Onset of improvement and response to mirtazapine in depression: a multicenter naturalistic study of 4771 patients

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Abstract: The purpose of this open multicenter study of 4771 patients with a DSM-IV diagnosis of Major Depressive Episode was to analyse the response to mirtazapine in general practice and primary care. Patients with a baseline score of at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS) were treated with mirtazapine for 6 weeks (30 mg/day) and clinically assessed by their psychiatrists at weekly intervals through the MADRS and Clinical Global Improvement (CGI) rating scales. The data analysis was carried out on an "intent-to-treat" basis to collect outcome information on all patients. Our results suggested that the efficacy of the antidepressant effect relates to a nonspecific process. Nearly all patients (95%) showed at least slight improvement at the end of the observation period, while the response to treatment was independent of the clinical forms of depression. In particular, all measures of efficacy displayed the maximum change within the first 2 weeks of treatment, with further improvement occurring at much slower rates. Significant improvement within the first 2 weeks of treatment was highly predictive of the final response, and can serve as a guideline for clinicians when deciding about increased dosage, augmentation, or change of medication in unresponsive patients. Detailed analyses of individual MADRS items showed that mirtazapine's pharmacological profile, unlike selective serotonin reuptake inhibitors, led relatively quickly to a significant reduction of suicidal thoughts, a fact of particular clinical relevance.

Keywords: depression, antidepressive agents, mirtazapine, treatment outcome, prognosis, suicide

Introduction

Mirtazapine is an antidepressant with a novel mode of action: it enhances noradrenaline and serotonin neurotransmission by its direct action on various alpha-adrenergic and serotonergic receptors. Mirtazapine increases the release of noradrenaline by blocking the alpha-2 presynaptic adrenoceptors (De Boer and Ruigt 1995). The increase of intrasynaptic noradrenaline concentrations activates in turn the alpha-1 adrenoceptors located on serotonergic neurons. Alpha-1 adrenoceptors increase the firing rate of serotonergic neurons (Haddjeri et al 1995, 1998) and the release of serotonin at the nerve terminals (De Boer et al 1995). In addition, by blocking alpha-2 heteroreceptors at the serotonergic nerve terminals, mirtazapine prevents the inhibitory effect of noradrenaline on serotonin release, which leads to further serotonin release (De Montigny et al 1995). Mirtazapine binds also with high antagonist affinity to the 5-HT2, 5-HT3, and H1 receptors. This prevents the overexcitation of serotonergic neurons and adds a sedative component to the spectrum

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of pharmacological actions of the drug. On the hormonal level, mirtazapine, unlike other antidepressants, decreases the release of corticotrophin (Schule et al 2002) and cortisol (Laakmann et al 2000).

Mirtazapine has been shown to be an efficacious antidepressant. Previous studies comparing mirtazapine with placebo have shown greater improvement of depressive symptoms with mirtazapine as early as the first week of treatment (Kasper 1995). Studies comparing mirtazapine with other antidepressants have demonstrated comparable efficacy: amitriptyline (Smith et al 1990; Bremner 1995; Zivkov and de Jongh 1995; Hoyberg et al 1996; Mullin et al 1996), clomipramine (Richou et al 1995), doxepin (Marttila et al 1995), fluoxetine (Wheatley et al 1998), citalopram (Leinonen et al 1999), paroxetine (Benkert et al 2000), sertraline (Behnke et al 2003), and venlafaxine (Guelfi et al 2001). All studies comparing mirtazapine with selective serotonin reuptake inhibitors (SSRIs) consistently showed a higher efficacy for mirtazapine in the early phases of treatment. The differences were significant at week 1 compared with paroxetine (Benkert et al 2000); at weeks 1 and 2 compared with sertraline (Behnke et al 2003); at week 2 compared with citalopram (Leinonen et al 1999); and at weeks 3 and 4 compared with fluoxetine (Wheatley et al 1998).

The main purpose of this study was to look at the time characteristics of improvement under mirtazapine in a naturalistic setting that reflects everyday clinical practice more realistically than controlled randomized studies do. We used an open-label design and included both outpatients and inpatients. To characterize the profile of clinical effects of mirtazapine, we analyzed: (1) the response to treatment in the total population as well as in clinically characterized subtypes of depression; (2) the effect of baseline severity on treatment response; (3) the chronology of the response (early improvement and prediction of response); and (4) the rates of change in single symptoms during treatment.

Methods

Sample

This open-label, prospective, multicenter study was carried out in France, under the naturalistic conditions of primary care in either psychiatric private practice (n = 4037 patients) or in hospital settings (n = 734 patients). Fees to psychiatrists were paid by Organon-France. In total, 4771 patients were recruited in 1185 centers.

Selection of patients

Inclusion criteria. Patients had to be 18 years or older, suffer from a DSM-IV major depressive episode, and display a minimum score of 20 on the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). Patients had to declare that they understood the goal of the study and gave their informed written consent.

