Differential Prediction of First Clinical Response to Serotonergic and Noradrenergic Antidepressants Using the Loudness Dependence of Auditory Evoked Potentials in Patients With Major Depressive Disorder

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Objective: Predictors of treatment response to serotonergic versus nonserotonergic, e.g., noradrenergic, antidepressants are of considerable clinical relevance as they could help to reduce the occurrence of patients' receiving weeks or even months of unsuccessful treatment. Several studies show that the response to selective serotonin reuptake inhibitors can be successfully predicted by using the loudness dependence of auditory evoked potentials (LDAEP), which denotes change in the amplitudes in response to different stimulus intensities and is to date one of the best validated indicators of the central serotonergic system. The aim of the current randomized prospective study was to investigate whether or not LDAEP also allows the differential prediction of treatment response to serotonergic versus noradrenergic antidepressants.

Method: Electrophysiologic recordings were performed on 48 subjects between 1999 and 2001. After exclusions due to artifacts, the study sample consisted of 35 unmedicated inpatients with a DSM-IV or ICD-10 diagnosis of major depressive disorder (mean ± SD age = 42.5 ± 10.8 years; 13 male, 22 female; mean ± SD score of 28.9 ± 5.7 on the Hamilton Rating Scale for Depression [HAM-D], the primary measure for psychopathology). The patients were then treated for 4 weeks with either the selective serotonin reuptake inhibitor citalopram or the noradrenaline reuptake inhibitor reboxetine.

Results: Analysis of variance ($F = 5.05$, $df = 1,31$; $p = .03$) revealed that responders (50% improvement in HAM-D score) to the citalopram treatment were characterized by a strong LDAEP at baseline, and responders to reboxetine were characterized by a weak LDAEP at baseline. Nonresponders to citalopram or reboxetine showed the inverse LDAEP characteristics, respectively.

Conclusion: This study is one of the first to demonstrate differential prediction of response to different classes of antidepressants. Patients at the beginning of an antidepressant treatment who show an initially strong LDAEP have a greater probability of responding to a serotonin-agonist antidepressant, whereas patients with a weak LDAEP will probably benefit more from a nonserotonergic, e.g., noradrenergic, antidepressant. If these results were replicated in a larger sample, this simple electroencephalographic method could be more broadly used in clinical practice to support clinicians in replacing the trial and error method with a more targeted and individualized approach to antidepressant treatment.

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Prediction of therapeutic response to antidepressant treatment is of great clinical value in view of the fact that at least 30% to 50% of patients with major depressive disorder do not respond to the first or the second medication administered.[1,2] Many patients suffering from depression have to undergo several therapeutic antidepressant trials before an effective treatment method is found. A waiting period of at least 2 to 3 weeks, often involving the appearance of side effects, is inevitable before a nonresponse can be definitively determined. The repeated trials are not merely time consuming but also put a great amount of stress on the patient and may even

heighten the risk of suicide. With the help of a neurobiological parameter that would enable the prediction of an individual's response to an antidepressant therapy, it would be possible not only to avoid these disadvantages and expedite the start of successful therapy, but also to prevent possible chronification or therapy resistance. Additionally, indirect (e.g., days of missed work) and direct (e.g., inpatient time) costs of treatment could be substantially reduced.

On the basis of today's pathophysiologic knowledge of depression,[3] a growing number of antidepressant treatments have been developed that more selectively influence either the central serotonergic or noradrenergic neurotransmission. For instance, selective serotonin reuptake inhibitors (SSRIs) and noradrenaline reuptake inhibitors (NARIs) highly selectively bind at serotonin and norepinephrine transporters, respectively. Thus, one promising way to predict the response to antidepressants would be to identify neurochemical subtypes of depressed patients. The use of SSRIs, with their long-term enhancement of serotonergic metabolism, should effect a favorable outcome especially with depressive patients whose disease is based more on low serotonergic activity, whereas the use of NARIs should be indicated in patients with normal serotonergic function and presumably lower noradrenergic function.[4]

The reliability of identifying these patients, however, is difficult, since no direct or specific indicators for either the serotonergic or the noradrenergic systems are available today.[5,6] The peripheral biochemical parameters that are used so far, neuroendocrinologic challenge tests[5] and the tryptophan depletion test,[6] have not yet been proven sufficiently valid, since they only indirectly and partly reflect the central serotonergic neurotransmission.

