Can We Really Accelerate and Enhance the Selective Serotonin Reuptake Inhibitor Antidepressant Effect? A Randomized Clinical Trial and a Meta-Analysis of Pindolol in Nonresistant Depression

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Objective: Since depression entails not only dramatic personal disruption but also a huge amount of medical and socioeconomic burden, slowness of antidepressant action and difficulties to attain remission are entangled issues to be solved. Given the controversial previous findings with enhancing strategies such as pindolol, we examined whether the speed of selective serotonin reuptake inhibitor (SSRI) action can be truly accelerated with optimized pindolol dosage. Additionally, we aimed at elucidating whether pindolol benefits emerge, particularly in a population with nonresistant depression.

Method: Thirty outpatients with major depressive disorder (*DSM-IV* criteria) recruited between December 2002 and November 2005 were randomly assigned to receive citalopram + pindolol (5 mg tid) or citalopram + placebo for 6 weeks in a double-blind randomized clinical trial. A meta-analysis of randomized controlled trials of pindolol augmentation in patients with nonresistant depression was also performed. Outcome criteria were based on the 17-item Hamilton Depression Rating Scale. For the meta-analysis, efficacy was assessed by the number of treatment responders at 2 weeks and 4–6 weeks.

Results: *Clinical trial outcomes:* Repeated-measures analysis of variance showed a significant group-by-time interaction ($P = .01$). Cumulative percentage showed a trend for sustained response (odds ratio [OR] = 2.09; 95% CI, 0.914–4.780; $P = .08$) and a well-defined increased likelihood of sustaining remission (OR = 5.00; 95% CI, 1.191–20.989; $P = .03$) in pindolol receivers. Median survival time until first response was 65% less in the pindolol group (22 days vs 30 days; $P = .03$). The negative binomial regression model yielded different rates of response per person-day for pindolol and placebo groups (7.6% vs 4.7%, respectively; $P = .03$). *Meta-analysis:* Outcome favored pindolol at 2 weeks' time (relative risk [RR] = 1.68; 95% CI, 1.18–2.39; $P = .004$) and also at 4–6 weeks' time (RR = 1.11; 95% CI, 1.02–1.20; $P = .02$).

Conclusions: Present findings represent further evidence of the acceleration and enhancement of efficacy with pindolol administered together with SSRIs, displaying a quicker and more pronounced decrease of symptoms in patients with nonresistant major depressive disorder.

Trial Registration: clinicaltrials.gov Identifier: NCT00931775

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Major depressive disorder is an important health problem in developed countries, with a 1-year and lifetime prevalence of 5%–10% and 15%–20%, respectively.[1] A large number of clinical trials with antidepressant drugs (mostly selective serotonin reuptake inhibitors [SSRIs]) show that approximately 40% of depressed patients fail to respond satisfactorily to first-line antidepressant drugs.[2] As occurrence of residual symptoms and treatment failures in a given episode are strong predictors of relapse, recurrence, and future chronic course,[3–5] efforts are to be directed to find therapeutic strategies able to attain and sustain patients' remission.

A second problem with current standard antidepressant drugs is their slowness of action. Irrespective of their initial mechanism of action and dosage regimen, all of them require several weeks to achieve a clinically meaningful improvement. A delayed onset of antidepressant effects can entail not only a more prolonged patient experience of suffering, but also a vast variety of poor outcomes, ranging from an increased risk of suicide to a greater illness burden, critical secondary psychosocial losses, and higher medical costs.[6] Hence, research focusing on the acceleration of antidepressant action and improvement in the overall clinical efficacy is of paramount importance for the direct clinical implications.

Pindolol is a partial antagonist of β-adrenoreceptors and serotonin $(5\text{-HT})_{1A}$ somatodendritic autoreceptors that has been shown to prevent the inhibition of serotonergic cell firing and to potentiate the increase in extracellular 5-HT produced by SSRIs. Since the first study on pindolol was published in 1994,[7] almost 20 placebo-controlled clinical trials and several open-label studies have been reported. Although the findings have been somewhat controverted, the addition of pindolol to SSRIs appeared to accelerate the antidepressant response in many of these studies,[7–10] and this view is also supported by the results of 2 meta-analyses.[11,12] These systematic reviews reported that the hastened benefit of pindolol coadministration was especially pronounced in the first weeks of treatment. However, since inconsistency among clinical trials appeared to be significant, Whale and

colleagues[12] proposed refractory depressive syndrome as one of the possible explanatory factors for the contradictory results for pindolol. The overall benefit of pindolol, particularly in patients with nonrefractory depression, is still to be ascertained.