Exclusion criteria. Nonstabilized somatic disease (seizures, renal, or hepatic insufficiency), history of blood dyscrasias, known allergic reaction to mirtazapine, current suicidal risk (according to the physician's judgment), pregnancy, breastfeeding, no contraception in women of reproductive age, current depressive episode of more than 1 year's duration or nonresponse to 2 antidepressant treatments, and monoamine oxidase inhibitor treatment during the previous 2 weeks.

Treatment

Mirtazapine was given over 6 weeks in a dose of 30 mg/day at bedtime (mean recommended dosage by the French registration authorities). Other psychotropic medication(s) (for instance benzodiazepines) prescribed for more than a month before inclusion were kept unchanged. Changes in psychotropic medications were allowed after the first week of treatment and were recorded. Somatic treatments were continued with dosages adapted as needed.

Diagnosis and measures

The diagnosis of depression was made according to DSM-IV criteria for major depressive episode. Patients were further characterized with DSM-IV specifiers for melancholy, atypical depression, severity (mild, moderate, severe with psychotic symptoms, severe without psychotic symptoms), and recurrence. Postpartum depression and seasonal depression were also diagnosed according to DSM-IV. The suicidal attempt group was defined as patients having a history of at least 1 suicide attempt. The bipolar feature group was defined by a history of cyclothymia or manic/hypomanic episodes.

The severity of depression was assessed at baseline with the MADRS, and at weeks 1, 2, and 6 with the MADRS and the Clinical Global Impression-Improvement scale (CGI-I) (Guy 1976). Anxiety was assessed with the Covi scale (Covi et al 1979) at baseline and weeks 1, 2, and 6. The investigators were not specifically trained in the use of the MADRS, CGI, or Covi scales because of the naturalistic

nature of the study design. There were also no tests of inter-rater reliability.

Criteria for improvement, response, and remission

In this paper, "improvement" refers to the early changes in the first 2 weeks and "response" refers to changes after 6 weeks of treatment. Improvement was defined as the percentage decrease on the MADRS or a 1-point increase on the CGI-I scale. Response was defined as a 50% decrease on the MADRS or a 2-point increase on the CGI-I scale. "Sustained" improvement or response are changes that persisted up to 6 weeks and were assessed as decreases in MADRS score in the range of –15% to –60%. Remission is defined as a MADRS global score of less than 10 points.

Statistics

The data analysis was carried out on the "intent-to-treat" basis (ITT) to include all available information on all patients.

At baseline, qualitative data were analysed by the chi-square test statistic and quantitative data by Wilcoxon tests. The time course of improvement and response was analysed using survival analysis, Cox models, and two-way ANOVAs (analysis of variance) or ANCOVAs (analysis of covariance). All correlations were evaluated through Pearson Product-Moment coefficients.

Analyses of MADRS global scores, MADRS items, remission, speed of change (defined as the percentage change per day), and anxiety scores were carried out in the ITT population with missing data having been compensated, where necessary through the Last Observation Carried Forward (LOCF) procedure. The relative change of MADRS items was compared with the paired t-test. Changes in item scores were calculated with ANOVA. Descriptive statistics were used to compare the speed of score reduction. Statistical tests were two-sided, and significance level was set to $p < 0.05$.

Results

At baseline

In all, 4768 patients (68% females) with mean age 45 ± 12 were treated. At baseline the mean MADRS score was 31.5 ± 6.1 (mean ± SD). The severity defined by DSM-IV criteria was mild in 1.4%, moderate in 36.5%, severe without psychotic features in 59.8%, and severe with psychotic features in 2.3% of the cases. Fifty-three percent of patients suffered from their first depressive episode; the remaining 47% from a recurrent episode. Atypical depression, post-partum depression, and melancholic depression, defined by DSM-IV criteria, were present in 6.4%, 0.6%, and 15.8%, respectively. The frequency of other seasonal depression was 15.2% among the cases of recurrent depression. The mean number of previous depressive episodes was 3.4 ± 3.1, and of past suicidal attempts 2.0 ± 2.0.

The mean scores and standard deviations of single MADRS items were: "apparent sadness" 3.8 ± 1.0; "reported sadness" 3.8 ± 0.9; "inner tension" 3.5 ± 0.9; "reduced sleep" 3.2 ± 1.4; "reduced appetite" 2.0 ± 1.6; "concentration difficulties" 3.4 ± 1.0; "lassitude" 3.7 ± 1.0; "inability to feel" 3.4 ± 1.0; "pessimistic thoughts" 2.8 ± 1.1; and "suicidal thoughts" 2.0 ± 1.2.

Anxiety assessed with the Covi scale presented a mean score of 6.2 ± 2 points. The psychiatric history showed that 11.7% of the patients had an additional psychiatric diagnosis (33.9% neurosis, 19.6% addiction, 17.6% personality disorder, 14.8% psychosis, 8.3% eating disorder, 5.2% manic episode and cyclothymia, and 0.6% unspecified).