Recent preclinical and clinical studies have shown that loudness dependence of auditory evoked potentials (LDAEP) generated in the primary, but not in the secondary, auditory cortex is a valid indicator for the central serotonergic system.[7–12] The LDAEP is a noninvasive standardized electroencephalographic (EEG) measure that assesses the increase of N1/P2 amplitude values with increasing tone loudness during auditory stimulation. The LDAEP of the N1/P2 component, generated in the primary auditory cortex, can be measured with the help of the so-called dipole source analysis.[13] The LDAEP of the primary auditory cortex (tangential dipole) is strong when serotonergic activity is low, and vice versa. This fact can be attributed to the high innervation of this brain region, but not of secondary regions, by serotonergic fibers.[14] Several studies have already demonstrated the clinical value of LDAEP in treatment prediction of serotonin-agonist antidepressants. Patients with a strong LDAEP before treatment, i.e., showing evidence for low serotonergic activity, responded significantly better to fluoxetine,[15,16] fluvoxamine,[7] fenfluramine,[17] and paroxetine[18] and to acute antidepressant or relapse prophylactic treatment with lithium[19–21] than did patients with a weak pretreatment LDAEP, i.e., with rather high or normal serotonergic activity. Up to now, no studies have been carried out to investigate which medication elicits the best response from this latter group of patients, who have a disturbance presumably in the noradrenergic system rather than in the serotonergic system.

In contrast to studies using only 1 medication,[22,23] the purpose of this randomized prospective study was to provide evidence that the LDAEP, analyzed post hoc by investigators isolated from the clinical part of the study, makes possible a differential prediction of treatment response to either serotonergic or noradrenergic antidepressants. The study examined whether depressed inpatients with a strong LDAEP of the primary auditory cortex, which indicates low serotonergic activity, respond better to an SSRI (citalopram) than to a NARI (reboxetine) and whether, vice versa, patients with a weak LDAEP benefit more from reboxetine than from citalopram. In this 4-week study, we focused on the first clinical antidepressant response, defined as a 50% reduction of psychopathologic severity on the Hamilton Rating Scale for Depression (HAM-D).[24]

METHOD

Patients and Study Design

A total of 48 acute inpatients with nonpsychotic major depressive disorder were consecutively recruited between 1999 and 2001 just after admission to hospital. These patients fulfilled the criteria for nonreactive, nonorganic, or nonneurotic depression, according to DSM-IV and ICD-10, without any further psychiatric comorbidity. Patients with addiction disorders, reduced intelligence at moderate or severe levels, or neurologic, severe somatic, or other disorders were not included in the study. Furthermore, patients who had used a benzodiazepine continuously for more than 10 days prior to the study or who had severe hearing problems, as measured with an audiometer (Philips; Eindhoven, the Netherlands), were also not included. The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki (48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996). All subjects gave their written informed consent after the complete study design and procedures had been fully explained to them.

The patients who were willing to participate underwent a 1-week washout phase from any previous medication. During this phase, up to 2 treatments with sleep deprivation were allowed. Only 7 patients performed sleep deprivation. On the morning of day 8, the neurophysiologic LDAEP baseline was recorded. The patients were then randomly assigned to 1 of 2 treatment groups.