Oral administration of an SSRI may take up to 4 weeks to reach steady-state plasma concentrations,[13] and this delay could interfere with the potential benefit of pindolol augmentation. Moreover, it has been argued that commonly used pindolol doses (2.5 mg tid) in the clinical trials may have been suboptimal to successfully blockade the 5-HT_{1A} autoreceptors, which might also account for the confusing findings. Consequently, if one could achieve steady SSRI plasma levels rapidly and coadminister sufficient doses of pindolol, then a more pronounced acceleration and enhancement of antidepressant effect might be observed.

Here we present the results of a randomized, double-blind, placebo-controlled trial designed to examine whether the speed of the clinical antidepressant action of SSRIs can be truly accelerated by administering double doses of pindolol (5 mg tid) and giving the SSRI (citalopram) intravenously during the first days of treatment (followed by oral dosage thereafter). This article also includes an updated meta-analysis (including the current clinical trial) that aims to investigate whether pindolol improves the antidepressant outcome in non–treatment resistant patients, focusing on its early and late efficacy (2 weeks and 4–6 weeks, respectively).

METHOD

Patients

Consecutive eligible patients aged 18 to 65 years referred by general practitioners at primary care centers or by psychiatric emergency services (Catalonian Public Health Service) were recruited from December 2002 to November 2005. These patients were then screened by 3 trained psychiatrists (D.P., S.O., and V.P.) at the Affective Disorders Unit of the Hospital de Sant Pau, Barcelona, Spain.

Inclusion criteria were as follows: subjects had to have a diagnosis of unipolar major depressive disorder (according to *DSM-IV* criteria) with moderate to severe symptoms (a score ≥ 18 on the 17-item Hamilton Depression Rating Scale [HDRS][14]), and the enrolled subjects had to be antidepressant-naive or antidepressant-free for at least 6 months. Exclusion criteria were concurrent psychiatric pathology (*DSM-IV* Axis I or *DSM-IV* Axis II, cluster A or B); failure to respond to drug treatment in the current depressive episode and no previous resistance to SSRIs; suicide risk score ≥ 3 on the HDRS; participation in other drug trials within the previous month; presence of delusions or hallucinations (whether or not mood-congruent); history of substance abuse (including alcohol) in the past 3 months; pregnancy or lactation; organic brain disease or history of seizures; serious organic illnesses such as hypothyroidism or hyperthyroidism, cardiac arrhythmias, asthma, and diabetes mellitus; myocardial infarction in the past 6 months; frequent or severe allergic reactions; concomitant use of other psychotropic drugs (benzodiazepines were allowed); use of β-blockers or catecholamine-depleting agents; and current structured psychotherapy.

Study Variables

Demographic, clinical, and concomitant treatment data were collected, including age, gender, and personal and familial history of psychiatric disorders. Likewise, other clinical data relevant to the study were recorded, such as number of previous episodes, age at first depressive episode, melancholic features, and medical history. Heart rate and blood pressure were also recorded at admission to the study and at each visit. Depression severity was assessed with the HDRS, the Montgomery-Asberg Depression Rating Scale (MADRS),[15] and the Clinical Global Impressions (CGI)[16] scale. Safety was assessed by side effects, biochemical variables, and vital signs.

Study Design

Patients entering the study were randomly assigned on day 1 to one of 2 treatment arms: citalopram 20 mg/d plus placebo or citalopram 20 mg/d plus pindolol 5 mg tid. On days 1 and 3, patients received intravenous citalopram (20 mg/d) in the treatment ward. Citalopram was administered over the course of 30 minutes while patients were lying down. From day 3 onward, patients were administered 20 mg of oral citalopram (once a day). The study lasted 6 weeks; clinical assessments were carried out on days 1, 3, and 7 and every 7 days (± 3 days) thereafter until day 42. Plasma levels of citalopram were assessed with blood samples taken on days 3 and 42 (end of the study). All unused medication was returned to the investigators. Compliance was assessed by direct questioning of patients and by counting returned capsules and pills at the follow-up visits. A nurse recorded vital signs, such as blood pressure and heart rate, and investigators were blind to these measurements. The primary outcome variables were HDRS scores over the trial period, sustained response, and sustained remission. Sustained response was defined as a 50% or greater decrease in the baseline HDRS score maintained until day 42, allowing a ± 5% variation during intermediate visits. Sustained remission was defined as an HDRS score of 8 or less, and, likewise, this cut-off had to be maintained until endpoint.