At 6 weeks (measured by MADRS and CGI-I)

MADRS. Figure 1 shows that 91% of the patients presented a sustained improvement of –15% MADRS baseline score reduction, and that 55% of the patients presented a sustained response of –50% MADRS baseline score reduction after 6 weeks of treatment. In contrast, only 30.9% of the patients obtained a complete remission.

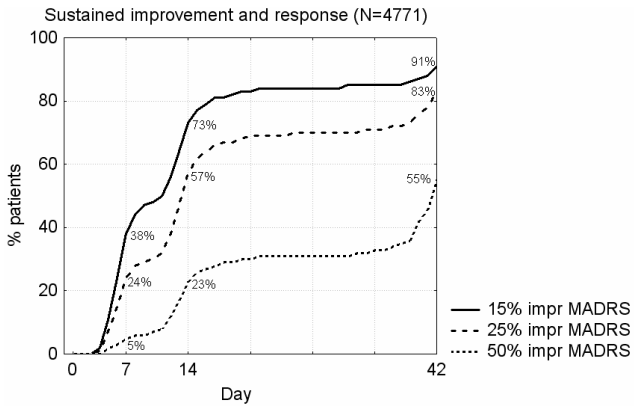

Figure 1 Sustained improvement and response. The percentage of patients with sustained –15%, –25%, –50% score reduction during the trial. Ninety-one percent of the patients achieve a sustained –15% score reduction at 6 weeks.
Abbreviation: MADRS, Montgomery-Asberg Depression Rating Scale.

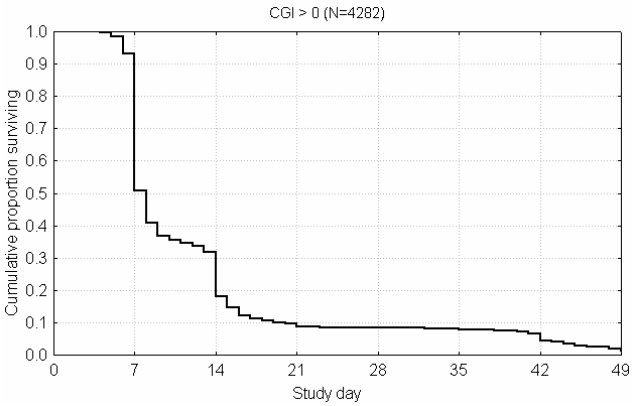

Figure 2 Survival analysis of "at least 1-point improvement" on the CGI-I scale. The survival analysis of "at least 1-point improvement" on the CGI-I shows that around 82% of the patients improved within 2 and 95% within 6 weeks.
Abbreviation: CGI, Clinical Global Improvement rating scale.

About one-third (n = 1694) of the patients were not treated with co-medication, such as benzodiazepines, hypnotics, and other psychotropic medications. Co-medication with hypnotics and antianxiety agents did not improve the antidepressant response. (The subgroup of patients with co-medications presented higher anxiety and depression scores at baseline compared with the subgroup without co-medication.)

CGI-I. Figure 2 shows the survival analysis of "≥ 1-point improvement" on the CGI-I scale. After 6 weeks of treatment, the cumulative proportion of surviving was 4.3%, thus indicating that more than 95% of the patients presented at least a 1-point increase on the CGI-I scale by the end of the study.

CGI-I scores and the MADRS scores were highly correlated throughout the study (r = 0.77, r = 0.74, r = 0.75 at 1, 2, 6 weeks, respectively; see Figure 7), indicating that the lack of rater training did not lead to unreliability in scoring in this very large sample.

Severity of depression and response to mirtazapine

Figure 3 shows the survival curves of –50% MADRS sustained response for the different MADRS baseline severity scores: < 25, 25–30, 30–35, 35–40, > 40. The therapeutic response was closely related to the baseline severity score of depression: the higher the baseline scores, the larger was the proportion of responders (p = 0.001).

Response at 6 weeks in different forms of clinically characterized depression

Survival analysis of sustained –50% MADRS response did not differ in a series of subtypes of depression. The characteristics studied were the four DSM-IV specifiers: melancholia (with: n = 739 vs without: n = 3952, p = 0.19); atypical depression (with: n = 301 vs without: n = 4390, p = 0.11); recurrent depression (with: n = 2221 vs without: n = 2505, p = 0.08); and the severity specifier (mild: n = 66, moderate: n = 1655, severe without psychotic symptoms: n = 2734, severe with psychotic symptoms: n = 106, p = 0.10 in the global comparison). Figure 4 shows the response (–50% MADRS) in the 4 severity subgroups. In the subgroup with severe psychotic symptoms (n = 109), response rates were significantly lower (p = 0.01) compared with the other subgroups (n = 4654 mild, moderate, and severe without psychotic symptoms).

