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Confirmation of the Neurophysiologically Predicted Therapeutic Effects of Trazodone on Its Target Symptoms Depression, Anxiety and Insomnia by Postmarketing Clinical Studies with a Controlled-Release Formulation in Depressed Outpatients

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Key Words

Trazodone · Controlled-release formulation · Postmarketing study · Hamilton Depression Scale · Zung Self-Rating Depression Scale · Zung Self-Rating Anxiety Scale · Ranking of most improved symptoms · Insomnia · Depressed mood · Anxiety · Tolerability

Abstract

Early human pharmaco-EEG and subsequent sleep laboratory studies identified trazodone, a 5-HT_2 antagonist and 5-HT reuptake inhibitor (SARI), as an antidepressant with therapeutic effects on its target symptoms depressed mood, anxiety and insomnia. On the occasion of the introduction of a controlled-release (CR) formulation (Trittico® 150 mg retard, marketed in Austria by CSC Pharmaceuticals Handels GmbH, Vienna, Austria) in Austria in July 2000, a multi-center, open, clinical postmarketing study on the therapeutic effects, safety and target symptoms of trazodone CR in depression was carried out at 80 offices of Austrian neuropsychiatrists. 549 outpatients (63% females) of all age groups suffering from five different subtypes of depression were enrolled in the study. After a 2-week fixed dose-titration regimen up to 150 mg and a 4-week adjustment period to the optimum dose, 66% of the patients remained on 150 mg, 20% increased the dose and 11% decreased it. Only 3.7% discontinued treatment. Rating by the neuropsychiatrists based on the Clinical Global Impression showed very much to much improvement in 78.3% of the patients, and no change or a deterioration in only 3.6%. In the Hamilton Depression Scale (HAMD) a statistically significant improvement from a baseline score of 21 to a score of 14 after 2 weeks was found, and a normalization to a score of 8 after 6 weeks. Therapeutic effects were similar in the five groups suffering from different subtypes of depression and in patients with and without comedication. Self-rating by the patients based on the Zung Self-Rating Depression Scale (SDS) and Zung Self-Rating Anxiety Scale (SAS) also showed a significant improvement in the 2nd and 6th week of therapy. Evaluation of the target symptoms of trazodone by ranking the most improved symptoms identified *insomnia* as the most improved psychopathological item in all three scales. While in the observer ratings also *suicidal tendencies* and *weight loss* were found much improved, in the self-rated Zung SDS *sadness* and *loss of drive* came second and third in the improvement ranking, in the self-rated

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Zung SAS *anxiety* and the *feeling of falling apart*. Tolerability was very good. In the 2nd week only 16.9% and in the 6th week only 7.6% of the patients reported side effects, mostly characterized by tiredness and rarely by nausea and vertigo. The present clinical study is in agreement with previous studies identifying trazodone as a safe and effective antidepressant, specifically regarding its target symptoms insomnia, depression and anxiety. It also confirms our own early predictions based on neurophysiological investigations concerning the mode of action of the drug.

Introduction

35 years after the introduction of trazodone as AF1161 by Silvestrini et al. [1], the compound is still of great interest for researchers and clinicians for many reasons. Trazodone was not only the first triazolopyridine derivative to be developed as an antidepressant, but its development was the result of a *disease-oriented research approach*. The so-called 'mental pain hypothesis of depression' was postulated by Silvestrini [2] as follows: Depression is associated with a state of 'mental pain'; 'somatic' and 'mental' pain have some fundamental mechanisms in common; mental pain is produced by a lowered threshold for the perception of suffering; drugs capable of increasing the threshold for somatic pain in animals should produce antidepressant effects in humans.

Drug screenings of trazodone showed a down-regulation of beta-adrenergic and serotonin (5-HT_2) receptors [3, 4], a blockade of 5-HT_2 receptors [4] and 5-hydroxytryptophane suppression of operant behavior [5, 6]. Trazodone was labeled as an 'atypical' antidepressant because of its unusual pharmacological properties [1, 7]: It proved inactive in classical screening tests, did not antagonize reserpine-induced sedation, did not potentiate yohimbine toxicity, inhibited aggressiveness and potentiated narcosis (like benzodiazepines and other sedatives), suppressed self-stimulation behavior and amphetamine actions and was markedly adrenolytic (like phenothiazines), and had minimal anticholinergic, autonomic and cardiovascular effects (unlike phenothiazines and tricyclic antidepressants).

Our own early human psychopharmacological studies using pharmaco-EEG confirmed that trazodone was an atypical sedative antidepressant [8]: In the wake-EEG based on digital computer period analysis, trazodone 50 mg was found to induce an increase in slow activities and an attenuation of fast beta activities as well as a decrease in the average frequency and frequency deviation of both the primary wave and the first derivative measurements. Sedative effects were also observed in sleep laboratory studies involving patients with nonorganic insomnia related to depressive episodes and recurrent depressive disorder [9] and nonorganic insomnia related to dysthymia [10].