The study was approved by the Ethics Committee of the Hospital de Sant Pau and was registered at http://clinicaltrials.gov with the Identifier NCT00931775. Written informed consent was obtained from all patients participating in the study. An independent researcher (Ignasi Gich, MD, Department of Clinical Pharmacology, Hospital de Sant Pau) who was not involved in the clinical trial carried out the randomization by means of computer-generated random numbers. Investigators, patients, and staff involved in the study had no access to the randomization list until the end of the study.

Data Treatment and Statistical Analysis

The planned sample size for this study was 60 randomly assigned patients (30 in each treatment group). This sample

size was chosen to provide approximately 75% power to detect a difference in the percentage of responders at endpoint of 60% for citalopram + placebo and 80% for citalopram + pindolol using a 1-sided .05-level test. Given the absence of adverse effects of pindolol in previous open-label trials, the use of 1-sided tests was considered to be more appropriate than increasing the sample size. Thus, 1-sided *P* values were used in safety and efficacy analyses. Data are given as mean (SD). All scores were computed using a last-observation-carried-forward approach. All analyses were done by intention to treat. An interim analysis was performed at n = 30 patients (half of the planned sample), which met the criteria to stop the trial.

Analysis of demographic and clinical data was carried out by Student *t* test or nonparametric tests when appropriate. The analysis of the HDRS change was carried out on the one hand using repeated-measures analysis of variance (ANOVA), with time (8 time points) as the within-subjects factor and group (citalopram + placebo vs citalopram + pindolol) as the between-subjects factor. A Huynh-Feldt correction was used when the assumption of sphericity was violated (uncorrected *df* reported). Further differences were assessed by means of post hoc analyses. On the other hand, we analyzed sustained response and sustained remission by means of a logistic regression model for repeated measurements using the generalized estimating equation (GEE) methodology to account for intrasubject correlations, and this methodology also delivers a summary estimate of the group effect averaged over the follow-up assessments. All randomly assigned patients who had a baseline and at least 1 postbaseline score were included in the analyses. One-way ANOVA (treatment group as the between-subjects factor) was used to examine group differences between other clinical variables.

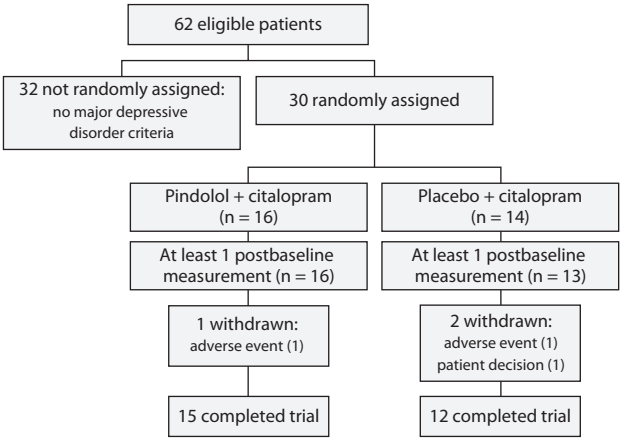
A parametric survival analysis was used to analyze the time (in days) until treatment response onset.[17] We selected the best-fitting model according to the Akaike information criterion (AIC) for 2 proportional hazards models (exponential and Weibull) and 4 accelerated failure time models (Gompertz, lognormal, log-logistic, and γ). The time to achieve response based on a criterion has been criticized for being sensitive to random variations. Therefore, we also used a negative binomial regression model to analyze the total number of responses recorded over the follow-up time.[18,19] This procedure allowed us to examine the recurrent events over time (ie, responses during the trial period) and is akin to reliably measuring speed to get a sustained response. The rates obtained with this model contain the total number of responses recorded over the trial period for each treatment arm, which eventually lead to an incidence rate ratio (active drug/placebo).