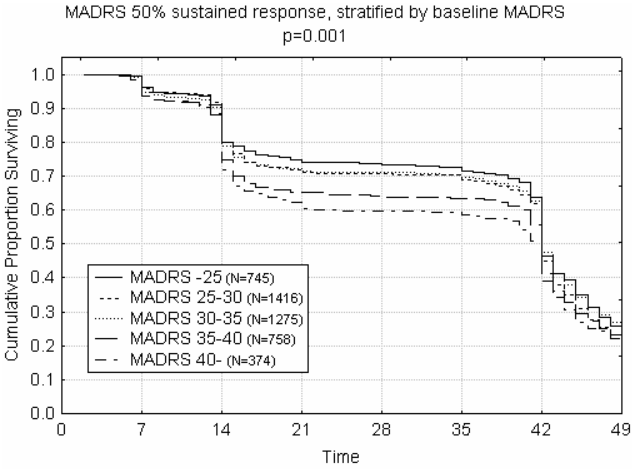

Figure 3 Survival analysis of sustained –50% MADRS response for different baseline severity scores. The –50% MADRS sustained response is related to baseline score. The higher the baseline scores, the larger the response.

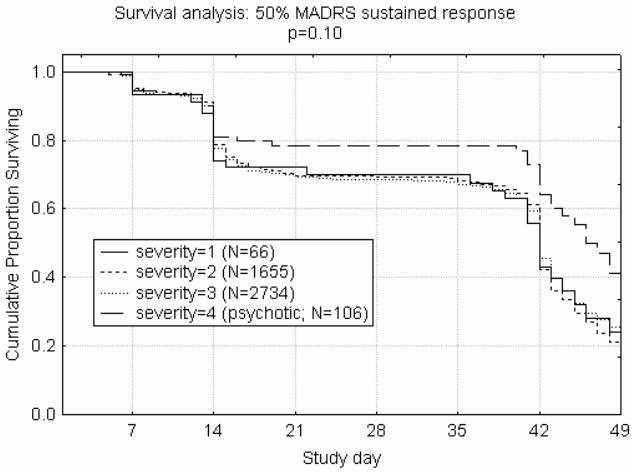

Figure 4 Survival analysis of sustained –50% MADRS response in depression characterized by severity (DSM-IV specifier: 1 = mild, 2 = moderate, 3 = severe without psychotic symptoms, 4 = severe with psychotic symptoms). The –50% MADRS sustained response is comparable in the severity subgroups defined by the DSM-IV severity-specifier.

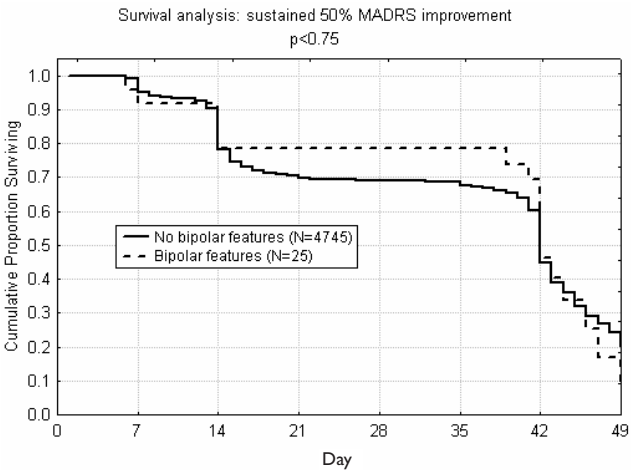

Figure 5 Survival analysis of sustained –50% MADRS response in depression characterized by bipolar features (as reported in the patient's previous psychiatric history). The –50% MADRS sustained response is similar (not significant) in the bipolar/no bipolar features groups. (Bipolar features are defined by a history of cyclothymia or manic/hypomanic episodes.)

Similarly, survival analysis of sustained response showed no differences between other clinically defined subgroups of depressive patients, such as DSM-IV postpartum depression (with: n = 18 vs without: n = 3211, p = 0.17); seasonal depression (with: n = 305 vs without: n = 1973, p = 0.79); or characteristics selected from the patients' previous psychiatric history, such as a history of previous suicide attempts (with: n = 998 vs without: n = 3770, p = 0.28); and the diagnosis of bipolar spectrum (with: n = 25 vs without: n = 4745, p < 0.75). Figure 5 shows the response (–50% MADRS) in the subgroups of patients with and without bipolar spectrum.