Table 1. Clinical Description of Responders and Nonresponders to a 4-Week Treatment With Either the Selective Serotonin Reuptake Inhibitor Citalopram or the Noradrenaline Reuptake Inhibitor Reboxetine[a]

	Citalopram		Reboxetine		Comparisons Across All Groups		
Variable	Responder (R)	Nonresponder (NR)	Responder (R)	Nonresponder (NR)	Statistic	df	Significance
Patients, N	13	7	6	9	$\chi^2 = 2.16$		NS
Age, y	46.9 ± 11.9	39.7 ± 8.1	40.7 ± 3.8	39.4 ± 13.6	F = 0.58	1,31	NS
Gender, N					$\chi^2 = 0.44$		NS
Male	5	1	3	4			
Female	8	6	3	5			
Dosage, mg/d	41.0 ± 14.5	55.0 ± 10.0[b]	6.4 ± 2.2	8.8 ± 2.4[c]	…	…	…
Duration of illness, y	5.9 ± 10.3	6.8 ± 4.5	6.9 ± 9.3	5.2 ± 5.8	F = 0.20	1,31	NS
No. of episodes	2.2 ± 2.1	2.8 ± 0.4	2.1 ± 1.7	1.9 ± 0.8	F = 0.74	1,31	NS
HAM-D baseline score (B)	30.0 ± 5.3	26.0 ± 5.4	28.7 ± 7.1	29.6 ± 5.6	F = 1.32	1,31	NS
HAM-D week 4 score (W4)	8.5 ± 3.6[d]	22.3 ± 4.2[e]	9.2 ± 7.3[f]	25.5 ± 7.4[g]	…	…	…
BDI baseline score (B)	27.4 ± 9.8	33.3 ± 6.3	25.8 ± 8.0	21.3 ± 18.6	F = 1.04	1,31	NS
BDI week 4 score (W4)	7.1 ± 5.3[h]	25.3 ± 10.2[i]	9.0 ± 5.6[j]	26.5 ± 5.0[k]	…	…	…

[a]Values are shown as mean ± SD except where indicated otherwise.
[b]R vs. NR: Z = –1.59, NS.
[c]R vs. NR: Z = –1.64, NS.
[d]B vs. W4: Z = –3.06, p = .002.
[e]B vs. W4: Z = –1.37, NS.
[f]B vs. W4: Z = –2.23, p = .02.
[g]B vs. W4: Z = –0.73, NS.
[h]B vs. W4: Z = –2.21, p = .03.
[i]B vs. W4: Z = –1.60, NS.
[j]B vs. W4: Z = –1.89, p = .05.
[k]B vs. W4: Z = –0.28, NS.
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, NS = not significant.
Symbol: … = not applicable.

Twenty-four patients were treated with the SSRI citalopram (maximum dosage of 60 mg/day, as clinically required), and 24 patients, with the NARI reboxetine (maximum dosage of 12 mg/day). Throughout the course of the study, patients were not allowed lithium or other prophylactics as supplements to the psychotropic drugs. Zopiclone, zolpidem, lorazepam, or low-potency neuroleptics were permitted in the case of restlessness and sleep problems, but comedication was limited to a period of less than 3 days. No treatment with sleep deprivation was allowed during the study period. In the course of the 4-week treatment period, 1 dropout occurred in the citalopram group, and, due to clinical reasons (i.e., deterioration of depressive symptomatology), there were 4 dropouts in the reboxetine group. These patients were all classified as nonresponders. Due to artifacts, the recording of the LDAEP at baseline could not be evaluated in 4 patients from the citalopram group and 9 patients from the reboxetine group. Of the remaining 35 patients (mean ± SD age = 42.5 ± 10.8 years; 13 male, 22 female; 12 in their first depression; mean ± SD score of 28.9 ± 5.7 on the HAM-D), 20 patients in the citalopram group and 15 patients in the reboxetine group were eligible for further analyses (Table 1).

Extensive sociodemographic and anamnestic data were documented. The psychopathologic state of the patients was rated on the day of baseline LDAEP recording and then weekly thereafter using the HAM-D.[24] The HAM-D rating was done by well-trained and experienced psychiatrists who were blinded concerning audio evoked potentials recording and analysis. The self-rated Beck Depression Inventory (BDI)[25] was also performed. Responders were defined as patients with a 50% reduction in the total HAM-D score at the end of the 4-week treatment with citalopram or reboxetine.