Biochemical studies identified trazodone as a SARI, i.e. a strong 5-HT_2 antagonist [11] and less potent serotonin reuptake inhibitor [12]. In regard to 5-HT_2 antagonism, trazodone shows high affinity – with antagonistic activity – for the 5-HT_{2A} receptor, and significant affinity – with similar antagonism – for the functionally similar 5-HT_{1C} receptor (since 1993 reclassified as a 5-HT_2 subtype and called 5-HT_{2C} receptor) [13, 14]. Trazodone causes a desensitization of somatodendritic serotonin autoreceptors [15] and has strong alpha-1-adrenolytic properties, minimal H_1 blocking effects and anticholinergic effects [12].

Clinical trials in the 1980s made trazodone the most widely prescribed antidepressant in the USA [16], which was mainly due to its good tolerability, especially in the elderly [17], its hypnotic properties in depression [9, 18], dysthymia [10, 19], SSRI-induced insomnia [20], sleep apnea [21] and benzodiazepine dependency [22, 23] as well as its anxiolytic properties [24, 25]. Trazodone was further found to be clinically useful after discontinuation of chronic benzodiazepine therapy [26], in agitation and hostility of patients with dementia and organic disorders [27], negative symptoms of chronic schizophrenia [28–30], bulimia nervosa [31], erectile dysfunction [32], tremor and iatrogenic dyskinesias [33, 34], alcoholism [35] and chronic pain disorders [36].

Concerning *pharmacokinetics*, trazodone is well absorbed after oral administration, with t_{max} obtained within about 1 h after ingestion on an empty stomach and about 2 h on a full stomach. Trazodone is 89–95% bound to plasma proteins, mostly albumin. The alpha-elimination half-life is 3–6 h, the beta-elimination half-life 5–9 h [37]. Trazodone is extensively metabolized in the liver through hydrolytic and oxidative reactions [38]. Twenty percent is converted by CYP3A4 to the active metabolite *l-m*-chlorophenylpiperazine (*m*-CPP) [39], which has a longer elimination half-life than trazodone (4–12 h) and higher concentrations in the brain than in plasma [40]. Thioridazine (a CYP2D6 inhibitor) increases plasma concentrations of both trazodone and *m*-CPP in depressed patients [41]. Smoking decreases plasma concentrations of trazodone, suggesting an involvement of CYP1A2 [42].

The pharmacokinetics of a controlled-release (CR) formulation of trazodone differs from that of trazodone in terms of gradual absorption, plasma peak reduction and longer persistence of the molecule in circulation. After a single oral dose of 100 mg Trittico® and Trittico® retard, Monteleone and Delrio [43] found t_{max} at 1.55 and 3.20 h, respectively, C_{max} at 1.60 and 1.01 μg/ml, respectively, AUC at 14.41 and 12.45 μgh/ml, respectively, and $t_{1/2}$ at 9.4 and 9.1 h, respectively.

The aim of the present study was to evaluate the therapeutic effects, safety and target symptoms of trazodone CR (Trittico® 150 mg retard) in depression on the occasion of the introduction of the retard formulation of the drug in Austria in July 2000.

Methods

Study Design and Patients

In the multicenter, open, clinical postmarketing study conducted at 80 offices of Austrian neuropsychiatrists between July and December 2000, 549 patients (62.4% women and 37.6% men) were enrolled. 10.9% were aged 18–29 years, 17.6% 30–39 years, 16.3% 40–45 years, 12.8% 46–50 years, 13.9% 51–55 years, 11.8% 56–60 years, 9.9% 60–69 years and 6.8% 70 years and older. The average age was 47.8 years. The study was performed in accordance with the rules and regulations for the conduct of clinical trials, stated in the Declaration of Helsinki, as revised by the World Medical Assembly in Somerset West.

Diagnoses

Diagnosis was based on ICD-10 criteria. 5.4% of the patients were suffering from bipolar affective disorder (F31, currently depressed with depressive episodes of mild to moderate severity), 51.6% from depressive episodes (F32, mostly of moderate severity), 26.2% from recurrent depressive disorder (F33, the current episode mostly being of moderate severity), 15.6% from persistent mood disorder (F34), mostly dysthymia (F34.1), and 1.2% from other mood disorders (F38, about 50% mixed affective episodes and 50% recurrent brief depressive episodes). 61.9% of the patients had before been receiving other medications and were switched to Trittico® 150 mg retard, while 38.1% were treated for the first time.

Drugs

During the first 2 weeks of the 6-week study period, a fixed dose-titration regimen was employed that started with 50 mg trazodone CR/day on the first 3 days and was increased to 100 mg/day on days 4–6 and 150 mg/day on days 7–14. After 2 and 6 weeks of therapy, the physicians were free to adjust the dose according to their judgement.