Chronology of response: early improvement and speed of response

MADRS global score

Using LOCF for the treatment of missing data, the mean percentage score change was –18.5 ± 18% after 1 week, –33.2 ± 25% after 2 weeks, and –46.1 ± 31% after 6 weeks of treatment. The proportion of patients with a sustained 20% improvement was 28.1% after 1 week, 55% after 2 weeks, and 75.4% after 6 weeks. The speed of improvement (percent change/day of treatment in the ITT population) differed during the trial: it was numerically larger in the first week compared with the following weeks. The speed of improvement was 2.65% per day during the first week, 2.14% during the second week, and 0.46% during weeks 3 to 6. Most of the treatment effect was seen during the first 2 weeks. The change after 1 week is clinically relevant. Patients displayed improvement immediately after entering into the study, with the maximum change during the first 2 weeks and with further improvement occurring at much slower rates.

MADRS item scores

Global scores of depression merge qualitatively different aspects of the depressive syndrome into 1 single quantity. By contrast, individual item analysis has its focus on these differences. We found the MADRS items to present very different mean baseline scores, ranging from 2.0 points for suicidal thoughts to 3.8 points for apparent and reported sadness (see baseline results). Taking this baseline variation into account, we compared items in terms of their percentage baseline score reduction or we compared items after stratification (comparison of items with equal baseline score).

Comparison of "suicidal thoughts" item with "apparent sadness" item

The percentage baseline score reduction for "suicidal thoughts" was larger than for "apparent sadness" at all assessment points: 22.6 ± 38% vs 17.7 ± 25% after 1 week, 37.7 ± 44% vs 33.8 ± 30% after 2 weeks, and 50.9 ± 48% vs 47.5 ± 36% after 6 weeks of treatment (n = 4380, p < 0.0001).

"Suicidal thoughts" item with different baseline scores

The baseline score of "suicidal thoughts" decreased quickly. The speed of improvement (percent score reduction per day) is given in Table 1 after 1, 2, and 6 weeks for each baseline score (ranging from 1 to 6). Speed of change is numerically higher during the first week in comparison with the following weeks. Indication of the way score decreases can also be given by the theoretical best fit curve: the best fit is quadratic (when baseline scores range from 2 to 6) or even cubic (when baseline scores are 3 or 4).

Comparison between patients with "suicidal thoughts", "reduced sleep" and "apparent sadness", and a baseline score of 3

The subgroups of patients in the ITT population with a baseline score of 3 differed in size for the three MADRS items "observed sadness" (n = 1065), "reduced sleep" (n = 899), and "suicidal thoughts" (n = 576), and were subjected to separate survival analyses. Figure 6 shows the survival analysis of "≥ 1-point decrease" for these three items. The proportion of patients showing a score reduction of at least 1 point was larger for the subgroup of patients with "suicidal thoughts" compared with the 2 other

Table 1 Speed of changes for "suicidal thoughts" and best fit curves (at the different MADRS baseline scores, ranging from 1 to 6)

Score at baseline	N	Speed at week 1	Speed at week 2	Speed at week 3–6	Theoretical curve that significantly fits the data
1	1355	2.71%	2.71%	0.71%	Linear
2	1735	3.78%	3.14%	0.66%	Linear, quadratic
3	684	4.95%	2.85%	0.58%	Linear, quadratic, cubic
4	517	5.35%	2.57%	0.66%	Linear, quadratic, cubic
5	73	5.48%	3.08%	0.50%	Linear, quadratic
6	21	6.95%	1.78%	0.34%	Linear, quadratic

NOTE: Speed is the % of score change between 2 assessments divided by the number of days between consecutive assessments (% change/day). Speed is computed for each MADRS baseline score selection (from 1 to 6; baseline score of 0 is not presented). Number of patients in each baseline score selection is given in the "N" column (384 patients present a baseline score = 0). Speed is always higher at week 1 and 2 compared with weeks 3–6, and is higher or equal in week 1 compared with week 2. For example, with a baseline score = 1, the table reads: 1355 patients presented a score of 1 MADRS point at baseline for the "suicidal thoughts" item, with this selection the speed of change is 2.71% at week 1 and 2 and only 0.71% from week 3 to week 6. For this selection, the theoretical curve that best fits the data is linear.

Abbreviation: MADRS, Montgomery-Asberg Depression Rating Scale.

subgroups of patients with "apparent sadness" or "reduced sleep" item.

Covi scale global score

The score reduction was –22.6 ± 36% after 1 week, –40.0 ± 41% after 2 weeks, and –51.5 ± 47% after 6 weeks of treatment (ITT with LOCF), thus indicating an early anxiety reduction under mirtazapine.

The predictive value of early improvement (at 1 week) for response at 6 weeks

MADRS and CGI-I

"Response" after 6 weeks of treatment was defined either as a sustained 50% MADRS baseline score reduction or a sustained 2-point increase (large improvement) on the CGI-I scale. MADRS and CGI-I scores were strongly correlated (Pearson coefficient: r = 0.77, 0.74 and 0.75 after 1, 2, and 6 weeks respectively). Figure 7 shows these correlations after 1 week.