Meta-Analysis

To combine our results with others, we updated data from a previous meta-analysis.[11] Besides rerunning the computerized search, an additional check was done by exploring the reference list in a recent systematic review.[12] We included randomized clinical trials investigating the benefits of pindolol plus SSRIs in patients suffering from unipolar depressive disorder without history of treatment resistance. Efficacy was assessed by the number of patients who responded to treatment at 2 weeks and 4–6 weeks (a decrease of > 50% in depression rating scores since random allocation). The HDRS was selected as the outcome measure, and the relative risk (RR) for clinical response was chosen as the effect size to extract and combine by using a random effects model. Between-trials heterogeneity was estimated by the I^2 index.[20] Additionally, the number needed to treat (NNT) was estimated by taking the inverse of the pooled risk difference.

Descriptive and repeated-measures analyses were carried out with SPSS version 15.0 (Command Syntax Reference 2006; SPSS Inc, Chicago, Illinois) and SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). Survival analyses and meta-analysis were performed with Stata 10 (StataCorp LP, College Station, Texas).

Figure 1. Flowchart of Patient Disposition From Screening Through Completion of Study



RESULTS

Clinical Trial Outcomes

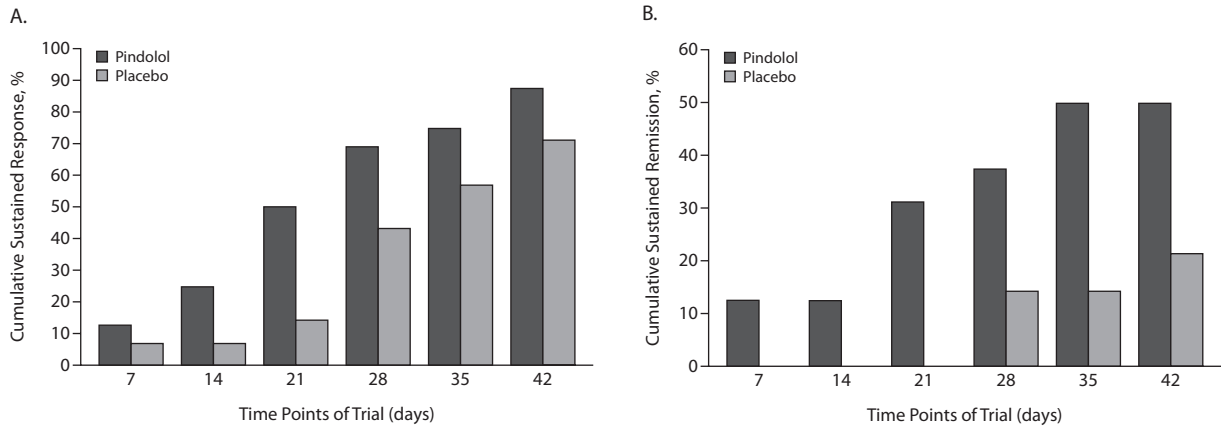
Thirty patients with a major depressive disorder diagnosis entered into the study; 16 were randomly assigned to the citalopram + pindolol group and 14 to the citalopram + placebo group (Figure 1). No differences were found between the 2 groups for any demographic or clinical variable (Table 1). Neither the percentage of first-depressive-episode patients (63% [n = 10] receiving pindolol and 64% [n = 9] receiving placebo) nor the percentage of melancholic patients (19% [n = 3] and 21% [n = 3], respectively) differed between groups. The mean ± SD duration of the current depressive episode was 2.96 ± 2.02 months. Only 1 patient from the citalopram + pindolol group and 2 patients from the citalopram + placebo group had previous episodes lasting longer than 6 months. Treatment was well tolerated by all patients with the exception of 1 patient from the citalopram + pindolol group who was withdrawn from the study due to side effects (nausea and diarrhea on the first

Table 1. Baseline Demographic and Clinical Characteristics of the 2 Treatment Groups (N = 30)