Auditory Evoked Potential Examination

Patients were seated with eyes open in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (SynAmps; Neuroscan Inc., El Paso, Tex.) in a slightly reclined chair, and they were asked to look at the wall 3 meters in front of them. No strict fixation was demanded. Evoked responses were recorded with 33 electrodes referred to the Cz electrode (32 channels). Sinus tones (1000 Hz, 40-millisecond duration with 10-millisecond rise and 10-millisecond fall time, interstimulus interval randomized between 1800 and 2200 milliseconds) of 5 intensities (60-, 70-, 80-, 90-, and 100-dB sound pressure level, generated by a PC stimulator) were presented binaurally in a pseudorandomized form via headphones. Data were collected with a sampling rate of 256 Hz and an analogous bandpass filter (0.16–70.00 Hz). Two-hundred–millisecond prestimulus and 600-millisecond poststimulus periods were evaluated for 100 sweeps of each intensity (500 sweeps altogether). Before averaging the data, the first 5 responses to each intensity were excluded in order to reduce short-term habituation effects. For artifact suppression, all trials were automatically excluded from averaging when the voltage exceeded ± 50 μV in any 1 of the 32 channels at any point

during the averaging period. For each patient, the remaining sweeps were averaged separately for the 5 intensity levels. The mean ± SD of averaged artifact-free sweeps of patients was 78.2 ± 13.5 per intensity. All analyses of audio evoked potentials data started after all patients had finished the study. The investigator analyzing the audio evoked potentials data was blinded concerning the clinical state and course of the patients.

Dipole source analysis was performed using the Brain Electrical Source Analysis (BESA).[26] The BESA decomposes the scalp-measured audio evoked potentials N1/P2 component from the 32 electrodes into 2 dipole source activities per hemisphere. One of the dipoles, located in the superior temporal region, has a tangential orientation and mainly reflects the activity of the primary auditory cortex. The other dipole, located in the temporal lobe, has a radial orientation and mainly reflects activity of the secondary auditory cortex. For each patient, an individual dipole model was calculated to obtain the best-fitting location and orientation of the dipoles using a standard dipole model based on the data of healthy volunteers (for details, see Hegerl et al.[27]). The magnitude of the tangential and radial dipole activity of each patient was measured separately for the 5 intensities as N1/P2-epoch amplitude (root mean squared effective amplitude over the epoch of the N1/P2 component; 63.5–217.0 milliseconds [μV]). The mean ± SD remaining variance that could not be explained by the dipole source analysis was 6.28% ± 4.09% of the scalp data in all 35 depressed patients.

The LDAEP was measured for tangential and radial dipole activity (primary and secondary auditory cortexes) using the median slope. The median slope was calculated from the slopes of all possible straight lines (N = 10) connecting the 5 amplitude values.[27] The LDAEPs of the tangential and radial dipole activity (the mean of the left and right dipoles, respectively, since there were no LDAEP differences between the hemispheres) were used as the main variables for statistical evaluation.

Statistical Analysis

All variables that were analyzed showed normal distribution, as revealed by the Kolmogorov-Smirnov test ($p > .05$). Values were expressed as mean ± SD. Group differences were assessed by analysis of variance (general linear model procedure) with 2 factors (medication group and response) and nonparametrically by the Mann-Whitney U test, due to the small sample size. Intraindividual effects were determined with the Wilcoxon test. Differences due to frequency of a variable were analyzed by the χ^2 test. Pearson correlation coefficients were calculated to determine the relationships between covariables (age, duration of illness, number of episodes, dosage of medication) and the electrophysiologic variables. Spearman correlation coefficients were calculated for relationships between psychopathology and electrophysiologic parameters. Statistical significance was set at $p \leq .05$. A p value of $\leq .10$ was regarded as statistical tendency.