Evaluation

Observer rating scales included the Hamilton Depression Scale (HAMD) [44] and safety evaluation in weeks 0, 2 and 6, the Clinical Global Impression (CGI) [45] in weeks 0 and 6, and an overall rating of efficacy and safety based on a school-mark system in week 6. Self-rating scales comprised the Zung Self-Rating Depression Scale (SDS) [46] and the Zung Self-Rating Anxiety Scale (SAS) [47] completed in weeks 0, 2 and 6. An overall rating of satisfaction with therapy based on a school-mark system was done in week 6.

Statistics

The statistical analysis was carried out using the SPSS software package (SPSS Inc., Chicago, Ill., USA; version 8.0.0 under Windows NT), based on descriptive data analysis [48] with one confirmatory statement on the HAMD score in its original 17-item version. The predetermined null hypothesis for the confirmatory statement was: There is no difference in the HAMD total score rated at baseline, week 2 and week 6 of trazodone CR therapy (maximum error probability = 0.05). Alpha adjustment by Bonferroni-Holm led to individual error probabilities of $p(1) < 0.025$ and $p(2) < 0.05$. All other variables were tested descriptively.

Normal distribution was tested by means of the Kolmogorov-Smirnov test. If in no cases the null hypothesis of normal distribution was rejected at alpha = 0.10, t tests were used. In the case of a violation of the assumption of normal distribution, a nonparametric Wilcoxon test was used for intragroup comparison and a Mann-Whitney U test for intergroup comparison.

Results

Medication

518 patients completed the 2-week dose-titration phase with 50 mg trazodone CR/day on the first 3 days, 100 mg/day on days 4–6 and 150 mg/day on days 7–14. Thereafter, 74.5% of the patients were maintained on a daily dose of 150 mg; in 18.9% the daily dose was increased (in 44.3% to 200 mg, in 41.2% to 300 mg, in 11.3% to 250 mg and in 3.1% to 225 mg), in 6.6% it was decreased (in 62.5% to 100 mg and in 37.5% to 50 mg) (fig. 1). At week 6, 65.5% of the 514 patients remained on a daily trazodone CR dose of 150 mg, in 19.5% the dose was increased (in 50.5% to 300 mg, in 34.3% to 200 mg, in 5.1% to 250 mg, in 4.0% to 225 mg, in another 4.0% to 450 mg and in 2% to 175 mg), in 11.3% the dose was decreased (in 55.2% to 100 mg, in 22.4% to 125 mg, in 17.2% to 50 mg and in 5.2% to 75 mg).

In only 19 patients (3.7%) trazodone was discontinued. Reasons for discontinuation were insufficient improvement in 7 patients and intolerability of side effects in 5 patients; 3 patients were not ill any more, 1 patient experienced an acute deterioration of the depression, 1 patient felt agitated, another did not want to continue therapy while another did not give any reasons for discontinuation.

The percentage of patients receiving concomitant medication decreased from a pretreatment value of 56.5 to 48.5% in the 2nd and 43.9% in the 6th week of trazodone CR administration. Alprazolam was the most frequently taken individual drug at baseline, with the number of

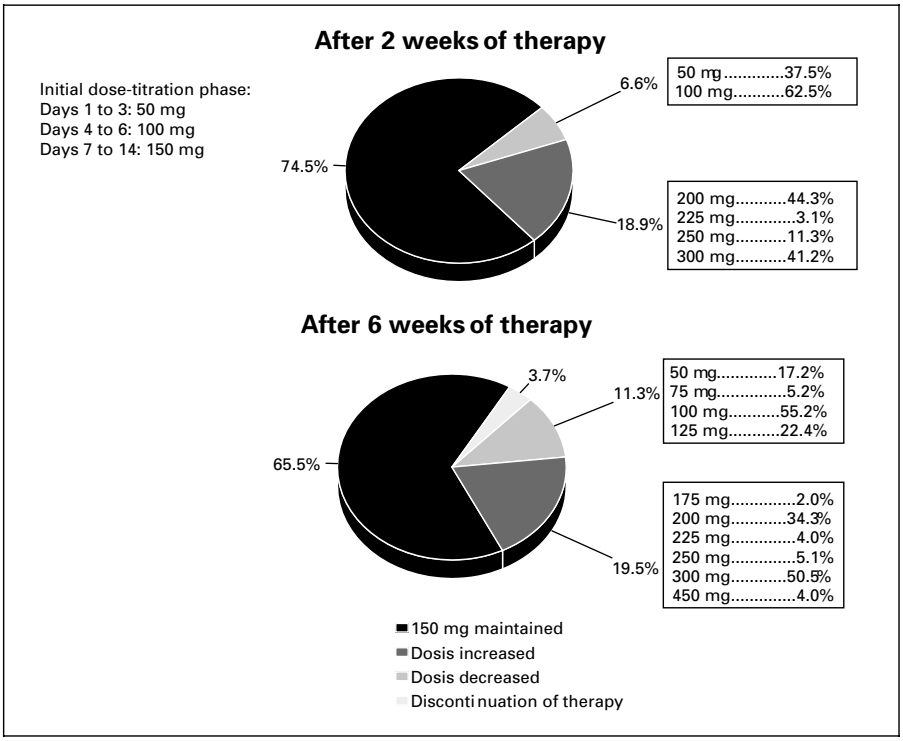

Fig. 1. Dosage changes of Trittico® 150 mg retard after 2 and 6 weeks of therapy. In 2/3 of the patients 150 mg was the optimum dose. Only 3.7% of the patients discontinued Trittico® 150 mg retard therapy.