Characteristic	Pindolol + Citalopram (n = 16)	Placebo + Citalopram (n = 14)	χ^2 or *t* Statistic	*P* Value
Gender, female, n (%)	10 (62.50)	11 (78.57)	$\chi^2 = 0.918$	NS
Age, mean ± SD, y	41.25 ± 8.48	38.21 ± 9.26	$t = 0.936$	NS
Familial psychiatric history, n (%)	8 (50.00)	4 (28.57)	$\chi^2 = 1.448$	NS
Previous depressive episode, n (%)	10 (62.50)	9 (64.28)	$\chi^2 = 0.010$	NS
Age at first depressive episode, mean ± SD, y	39.53 ± 9.57	35.38 ± 11.19	$t = 1.057$	NS
No. of depressive episodes, including current episode, mean ± SD	1.47 ± 0.83	1.38 ± 0.65	$t = 0.287$	NS
Receiving concomitant treatment, n (%)			$\chi^2 = 2.892$	NS
None	4 (25.00)	4 (28.57)		
Benzodiazepines	10 (62.50)	5 (35.71)		
Hypnotic	2 (12.50)	3 (21.43)		
Benzodiazepines plus hypnotic	1 (6.25)	2 (14.29)		
Hamilton Depression Rating Scale score, mean ± SD	24.56 ± 3.44	23.21 ± 3.68	$t = 1.036$	NS
Montgomery-Åsberg Depression Rating Scale score, mean ± SD	32.19 ± 5.06	29.93 ± 5.73	$t = 1.147$	NS
Clinical Global Impressions score, mean ± SD	4.56 ± 0.51	4.5 ± 0.52	$t = 0.331$	NS

Abbreviation: NS = not significant.

Figure 2. Cumulative Percentages of Patients With Sustained Response (A) and Sustained Remission (B) Throughout the Trial Period

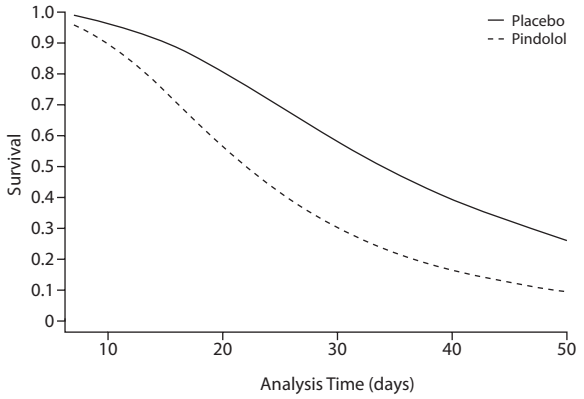


day of treatment). Biochemical parameters and vital signs were stable during the study, with no differences between groups throughout the trial with the exception of heart rate at the end of the study: although there was no clinical relevance, the citalopram + pindolol group showed fewer beats per minute (73 vs 82; $P = .02$). Plasma levels of citalopram at day 3 and day 42 did not differ between groups. At day 3, citalopram mean ± SD plasma values were 30.33 ± 29.69 μg/L in the citalopram + pindolol group and 43.08 ± 43.05 μg/L in the citalopram + placebo group ($t = -0.91$, $P = .37$). At day 42, these mean ± SD values were 21.15 ± 21.44 μg/L in the citalopram + pindolol group and 38.31 ± 26.13 μg/L in the citalopram + placebo group ($t = -1.83$, $P = .08$). There were also no differences within groups when plasma levels were compared longitudinally ($P > .4$), thus showing steady levels from the beginning.

Regarding the main analysis of HDRS scores, the repeated-measures ANOVA showed a significant time × group interaction ($F_{7,196} = 3.5$, $P = .01$). Post hoc analysis showed a significant difference between the 2 groups on the HDRS scores at day 42 ($F_{1,29} = 5.1$, $P = .03$). Figure 2 displays the cumulative percentages for sustained response and sustained remission at every time point for both groups. Applying the GEE analyses, there was a modest trend for sustained response in those who received pindolol (OR = 2.09; 95% CI, 0.914–4.780; $P = .08$); however, pindolol treatment clearly increased the likelihood of sustaining remission (OR = 5.00; 95% CI, 1.191–20.989; $P = .03$). In the survival analysis, the median survival times until first response were 22 days for the pindolol group and 30 days for the placebo group. Of the parametric survival models evaluated, the log-logistic showed the best fit (AIC = 64.7), with the lognormal as the second best-fitting model (AIC = 65.2). Figure 3 depicts the survival distribution according to the log-logistic model. The coefficient for treatment, expressed as the time ratio of the pindolol group over the placebo group, was 0.65 (SE = 0.15; 90% lower confidence limit [CL], 0.44; 1-sided $P = .03$), indicating that the observed median survival time until first response in the pindolol group was 65% less than in the placebo group.

Based on the negative binomial regression model, the rates of response per person-day were 7.6% for the pindolol group versus 4.7% for the placebo group. These results favored the pindolol arm over the placebo arm (incidence-rate

Figure 3. Log-Logistic Survival Analysis for Absorbing Events



ratio = 1.62; 90% lower CL, 1.05; 1-sided $P = .03$). The model showed an adequate fit (paired t test for the difference of observed and fitted values: $t_{29} = 0.03$, $P = .98$).