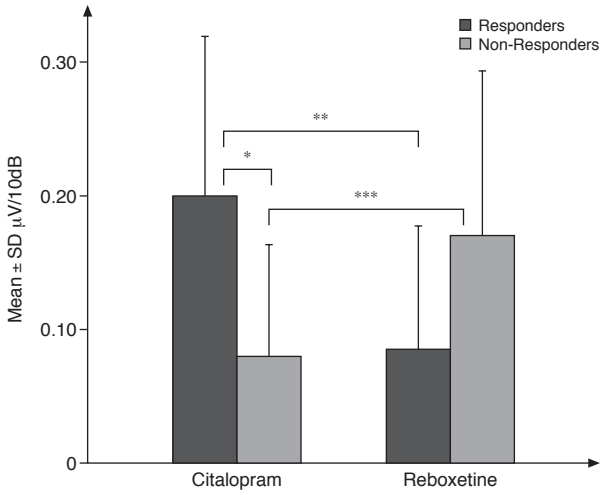
RESULTS

At week 4, thirteen patients receiving citalopram were responders, and 7 were nonresponders. In the reboxetine group, there were 6 responders and 9 nonresponders. Responders and nonresponders in the citalopram and reboxetine treatment groups did not differ in age, duration of illness, number of episodes, or psychopathologic state (as measured by the HAM-D and BDI) on the day of LDAEP recording (Table 1). There were no significant effects of interaction of the factors "medication group" and "response" in regard to these variables. In addition, there were no differences in the frequencies of responders/nonresponders and of gender in the citalopram and reboxetine groups. A significant reduction of depressive symptomatology was found in both responders to citalopram and responders to reboxetine, but not in nonresponders of either group (see Table 1).

Analyses of covariables revealed no significant effects on LDAEP of the primary (tangential dipole) or secondary (radial dipole) auditory cortex. There was no significant influence of age ($r = –0.01$), duration of illness ($r = –0.21$), number of episodes ($r = –0.18$), HAM-D score ($r = –0.06$), BDI score ($r = –0.26$), or dosage of medication (citalopram: $r = –0.10$, reboxetine: $r = 0.26$) on the LDAEP of the tangential dipole. Nor was there any significant influence of age ($r = –0.13$), duration of illness ($r = –0.19$), number of episodes ($r = –0.2$), HAM-D score ($r = 0.01$), BDI score ($r = 0.12$), or dosage of medication (citalopram: $r = –0.17$, reboxetine: $r = 0.29$) on the LDAEP of the radial dipole. The mean ± SD LDAEP did not differ between male and female patients (tangential dipole: 0.17 ± 0.16 vs. 0.13 ± 0.11 μV/10dB, respectively; $Z = –0.73$, NS) (radial dipole: 0.13 ± 0.14 vs. 0.10 ± 0.10 μV/10dB, respectively; $Z = –0.69$, NS), as gender was unequally distributed in the citalopram group. An additional LDAEP analysis for men and women was performed for this group. Again, there was no difference in mean ± SD LDAEP between male (N = 6) and female (N = 14) depressed patients (tangential dipole: 0.23 ± 0.20 vs. 0.13 ± 0.09 μV/10dB, respectively; $Z = –1.07$, NS) (radial dipole: 0.12 ± 0.10 vs. 0.09 ± 0.07 μV/10dB, respectively; $Z = –0.83$, NS).

An analysis of variance with the factors "medication group" and "response" revealed significant differences between responders and nonresponders to the 4-week treatment with citalopram or reboxetine in LDAEP at baseline ($F = 5.05$, $df = 1,31$; $p = .03$). Nonparametric post hoc tests revealed that responders to citalopram were characterized by stronger LDAEP of the primary auditory cortex than both the nonresponders to citalopram

Figure 1. Loudness Dependence of Auditory Evoked Potentials (LDAEP) of Responders and Nonresponders to Citalopram or Reboxetine Recorded Before Starting the 4-Week Treatment



*p = .04, **p = .07, ***p = .10.