patients receiving it declining from 44 to 20 in the 2nd and to 17 in the 6th week of trazodone administration. Concerning pharmacological classes, however, SSRIs were the most frequently administered concomitant drugs, taken by 105 patients at baseline, 116 patients in the 2nd and 123 patients in the 6th week of trazodone CR (sertraline 34/34/35; citalopram 29/33/41; paroxetine 24/26/23; fluoxetine 18/23/24). The frequency of prescription of the thymoprophylactic lithium hardly changed (9/10/9).

Observer Rating of Depression Based on the HAMD

Confirmatory statistics on the *HAMD total score* demonstrated a significant improvement of the total group from 20.9 at baseline to 13.9 in the 2nd and 7.6 in the 6th week of trazodone CR (Friedman's rank analysis of variance: $\chi^2_{FR} = 871.4$; $p < 0.01$; fig. 2). The predetermined null hypothesis for the confirmatory statement that there is no difference in the HAMD total score rated at baseline, week 2 and week 6 of trazodone CR therapy (maximum error probability = 0.05) could be rejected as the individual error probabilities of p(1) = 0.000 surpassed the demanded error probability of <0.025 after alpha adjustment by Bonferroni-Holm and p(2) = 0.000 surpassed the expected p(2) values of <0.05. In order to determine whether patients with/without comedication differed from the total group, we recalculated the HAMD scores of these two subgroups of patients. Patients with comedication were generally found to be more disturbed than those without (fig. 2). However, in both groups a similar and highly significant improvement under trazodone treatment was observed. Descriptive statistics showed a similar overall treatment effect in all diagnostic subcategories. Patients with depressive episodes (n = 258/248/238) improved from baseline values of 20.8 to 13.3 and 6.7 in weeks 2 and 6, respectively; patients with recurrent depressive disorder (n = 130/120/115) from 22.8 to 15.8 and 9.0, patients with a continuing affective disorder (n = 80/76/75) from 18.2 to 12.6 and 7.9, currently depressed patients with bipolar affective disorders (n = 28/27/27) from 21.0 to 14.7 and 7.4, and patients with other affective disorders (n = 6/5/5) from 22.0 to 13.2 and 7.0.

Friedman's rank analysis of variance of the *17 HAMD symptoms* for the total group of patients showed significant differences between baseline, the 2nd and 6th week of trazodone CR ($p < 0.001$). The greatest improvement was observed for *early insomnia* ($\chi^2 = 714$), followed by *middle insomnia* ($\chi^2 = 694$), *depressed mood* ($\chi^2 = 693$), *work and activities* ($\chi^2 = 589$), *psychic anxiety* ($\chi^2 = 561$), *late insomnia* ($\chi^2 = 559$), *somatic anxiety* ($\chi^2 = 500$), *feel-*

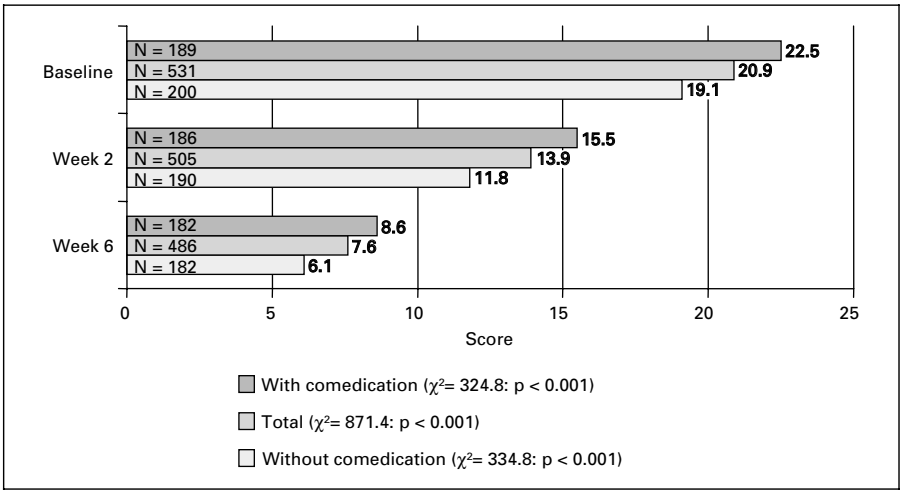

Fig. 2. Observer-rated HAMD score before and during trazodone CR therapy. Regardless of comedication, the total HAMD score improved significantly and became normalized at week 6.