Meta-Analysis

To update the previous meta-analysis, we included the results of the current trial with those of 11 other independent data sets: 9 published trials included in the previous meta-analysis,[8,9,21–26] one trial by Whale et al[12] that was unpublished at the time of our analysis (data were available online as GlaxoSmithKline clinical study, 29060/512), and a new trial,[10] not previously available for systematic reviews, which included specific data for clinical response at 2 weeks, kindly provided by its principal author (C. Geretsegger, MD, unpublished data, March 2009). Figure 4 shows the updated evidence on the efficacy of pindolol augmentation at early and late clinical response in depressive patients (results at 10 days to 2 weeks and results at 4–6 weeks, respectively).

The random effects pooled estimate of the RR for early clinical response, updated with the results of the current trial, favored the efficacy of the augmentation with pindolol (RR = 1.68; 95% CI, 1.18–2.39; $P = .004$), with a between-study heterogeneity I^2 estimate of 51.3% (95% CI, 5.8%–74.8%), representing moderate heterogeneity. The risk difference was 0.17 in favor of pindolol (95% CI, 0.07–0.27), and, thus, the NNT to obtain a clinical response was 6 (95% CI, 4–15). According to a sensitivity analysis, no single trial exerted a significant influence on the pooled estimate. By deleting 1 trial at a time, the pooled RR ranged from 1.52 to 1.82, and the I^2 ranged from 43% to 56%. No compelling evidence of small effects bias was present (Begg test, $P = .49$; Egger test, $P = .30$).

The random effects pooled estimate of the RR for late clinical response was also significant and still slightly favored the efficacy of the augmentation with pindolol (RR = 1.11; 95% CI, 1.02–1.20; $P = .02$). The between-study heterogeneity I^2 estimate was 0.0% (95% CI, 0.0%–55.4%). The risk difference was 0.07 in favor of pindolol (95% CI, 0.01–0.13), and, thus, the NNT to obtain a late clinical response was 13 (95% CI, 8–67). The sensitivity analysis showed that no single trial exerted a significant influence on the pooled estimate. By deleting 1 trial at a time, the pooled RR ranged from 1.09 to 1.12, and the I^2 ranged from 0% to 2.5%. No evidence of small effects bias was present (Begg test, $P = .89$; Egger test, $P = .92$).

DISCUSSION

The results of this study represent further evidence of the acceleration and enhancement of efficacy with pindolol administered together with SSRIs. Pindolol augmentation implied a speedup of citalopram effect, observed in a more rapid and pronounced decrease of clinical scores in a sample with nonrefractory major depressive disorder.

