackett D, Haudiquet V, Salinas E. A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. *Eur Psychiatry* 2003; 18: 182-7.

Kalviainen R, Brodie MJ, Duncan J, *et al.* A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. *Epilepsy Res* 1998; 30: 31-40.

Khan A, Brown WA. Who should receive antidepressants: suggestions from placebo treatment. *Psychopharmacol Bull* 1991; 27: 271-4.

Khan A, Cohen S, Dager S, Avery DH, Dunner DL. Onset of response in relation to outcome in depressed outpatients with placebo and imipramine. *J Affect Disord* 1989; 17: 33-8.

Khan A, Dager SR, Cohen S, Avery DH, Scherzo B, Dunner DL. Chronicity of depressive episode in relation to antidepressant-placebo response. *Neuropsychopharmacology* 1991; 4: 125-30.

Khan A, Detke M, Khan SR, Mallinckrodt C. Placebo response and antidepressant trial outcome. *J Nerv Ment Dis* 2003; 191: 211-8.

Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol* 2002; 22: 40-5.

Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-blind clinical trials: a review of interactions with medications. *Lancet* 1994; 344: 1347-9.

Lichtigfeld FJ, Gillman MA. The effect of placebo in the alcohol withdrawal state. *Alcohol Alchol* 1989; 24: 109-12.

Lipman JJ, Miller BE, Mays KS, Miller MN, North WC, Byrne WL. Peak B endorphin concentration in cerebrospinal fluid: reduced in chronic pain patients and increased during the placebo response. *Psychopharmacology (Berl)* 1990; 102: 112-6.

Muntaner C, Cascella NG, Kumor KM, Nagoshi C, Herning R, Jaffe J. Placebo responses to cocaine administration in humans: effects of prior administration and verbal instructions. *Psychopharmacology (Berl)* 1989; 99: 282-6.

Nelson JC, Mazure CM, Jatlow PI. Does melancholia predict response in major depression? *J Affect Disord* 1990; 18: 157-65.

Nierenberg AA. Predictors of response to antidepressants general principles and clinical implications. *Psychiatr Clin North Am* 2003; 26: 345-52.

Niklson IA, Reimitz PE. Baseline characteristics of major depressive patients in clinical trials in Europe and United States: is there a transatlantic difference? *J Psychiatr Res* 2002; 35: 71-81.

Oosterbaan DB, Balkom AJ, Spinhoven P, van Dyck R. The placebo response in social phobia. *J Psychopharmacol* 2001; 15: 199-203.

Pollo A, Vighetti S, Rainero I, Benedetti F. Placebo analgesia and the heart. *Pain* 2003; 102: 125-33.

Posternak MA, Zimmerman M, Keitner GI, Miller IW. A reevaluation of exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry* 2002; 159: 191-200.

Quitkin FM, Rabkin JG, Ross D, Stewart JW. Identification of true drug response to antidepressants. *Arch Gen Psychiatry* 1984; 41: 782-6.

Rapaport MH, Pollack MP, Wolkow R, Mardekian J, Clary C. Is placebo response the same as drug response in panic disorder? *Am J Psychiatry* 2000; 157: 1014-6.

Ribeiro SC, Tandon R, Grunhaus L, Greden JF. The DST as a predictor of outcome in depression: a meta-analysis. *Am J Psychiatry* 1993; 150: 1618-29.

Shear MK, Leon AC, Pollack MH, Rosenbaum JF, Keller MB. Pattern of placebo response in panic disorder. *Pharmacology Bull* 1995; 31: 273-8.

Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P, for the European Levetiracetam Study Group. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000; 41: 1179-86.

Stassen HH, Angst J, Delini-Stula A. Severity at baseline and onset of improvement in depression/meta-analysis of imipramine and moclobemide *versus* placebo. *Eur Psychiatry* 1994; 9: 129-36.

Stewart JW, Quitkin FM, Liebowitz MR, McGrath PJ, Harrison WM, Klein DF. Efficacy of desipramine in depressed outpatients. Response according to research diagnosis criteria diagnoses and severity of illness. *Arch Gen Psych* 1983; 40: 202-7.

Stewart JW, Quitkin FM, McGrath PJ, *et al.* Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. *Arch Gen Psych* 1998; 55: 334-43.

Stolk P, Ten Berg MJ, Hemels ME, Einarson TR. Meta-analysis of placebo rates in major depressive disorder trials. *Ann Pharmacother* 2003; 37: 1891-9.

Storosum JG, Elferink AJ, van Zwieten BJ, van den Brink W, Huyser J. Natural course and placebo response in short-term, placebo-controlled studies in major depression: a meta-analysis of published and non-published studies. *Pharmacopsychiatry* 2004; 37: 32-6.

Thompson WG. Placebos: a review of the placebo response. *Am J Gastroenterol* 2000; 95: 1637-43.

Volz HP, Muller H, Sturm Y, Preussler B, Moller HJ. Effect of initial treatment with antidepressants as predictor of outcome after 8 weeks. *Psychiatry Res* 1995; 58: 107-15.

Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies in major depression: variable, substantial, and growing. *JAMA* 2002; 287: 1840-7.

Wilcox CS, Cohn JB, Linden RD, *et al.* Predictors of placebo response: a retrospective analysis. *Psychopharmacol Bull* 1992; 28: 157-62.

Woodman CL, Noyes Jr. R, Ballenger JC, Lydiard RB, Sievers G, Mihalko D. Predictors of response to alprazolam and placebo in patients with panic disorder. *J Affect Disord* 1994; 30: 5-13.

Zammit GK, Rosenbaum AH, Stokes P, Davis J, Zorick F, Roth T. Biological differences in endogenous depressive placebo responders: dexamethasone suppression test and sleep EEG data. *Biol Psychiatry* 1988; 24: 97-101.