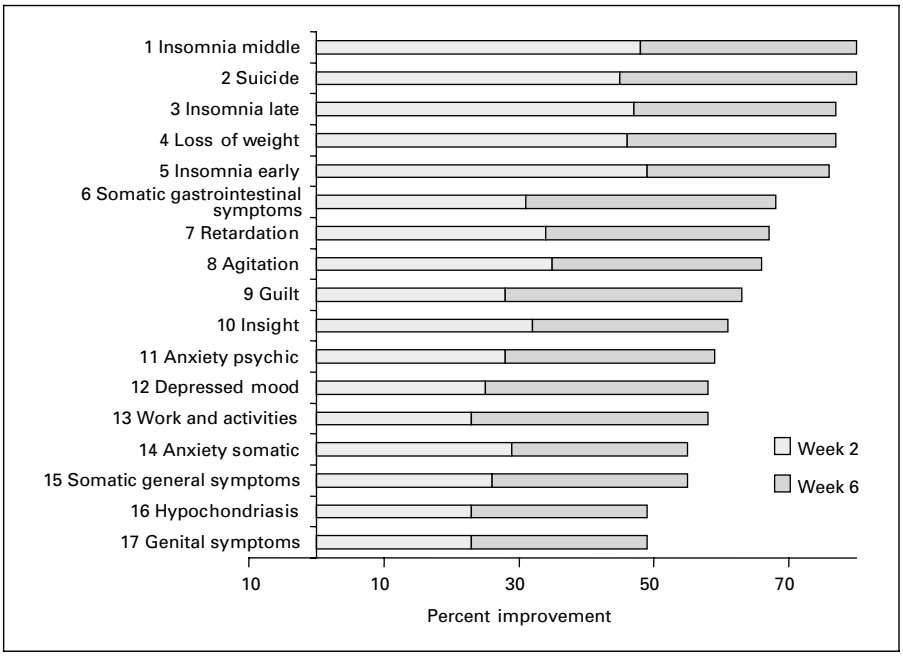

Fig. 3. Ranking of observer-rated symptoms of depression based on the improvement (%) of HAMD baseline values after 2 and 6 weeks of trazodone CR. Three of the first five most improved symptoms are related to insomnia.

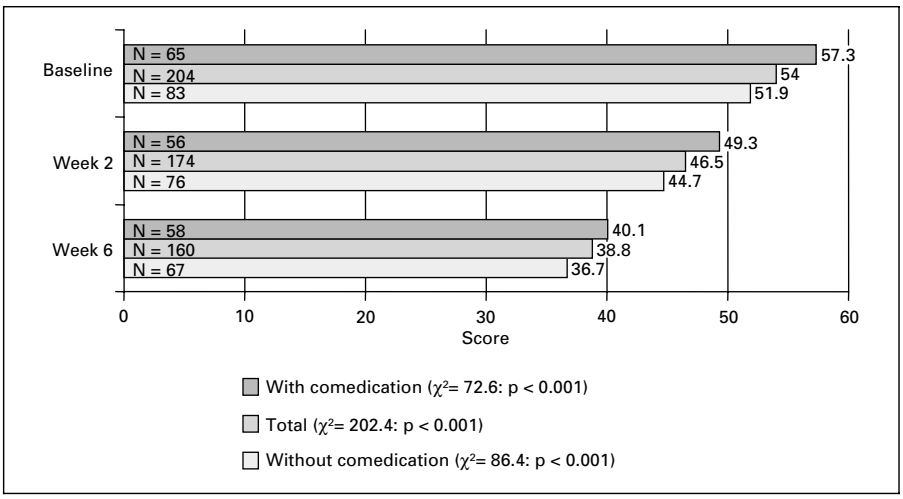

Fig. 4. Self-rated Zung SDS score before and during trazodone CR therapy. Regardless of comedication, the Zung SDS score improved highly significantly after 2 and 6 weeks of therapy.

Table 1. Comparison of the percent improvement rates of baseline values in 17 HAMD items after 6-week therapy with trazodone CR

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	–													**			
2		–									*			**	**		
3	**	**	–	**			**	**	**	**	**	**	**	**	**		
4	**	**		–			**	*	**	**	**	**	**	**	**		*
5	**	**		*	–		**	**	**	**	**	**	**	**	**		**
6	**	**				–	**	**	**	**	**	**	**	**	**		
7							–							**	*		
8	**						**	–		*	**		**	**	**		
9	*								–		**		*	**	**		
10										–				**	*		
11											–						
12	*						*			**	**	–	*	**	**		
13													–				
14														–			
15															–		
16	**	*					**			**	**		**	**	**	–	
17														**			–