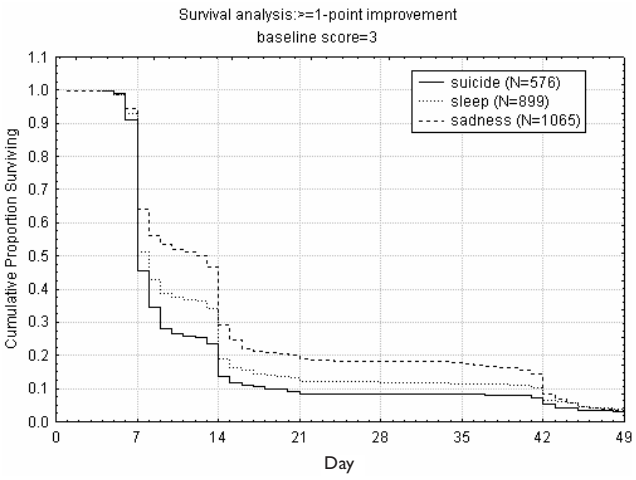

Figure 6 Survival analysis of "≥ 1-point reduction" for the MADRS items "apparent sadness", "reduced sleep", and "suicidal thoughts" among patients with baseline scores of 3. The figure shows the improvement (≥ 1-point reduction) of 3 MADRS items. Items having a baseline score = 3. The improvement of "suicidal thoughts" is numerically larger than the improvement of "apparent sadness" and "reduced sleep" (descriptive statistics).

Prediction of the response at 1 week

Early improvement during the first two weeks of treatment predicted patient response at the end of the study (6 weeks) at surprisingly high rates of correctly classified patients (Table 2).

Prediction of response (–50% MADRS baseline score reduction) after 6 weeks

Already after 1 week of treatment, a 1-point improvement on the CGI-I scale or a 20% or 30% improvement on the MADRS scale clearly predicted final response. With a 1-point improvement on CGI-I scale, the percentage of

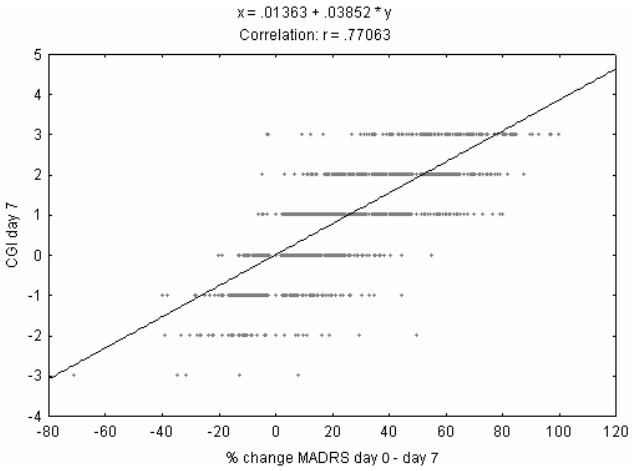

Figure 7 Correlation between MADRS and CGI-I scores. CGI-I and % of changes on the MADRS are closely related. (r = 0.77 at 1 week).

Table 2 Early improvement as a predictor of response after 6 weeks

Improvement	**+1 CGI-I**				**–20% MADRS**				**–30% MADRS**			
Time	*1 week*		*2 weeks*		*1 week*		*2 weeks*		*1 week*		*2 weeks*	
Prediction at 6 weeks	–50% MADRS	+2 CGI-I	–50% MADRS	+2 CGI-I	–50% MADRS	+2 CGI-I	–50% MADRS	+2 CGI-I	–50% MADRS	+2 CGI-I	–50% MADRS	+2 CGI-I
Sensitivity	0.78	0.75	0.94	0.95	0.43	0.38	0.81	0.76	0.27	0.23	0.68	0.60
Specificity	0.65	0.69	0.59	0.65	0.89	0.88	0.73	0.85	0.96	0.95	0.88	0.86
+ predict.val.	0.71	0.76	0.72	0.78	0.81	0.80	0.77	0.88	0.88	0.85	0.87	0.85
– predict.val.	0.72	0.68	0.90	0.90	0.58	0.52	0.77	0.70	0.54	0.48	0.71	0.62
%correct cla	**71.6**	**72.2**	77.6	81.7	**64.7**	**59.3**	77.2	74.8	**59.6**	**54.0**	77.3	71.2
False + rate	0.35	0.31	0.41	0.35	0.11	0.12	0.27	0.15	0.04	0.05	0.12	0.14
False – rate	0.22	0.25	0.06	0.05	0.57	0.62	0.19	0.24	0.73	0.77	0.32	0.40
Area under ROC	0.71	0.72	0.77	0.79	0.66	0.63	0.77	0.75	0.62	0.59	0.78	0.73

NOTE: Improvement at 1 and 2 weeks strongly predicts the response at 6 weeks. A 1-point increase on the CGI-I at 1 week correctly predicted the final response (2-points improvement on the CGI-I) in 72.2 % of the cases.