(Z = –2.12, p = .04) and, as a statistical tendency, the responders to reboxetine (Z = –1.86, p = .07) (Figure 1). Nonresponders to citalopram tendentially showed weaker LDAEP than nonresponders to reboxetine (Z = –1.63, p = .10). There was no statistically significant difference between responders and nonresponders to reboxetine. In addition, the mean ± SD LDAEP of the secondary auditory cortex did not differ between the responders and nonresponders of the citalopram and reboxetine groups (citalopram: 0.12 ± 0.06 vs. 0.06 ± 0.09 µV/10dB, respectively; reboxetine: 0.13 ± 0.18 vs. 0.14 ± 0.15 µV/10dB, respectively; F = 0.76, df = 1,31; NS).

DISCUSSION

This randomized prospective study provides evidence for the differential prediction of first clinical response to serotonergic or noradrenergic antidepressants using the LDAEP of the primary auditory cortex in acutely depressed patients with major depressive disorder. The results suggest that depressed patients with low serotonergic activity, indicated by a strong LDAEP of the primary auditory cortex, have a greater probability of responding to treatment with a serotonin-agonist medication, such as an SSRI, when started immediately. Patients with normal or elevated serotonergic activity, as indicated by a weak LDAEP, might have a better first response to a nonserotonergic agent, for example, a NARI. The response of patients with major depressive disorder to the first-given antidepressant may substantially increase when LDAEP, among other measures, is used prospectively as a predictor in future studies and in clinical practice. This study focused on first clinical response, utilizing a 4-week observation and treatment period, with a 50% reduction of HAM-D total score as the criterion for response.

As in several previous studies, the LDAEP of only the primary, but not the secondary, auditory cortex was related to serotonergic activity and, thus, to the differential outcome prediction for serotonergic versus noradrenergic agents. For example, microinjection of a 5-HT_{1A} agonist (8-hydroxy-2-di-n-propylamino-tetralin [8-OH-DPAT]) into the dorsal raphe nuclei inhibits the firing rate of serotonergic neurons by means of an autoreceptor inhibitory feedback mechanism and leads to a stronger LDAEP as recorded epidurally in the primary, but not in the secondary, auditory cortex in animals, while a 5-HT_{1A} antagonist (spiperone), which increases serotonergic cell firing, leads to a weaker LDAEP compared to baseline measurements.[28] In a human study, furthermore, Tuchtenhagen and colleagues[29] reported stronger LDAEP of only the primary auditory cortex in chronic users of the serotonin-lowering drug "ecstasy" than in normal controls or cannabis users.

Given the close relationship between the LDAEP of the primary auditory cortex and the central serotonergic neurotransmission, it is not surprising that responders and nonresponders to the 4-week treatment with the SSRI citalopram could be differentiated by LDAEP. This finding is in line with the previous findings in depressed patients concerning fluvoxamine,[7] fluoxetine,[15,16] and paroxetine[18] mentioned in the introduction. Responders to treatment with an SSRI were characterized by a stronger LDAEP prior to treatment, indicating a lower central serotonergic neurotransmission than the nonresponders. Our study, however, demonstrates for the first time that the LDAEP may also enable the prediction of treatment response to a nonserotonergic antidepressant such as reboxetine, although this relationship is a more indirect one. With regard to mean values, responders to reboxetine exhibited a weaker LDAEP than nonresponders, but this result was not statistically significant. This lack of significance could be due to the small sample sizes of 6 and 9 patients in the responder and nonresponder groups, respectively. There were, however, statistical tendencies for responders to citalopram to be characterized by a stronger LDAEP than responders to reboxetine and for nonresponders to citalopram to show weaker LDAEP than nonresponders to reboxetine. These results are even more remarkable since they were accomplished with rather small groups of depressed patients. Interestingly, and in contrast to the citalopram group, there were more nonresponders (and clinical dropouts) than responders in the reboxetine group. The fact that some of the results revealed only statistical tendency seems mainly attributable to the small size of the reboxetine group. More patients in this group had a substantial amount of artifacts and therefore had to be rejected from further analyses. Although the 2