HAMD item 1 = depressed mood; 2 = guilt; 3 = suicide; 4 = insomnia – early; 5 = insomnia – middle; 6 = insomnia – late; 7 = work and activities; 8 = retardation; 9 = agitation; 10 = anxiety – psychic; 11 = anxiety – somatic; 12 = somatic gastrointestinal symptoms; 13 = somatic general symptoms; 14 = genital symptoms; 15 = hypochondriasis; 16 = weight loss; 17 = insight. Rows: * $p < 0.01$; ** $p < 0.001$ improvement; columns: * $p < 0.01$; ** $p < 0.001$ deterioration (Wilcoxon).

ings of guilt (χ^2 = 426), *retardation* (χ^2 = 517), *general somatic symptoms* (χ^2 = 404), *hypochondriasis* (χ^2 =370), *gastrointestinal somatic symptoms* (χ^2 = 341), *agitation* (χ^2 = 334), *suicide* (χ^2 = 302), *genital symptoms* (χ^2 = 302), *loss of weight* (χ^2 = 187) and *insight* (χ^2 = 141).

Ranking of observer-rated symptoms of depression based on the percent improvement of HAMD baseline values after 2 and 6 weeks of trazodone CR showed *middle insomnia* to be the most therapy-responsive psychopathological item, having improved by 80.5% in week 6 (and 47.8% already in week 2; fig. 3). The symptom ranked second was *suicide* (80.2 and 44.7% improvement in weeks 6 and 2, respectively), followed by *late insomnia* (77.4/47.3%), *loss of weight* (76.6/45.8%) and *early insomnia* (75.7/49.2%). Thus, 3 of the 5 psychopathological items ranked first concerned sleep disturbances. Interestingly, in the 2nd week *early insomnia* showed the most pronounced therapeutic response. The ranking of the other HAMD symptoms may be seen in figure 3.

Comparison of the percent improvement rates of the 17 HAMD symptoms after 6 weeks of trazodone CR demonstrated that the improvement of *middle insomnia* was significantly greater than that observed in all other psychopathological items except *suicide*, *late insomnia* and *weight loss* ($p < 0.01$, Wilcoxon; table 1).

Self-Rating of Depression Based on the Zung SDS

The *SDS total score* also showed a highly significant improvement (Friedman's rank analysis of variance, $p < 0.001$) of the total group from a pretreatment value of 54 to 46.5 and 38.8 in weeks 2 and 6 of therapy (fig. 4). Patients showed similar improvements, regardless of comedication ($p < 0.001$).

Friedman's rank analysis of variance of the *20 individual SDS symptoms* for the total group of patients demonstrated a significant improvement of all items ($p < 0.001$), with *feeling sad* showing the most pronounced differences between the 3 observation points (χ^2 = 198), followed by *sleep-disturbed* (χ^2 = 196), *hopeless* (χ^2 = 159), *loss of drive* (χ^2 = 151), *joyless* (χ^2 = 146), *indecisive* (χ^2 = 140), *useless* (χ^2 = 135), *empty life* (χ^2 = 132), *irritable* (χ^2 = 132), *crying* (χ^2 = 130), *tired* (χ^2 = 129), *tachycardic* (χ^2 = 116), *morning low* (χ^2 = 87), *unclear mind* (χ^2 = 77), *restless* (χ^2 = 72), *suicidal* (χ^2 = 69), *loss of libido* (χ^2 = 65), *loss of appetite* (χ^2 = 56), *constipated* (χ^2 = 54) and *weight loss* (χ^2 = 28).