Abbreviations: CGI-I, clinical global improvement; MADRS, Montgomery-Asberg Depression Rating Scale; cla, classification. Bolded numbers are those presented in the text.

correctly classified patients was found to be as high as 71.6%. The positive and negative predictive values were 71% (patients with a 1-point improvement after 1 week and a response after 6 weeks), and 72% (no improvement after 1 week and no response after 6 weeks).

Prediction of response (2-point improvement on the CGI-I scale) after 6 weeks

After 1 week of treatment, a 1-point improvement on the CGI-I scale correctly predicted the final response in 72.2% of the cases. The positive predictive value was 76% (patients with a 1-point improvement after 1 week and a response after 6 weeks). The negative predictive value was 68% (no improvement after 1 week and no response after 6 weeks).

Discussion

Our results have shown that:

1. Response depends on the severity of depression.
2. Response is independent of the clinical form of depression.
3. Improvement after 1 week of treatment is clinically meaningful and highly predictive of final response.
4. Nearly all patients benefit from treatment to some extent.
5. There is a rapid, pronounced reduction of suicidal thoughts and anxiety under treatment.

Dependency of response on severity of depression

Response to mirtazapine clearly depended on the severity of depression as the responder rates increased with severity of depression. This finding is characteristic for true antidepressants, whereas response to placebo has been shown to decrease with the severity of depression. This divergence of efficacy in relation to severity is one of the most convincing characteristics of true antidepressant effect (Angst 1993). The fact that severely depressed psychotic patients did not respond as well as nonpsychotic patients is in agreement with many other antidepressant actions; in practice, co-medication with an antipsychotic is usually recommended.

Independence of response from the clinical form of depression

The antidepressive activity is comparable in all clinically characterized patient groups. No differences were found between the subgroups diagnosed with and without melancholic depression, atypical depression, severe depression, postpartum depression, seasonal depression, recurrent depression, depression with and without past suicide attempts, or with and without bipolar features. Therefore, response to antidepressant treatment is independent of the clinical form of depression; the antidepressant effect is nonspecific.

Improvement at 1 week is clinically meaningful and predictive of final response

After 1 week the MADRS score decreased by 18.5%. The speed of improvement was maximal in the first week of treatment. After 2 weeks, the rate of baseline score reduction decreased markedly. The period during which improvement

is >2%/day only lasted 2 weeks. These results confirm previous studies and meta-analyses in which the clinical effect of antidepressant treatments differed from placebo within 1 week and even on the fourth day of treatment (Stassen et al 1993, 1996; Stassen and Angst 1998). Early improvement did not result from lateral effects (stimulation or sedation) since it strongly predicted response after 6 weeks of treatment.

The early therapeutic effect of antidepressants is consistent with recent research that showed changes in noradrenergic and serotonergic neurotransmission produced an immediate effect. Enhancing neurotransmission with antidepressants induced positive behaviors within three hours even in healthy subjects. Administration of noradrenergic (Harmer, Hill, et al 2003) or serotonergic (Harmer, Bhagwagar, et al 2003) antidepressants increased the facial recognition of happiness by healthy volunteers. Noradrenergic antidepressants also promoted cooperative behavior. An acute dose of reboxetine increased both cooperative communication and cooperative behavior (Tse and Bond 2002a).

In contrast, reducing neurotransmission in the noradrenaline or in the serotonin system induced negative effects, such as an acute depressive relapse (Heninger et al 1996; Delgado and Moreno 1999; Delgado et al 2002), which occurred especially when the monoamine systems had been previously stimulated by an antidepressant and accordingly the postsynaptic receptors down-regulated.

The improvement seen after 1 week was highly predictive of the final response. With the 7-point CGI-I scale a "1-point increase or more" was found to be the most efficient tool to predict response. At 1 week a "≥1-point increase" allowed correct classification of responders in 71.6% (when the response was defined as a "50% MADRS reduction"), or in 72.2% (when the response was defined as "large improvement" with the CGI-I scale). According to Figure 7, a 1-point increase in CGI-I corresponds roughly to a 20% decrease in MADRS, a clinically meaningful improvement especially during the early phase of treatment.

Generally, when improvement is observed throughout the first week of treatment, it is very likely that the complete response will be observed within 6 weeks. Early improvement could serve clinicians as a guideline in deciding about increased dosage, augmentation, or change of medication in unresponsive patients. The use of a depression scale in everyday private practice is, however, rather troublesome and time-consuming except for the intuitive, easy-to-use CGI-I scale. Empirical data suggest keeping the treatment unchanged if improvement is observed (at least a small improvement which corresponds to a 1-point increase with the CGI-I), and to enhance dosage if improvement is not observed within the first week.