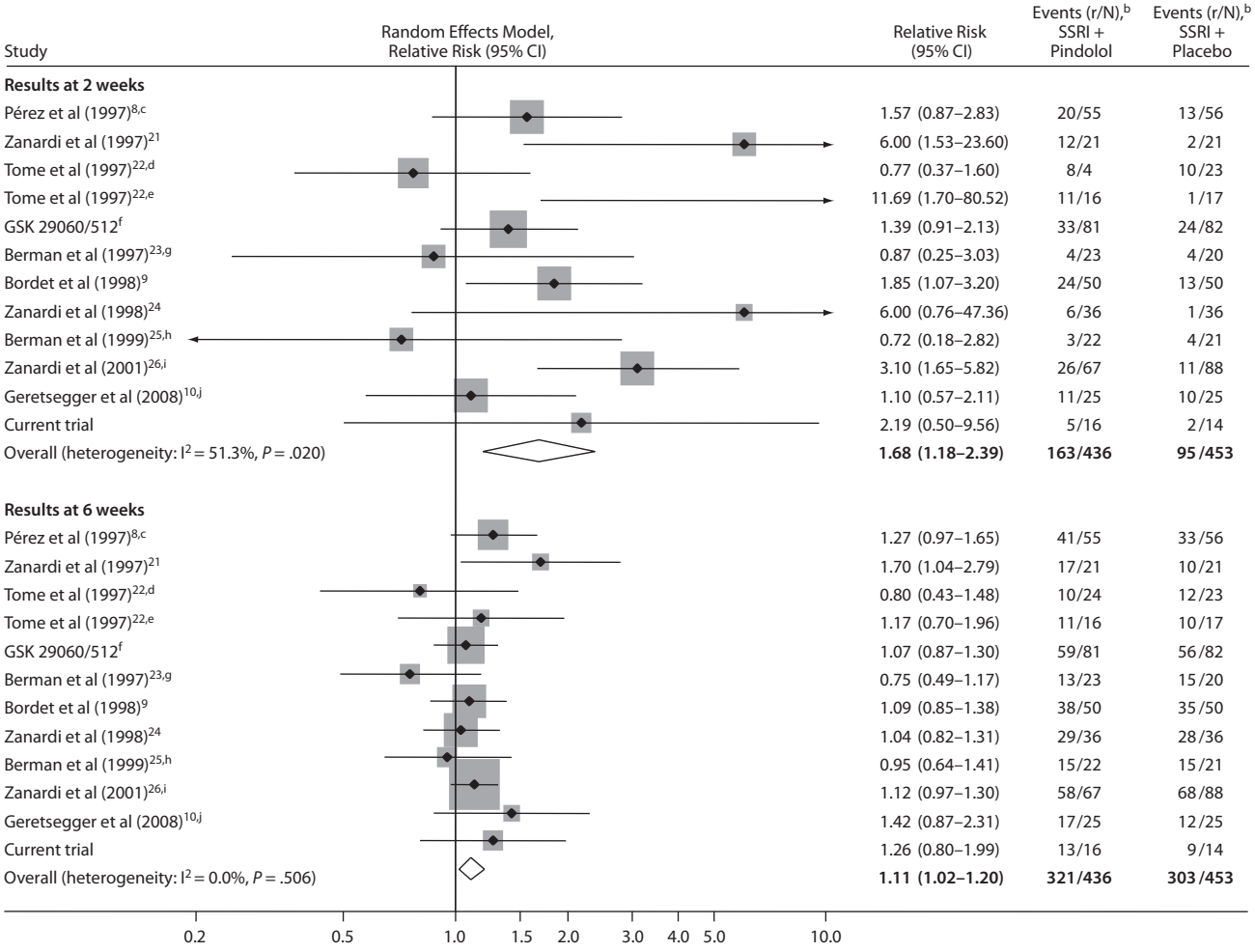
Our findings show that clinical improvement, in terms of HDRS scores, rates of sustained response and remission, and the survival curves, is more marked and quicker in patients treated with pindolol. It is worth mentioning that pindolol coadministration gave rise to a 5-fold likelihood of achieving remission within the trial period. In fact, more than 30% of patients in the pindolol arm had already achieved sustained remission at day 21, and the percentage increased to 50% by the end of the study. Moreover, patients who received pindolol took 65% less time to achieve clinical response. A negative binomial regression approach was performed in order to avoid random variations of the outcome scores through time. The results indicate that the pindolol group achieved a rate of response per person-day two-thirds higher than those receiving placebo. This ratio, in turn, might be considered as a measurement unit of both magnitude and speed of drug action for future trials. Previous trials have lacked such a unit of measurement that usefully enables comparison among studies.

On the basis of a positron emission tomography (PET) imaging study, Rabiner and colleagues[27] suggested that commonly used pindolol doses in previous clinical trials may not be sufficient to produce reliable occupancy of 5-HT_{1A} autoreceptors in the human brain. The same group reported that not only the degree of occupancy but also the preferential binding of pindolol to the 5-HT_{1A} autoreceptors (vs postsynaptic sites), which seems crucial for the proposed mechanism of pindolol action, was lower in patients receiving SSRI without a fully recovered depressive episode than in healthy volunteers.[27,28] This group related these intriguing findings with previous exposure to SSRI treatment and with depressive illness per se.

In our trial, incremental doses of pindolol, together with adequate SSRI plasma levels from the beginning, did elicit robust advantage in comparison to placebo. Interestingly, the potential adverse effects of β-adrenoreceptor blockade with double doses did not appear in any of the patients throughout the trial (with the exception of nonrelevant lower heart rate in patients receiving pindolol).