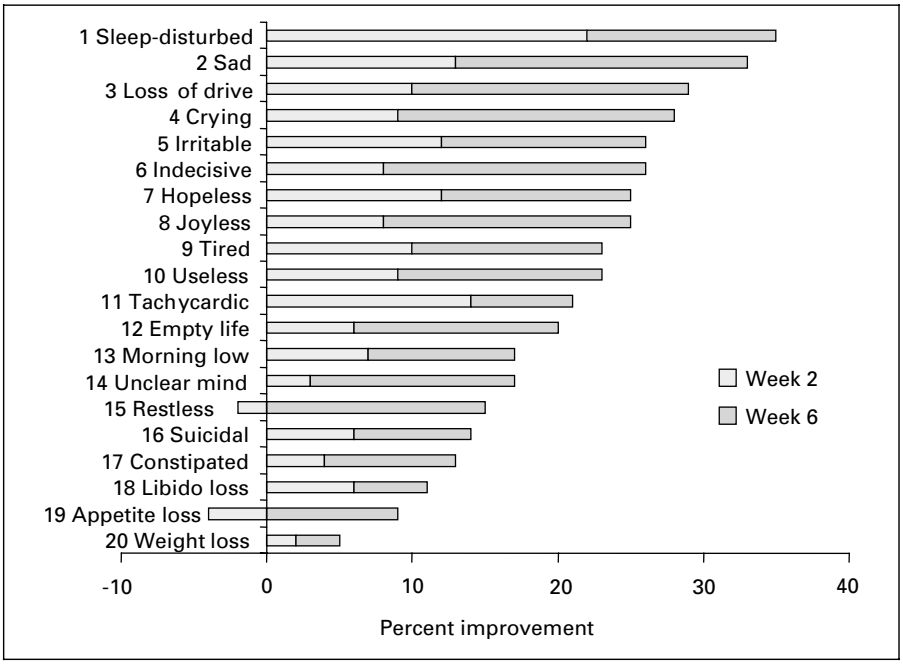

Fig. 5. Ranking of self-rated symptoms of depression based on the improvement (%) of Zung SDS baseline values after 2 and 6 weeks of trazodone CR. Sleep disturbance, sadness and loss of drive were the three items showing the most pronounced therapeutic response under trazodone CR.

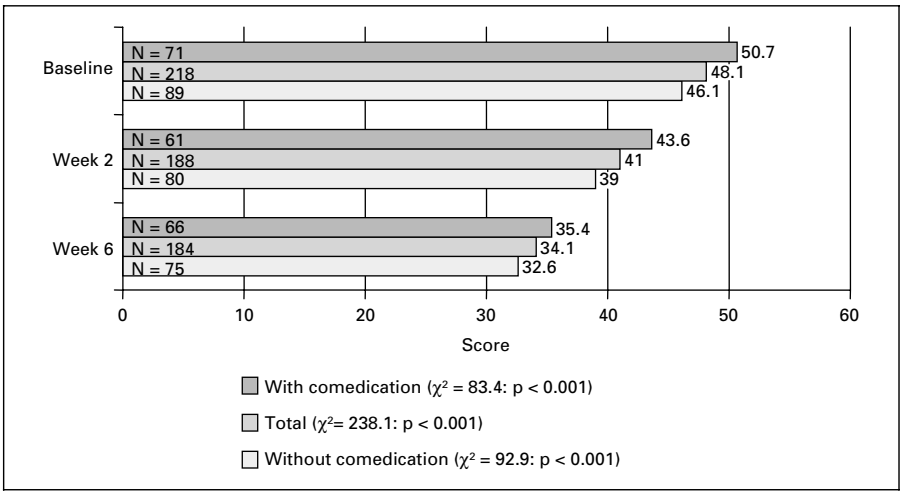

Fig. 6. Self-rated Zung SAS score before and during trazodone CR therapy. Regardless of comedication, the Zung SAS score improved highly significantly after 2 and 6 weeks of therapy.

Ranking of self-rated symptoms of depression based on the percent improvement of SDS baseline values after 2 and 6 weeks of trazodone CR again showed *sleep disturbance* to be the most improved item (–34.9% and –22.2% in week 6 and 2, respectively), followed by *feeling downhearted, blue and sad* (–33.4/–13.1%) and *loss of drive* ('I find it easy to do the things I used to') (–29.0/–9.8%; fig. 5). '*I notice that I am losing weight*' was the least improved item (–4.8/–2.4%).

Comparison of the percent improvement of the 20 SDS symptoms after 6 weeks of trazodone CR demonstrated that the improvement of troubles sleeping through the night *(sleep disturbed)* was significantly more pronounced than that of all the other symptoms but feeling downhearted and blue *(sad)*, which on the other hand differed from all the other symptoms but *sleep-disturbed* and *loss of drive* ($p < 0.01$, Wilcoxon, table 2).

Self-Rating of Anxiety Based on the Zung SAS

Also in regard to self-rated anxiety, Friedman's rank analysis of variance of the *total SAS score* showed a highly significant improvement ($p < 0.001$) of the total group as well as patients with and without comedication in weeks 2 and 6 as compared with baseline (fig. 6). The SAS score of

Table 2. Comparison of the percent improvement rates of baseline values in 20 Zung SDS items after 6-week therapy with trazodone CR

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	–	**	*		**	**	**	**	**	**	**		**	*	*	*	**	**	**	*
2		–																		
3		**	–		**	**	**	**					*					**	**	
4		**	**	–	**	**	**	**	**	**	**	*	**	**	**	**	**	**	**	**
5					–															
6						–														
7							–													
8								–												
9						**	**	**	–										*	
10		*			*	**	**	**		–									*	
11						*	**	*			–									
12		**			**	**	**	**	*		*	–	**					**	**	
13							*						–							
14		**			**	**	**	**					*	–				*	**	
15		**			*	**	**	**					*		–			*	**	
16		**			*	**	**	**								–			**	
17		*				**	**	**									–		*	
18						*	**	*										–		*
19																			–	
20		**			*	**	**	**											**	–

SDS item 1 = sad; 2 = morning low; 3 = crying; 4 = sleep-disturbed; 5 = loss of appetite; 6 = loss of libido; 7 = loss of weight; 8 = constipated; 9 = tachycardic; 10 = tired; 11 = unclear mind; 12 = loss of drive; 13 = restless; 14 = hopeless; 15 = irritable; 16 = indecisive; 17 = useless; 18 = empty life; 19 = suicidal; 20 = joyless. Rows: * $p < 0.01$; ** $p < 0.001$ improvement; columns: * $p < 0.01$; ** $p < 0.001$ deterioration (Wilcoxon).

the total group improved from 48.1 at baseline to 41 and 34.1 in weeks 2 and 6, respectively. Again, patients with comedication were found more psychopathologically disturbed than those without comedication, but both subgroups showed very similar improvement rates ($p < 0.001$).