Nearly all patients benefit from treatment to some degree

Minimal improvement, defined as a "≥1-point improvement" on the CGI-I scale, was observed in more than 95% of patients by the end of the study. Nearly all patients were improved, at least slightly, during the trial. On the other hand, the degree of response was far from complete, since less than 60% of the patients displayed a sustained response (50% reduced MADRS score).

The major finding of this study is that the antidepressant effect appears to be a generalized effect benefiting nearly all patients, independent of the clinical form of depression. This generalized effect can also be observed in healthy subjects during chronic treatment. Recent research showed in healthy volunteers that chronic administration of noradrenergic antidepressant promoted social bonding (Tse and Bond 2003), and that chronic administration of serotonergic antidepressant increased affiliative behavior (Tse and Bond 2002b).

In contrast, the antidepressant effect is limited in time. In our study, the improvement period (rate of improvement >2%/day) lasted only 2 weeks. Subsequent improvement was much slower (<0.5%/day). This slowdown presumably resulted from homeostatic regulation, since there is still "room for improvement" after the initial 2-week window. The 30.9% remission rate at 6 weeks shows clearly that antidepressant response is limited.

The homeostatic regulation keeps mood variations under strict control and opposed to pharmacological manipulations. The regulation includes the limited availability of neurotransmitters (Moskowitz et al 2001), the 5HT-moduline system (Fillion et al 1997), and many monoamine negative feedback mechanisms such as the decreased firing rate observed at the beginning of a selective serotonin reuptake inhibitor (SSRI) antidepressant treatment (Artigas 2001; Blier 2003) and the postsynaptic receptor down-regulation that follows (after 2 weeks) increase in neurotransmission.

Our hypothesis is that the generalized, nonspecific antidepressant effect results from an increase in monoamine neurotransmission that, due to homeostatic regulations, only

lasts a limited time. Could an increase in treatment dosage after 2 weeks increase the duration of the improvement period? Previously we showed that augmentation strategy increased response among initial nonresponders to fluoxetine (Ferreri et al 2001). Our testable hypothesis is that neurotransmission could be increased for a longer period of time if the dosage were increased daily rather than kept constant. For example, would a 1-mg increase per day for 14 days (105 mg total) be more efficacious than 7.5 mg/day (105 mg total) over the same time period?

Large and fast reduction of suicidal thoughts and anxiety under treatment

Items from the MADRS can be analysed separately and compared. Comparisons of items with different baseline scores should be assessed by the percent change or by stratification (comparison of items with equal baseline score). Three negative emotions described by Ekman (1999) are represented by some MADRS items: sadness = apparent and reported sadness; fear = inner tension. Anger is not directly represented by a MADRS item, but since self-aggression and anxiety are involved in suicidal tendency, we propose that anger is partly represented by the "suicidal thoughts" item.

"Suicidal thoughts" item

In the ITT population, the percent score reduction of "suicidal thoughts" is larger than for "apparent sadness" ($p < 0.0001$ at all assessment times using LOCF). The reduction of "suicidal thoughts" is observed early after the start of treatment. At 1 week the percentage of score change is –22.6 ± 38%, and more than 50% of the patients have a "≥ 1-point" increase. The improvement of "suicidal thoughts" is rapid with mirtazapine, faster than that of "sadness". From a pharmacological perspective, it should be noted that mirtazapine reduces the release of cortisol (Laakmann et al 2000) and presents a strong H1 antagonism, both of which could account for the reduction of "suicidal thoughts". Although anxiety is an important clinical factor in suicidal risk, we found that a relationship between the two was no different from the relationship of suicidal ideation with other MADRS items. Further study is clearly needed of this important effect of mirtazapine on suicidal thoughts.

Previously we have described (Lavergne et al 2001) that for each MADRS baseline score selection (from 1 to 6) the Area Under Curve (AUC; sum of score changes at 1, 2, and 6 weeks) of the "suicidal thoughts" item is larger than that of the 7 other "psychic" items (apparent and reported sadness, inner tension, concentration difficulties, lassitude, inability to feel, pessimistic thoughts). The AUC of "suicidal thoughts" exceeds the AUC of all "psychic" items by at least 79% when items have a baseline score = 1; 46% when the baseline score = 2; 36% when baseline score = 3; 24% when baseline score = 4; 24% when baseline score = 5; and by 12% when baseline score = 6.

Anxiety

Anxiety assessed with the Covi scale is rapidly reduced by mirtazapine. At 1 week the score change is –22.6 ± 36%. Sorensen et al (1985) have observed this antianxiety effect within a day. Mirtazapine presents a "peaceful" emotional profile with a rapid reduction of fear and anger as demonstrated by the fast reduction of anxiety and "suicidal thoughts".

Conclusion

Mirtazapine is equally effective for all clinical forms of depression and benefits nearly all patients to a certain degree. The improvement is clinically meaningful in the first week, predictive of the final response, and should guide treatment dosage as most of the therapeutic effect is observed during the first 2 weeks.

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