groups were quite comparable in all variables studied, including psychopathology, the artifact rate in the reboxetine group was higher, which seems to be a random effect; however, a bias due to this fact cannot be completely excluded. Currently, there is a replication study underway with a larger sample size for each group. Nevertheless, the study presented here was conducted as carefully as possible. Blindedness of clinicians on the ward (rating the psychopathologic state of the patients) and investigators in the laboratory (analyzing the LDAEP data after the patients had completely undergone the study protocol) to each other's respective procedures was an essential condition of the study. Blindedness for the raters concerning medication was not necessary in our opinion, since they were blinded to the main variable of the study, the LDAEP, and since the 2 medications should not have been compared with each other clinically. Thus, a quite naturalistic design for a day-by-day clinical situation was obtained in this study.

Predicting treatment response to antidepressants has been a challenge to psychiatric research for decades. Up to now, the decision of whether to start psychopharmacologic treatment of major depressive disorder with a serotonergic or a noradrenergic antidepressant has been based mainly on clinical observations. As a consequence, the number of nonresponders has been considerably high. Valid, objective, neurobiological predictors are not yet available. Preliminary and inconsistent results were obtained for prediction of treatment response, mainly to SSRIs, using, for example, the level of folate,[30] serum prolactin concentration after challenge with fenfluramine,[31] growth hormone level after challenge with apomorphine,[32] excitatory amino acid levels,[33] positron emission tomography,[34] and genetic polymorphisms.[35] Electrophysiologic parameters such as auditory dichotic listening[36] or resting EEG[37] could be promising, especially in combination with the LDAEP. However, there have not been any studies carried out, to our knowledge, that investigate the differential prediction of treatment response to serotonergic versus noradrenergic antidepressants in depressed patients. Our study revealed that the LDAEP of the primary auditory cortex could be a promising predictor for the differential response to modern antidepressant treatment and, thus, possibly represents progress in the field of psychopharmacology and psychiatry. Furthermore, covariables such as age, gender, duration of illness, number of episodes, or severity of depressive symptomatology did not significantly influence the LDAEP. This evidence attests to the suitability of the LDAEP as a predictor for standard clinical situations, especially with inpatients, who composed our study sample.

It can be speculated that LDAEP could help in clinical practice as a differential predictor of the probability of first therapeutic response to treatment with serotonergic or noradrenergic antidepressants. Patients with major depressive disorder would benefit from a valid prediction, since they would recover faster and be spared unnecessary side effects or heightened risk of suicide. It must be noted, however, that the usage of LDAEP as a predictor will not replace the crucial role of clinical judgment in optimal patient management. Rather, by supplying additional information, this method offers valuable assistance for clinicians when they make decisions about medication for a specific patient. Furthermore, the LDAEP procedure as a noninvasive EEG method can be performed easily and quickly and could thus be introduced into the daily routine of hospitals, outpatient services, and clinical practices after this method has been further evaluated. Finally, it is obvious that LDAEP will be especially helpful in choosing the first antidepressant in patients with major depressive disorder who are just beginning pharmacologic treatment. For patients with a longer history of depression, who often need special combinations of multiple psychotropics, or in patients with a comorbidity, the simple LDAEP approach seems to be currently unsuitable. The potential value of the LDAEP in these cases has to be investigated in further studies. Additionally, it must be taken into account that there are more than 2 subtypes of depression defined neurochemically and that these subtypes are often characterized by an overlapping neurochemistry. Thus, it is not an automatic certainty that a patient who does not respond to an SSRI will respond to a noradrenergic medication. From a clinical point of view, there are some patients who will not respond to monotherapy but to a combination of medications, e.g., an antidepressant combined with a mood stabilizer or an atypical neuroleptic, and there are a few patients who will not respond to any treatment.

Drug names: apomorphine (Apokyn), citalopram (Celexa and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), zolpidem (Ambien), zopiclone (Lunesta).

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