It should be noted that our sample was made up of patients without previous history of treatment resistance, and they had not received antidepressants for at least 6 months. In addition, most of the patients had had either

Figure 4. Random Effects Pooled Estimates of Risk Ratios in Randomized Trials of SSRI + Pindolol Versus SSRI + Placebo for Early Response (2 weeks) and Late Response (4–6 weeks)[a]



[a]The gray squares are proportional to individual study weights.
[b]r is the frequency of clinical response attained at 2 weeks and at 4–6 weeks for each treatment arm, and N is the total number of randomly assigned subjects.
[c]Data were obtained by reanalyzing the individual patient data of Pérez et al.[8]
[d]Data were from one of the centers included in Tome et al,[22] as recorded independently by the GSK clinical study BRL-029060/437. Data were accessed December 10, 2008, at http://download.gsk-clinicalstudyregister.com/files/1718.pdf.
[e]Data were from the second center included in Tome et al,[22] as recorded independently by the GSK clinical study BRL-029060/437. Data were accessed December 10, 2008, at http://download.gsk-clinicalstudyregister.com/files/1718.pdf.
[f]GlaxoSmithKline clinical study 29060/512—data unpublished at the time of our analysis. Data were accessed December 10, 2008, at http://download.gsk-clinicalstudyregister.com/files/2107.pdf. Study data were later published by Whale et al.[12]
[g]Data were for the first cohort of the cumulative trial, further reported in Berman et al.[23]
[h]Data were extracted only for the second cohort in Berman et al.[25]
[i]The original report did not give enough information for our analysis, but Whale et al,[12] in their systematic review, reported weekly data.
[j]Additional unpublished data provided by C. Geretsegger, MD, March 2009.
Abbreviations: GSK = GlaxoSmithKline, SSRI = selective serotonin reuptake inhibitor.

1 or no previous depressive episode. A recent brief report[29] has proven that pindolol augmentation accelerates and enhances the antidepressant action of SSRIs at the onset of the illness but not when the patient has already been treated with serotonin-based therapies. Segrave and Nathan[30] had already suggested in a review that untreated patients with few previous episodes would be more likely to respond to pindolol augmentation. It is conceivable that the controversial differences found in previous trials stem from the different types of enrolled patients (first depressive episodes, treatment resistant, and chronically ill patients). As can be inferred in light of the PET studies mentioned above, we hypothesize that differences in the regulation of 5-HT_{1A} receptors in refractory patients or patients previously treated with SSRI may diminish the ability of pindolol coadministration to eventually induce an enhancement of 5-HT neurotransmission and its downstream effects, which are likely to be determinants of clinical outcomes (ie, higher rates of response and remission and shorter delay to response).

Indeed, the results of our meta-analysis confirm the hastening effect of pindolol in patients with nonresistant depression. According to 2 previous studies,[11,12] such effect

takes place mostly at 2 weeks of treatment, and, for this clinical population (ie, with nonrefractory depression), although the effect tends to diminish over time, the advantage still remains beyond a month.

Longer duration of depression has been consistently associated with worse health-related quality-of-life outcomes,[31] socioeconomic disadvantage, and greater Axis I and medical comorbidity.[32] Moreover, more prolonged periods of time depressed have been associated with hippocampal volume reductions.[33,34] From the results described above, achieving an early response to antidepressants and, even more relevant, maintaining remission from the first weeks of treatment might be associated with long-lasting benefits by limiting devastating psychosocial and deleterious neurobiological effects secondary to recurrent or unremitting depressive illness, as has already been suggested.[35] In truth, Tome and Isaac[36] provided evidence of the maintained beneficial effect 1 year after having added pindolol for the first 6 weeks of treatment. Nevertheless, further studies should evaluate the long-term outcomes of pindolol coadministration beyond focusing on HDRS score decreases (ie, clinical response).

Limitations

First, these results should be taken with caution given that generalizability cannot be assured. The recruited patients showed low psychiatric and medical comorbidity, which is known to be closely related with poorer prognosis. In any case, our sample is surely representative of outpatients with a moderate-severe depression normally seen in mental health services. Second, some of the analyses might lack statistical power given the small sample size. For instance, GEE results of sustained response or pairwise comparisons in each visit would have been significant in light of the substantial tendency depicted by the data. However, the main outcomes of the clinical trial were already significant with half of the planned sample, thus stopping recruitment. Finally, although doses of pindolol were double the common dose, we cannot assure that the beneficial effects reported here are totally caused by higher 5-HT_{1A} autoreceptor binding, and neither can collateral effect on other neurotransmitter systems be ruled out. Therefore, the need for new studies with neuroimaging techniques becomes manifest, so as to be able to clarify these issues.

Drug name: citalopram (Celexa and others).

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