Friedman's rank analysis of variance of the *20 individual SAS symptoms* for the total group of patients demonstrated that feeling more nervous and anxious than usual *(anxious)* was the item that showed the biggest differences between the three treatment periods ($\chi^2 = 201$), followed by sleep-disturbed ($\chi^2 = 186$), weak and tired ($\chi^2 = 161$), panicky ($\chi^2 = 151$), feeling afraid ($\chi^2 = 150$), falling apart ($\chi^2 = 149$), heart beating ($\chi^2 = 147$), nightmares ($\chi^2 = 119$), shaking and trembling ($\chi^2 = 103$), head/backache ($\chi^2 = 100$).

Ranking of self-rated symptoms of anxiety based on the percent improvement of SAS baseline values after 2 and 6 weeks of trazodone CR showed *sleep disturbance* to be the most improved item (–32.0 and –18.3% in week 6 and 2, respectively), followed by *feeling anxious* (–32.1/–11.7%) and *falling apart* (–28.3/–12.5%; fig. 7). The least improved item was *numbness and tingling* (–12.1/–2.4%).

Comparing the percent improvement of the 20 SAS symptoms after 6 weeks of trazodone CR, one can see that the improvement of *sleep disturbance* was significantly superior to the changes in all the other psychopathological items but *feeling anxious*, *afraid*, *falling apart* and *weak and tired* ($p < 0.01$, Wilcoxon; table 3). The improvement of the item *anxious* was superior to that of the other items but *falling apart, feeling weak and tired* and *sleep-disturbed.*

Side Effects

Side effects were reported by 16.9% of the patients (n = 515) after 2 weeks and only 7.6% of the patients (n = 513) after 6 weeks of treatment with trazodone CR (fig. 8).

In detail, after 2 weeks of therapy, daytime tiredness was reported by 37 patients, vertigo by 15, nausea by 9, morning tiredness by 7, dizziness by 5, agitation by 4, headache, sedation, restless sleep and gastrointestinal side effects by 3 patients each and morning hangover, dry

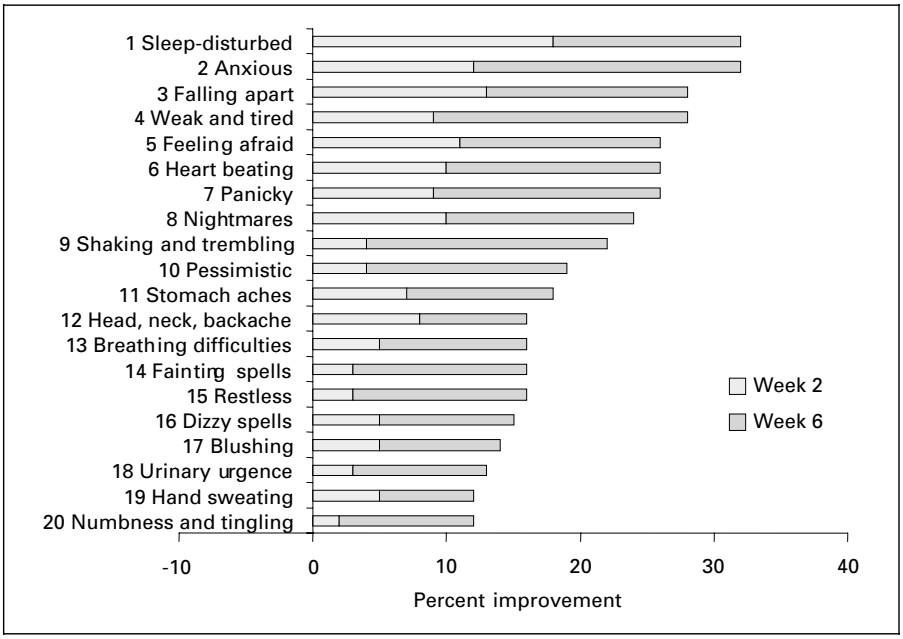

Fig. 7. Ranking of self-rated symptoms of anxiety based on the improvement (%) of Zung SAS baseline values after 2 and 6 weeks of trazodone CR. The three top ranking symptoms of the Zung SAS were sleep disturbance, feeling anxious and feeling like falling apart.

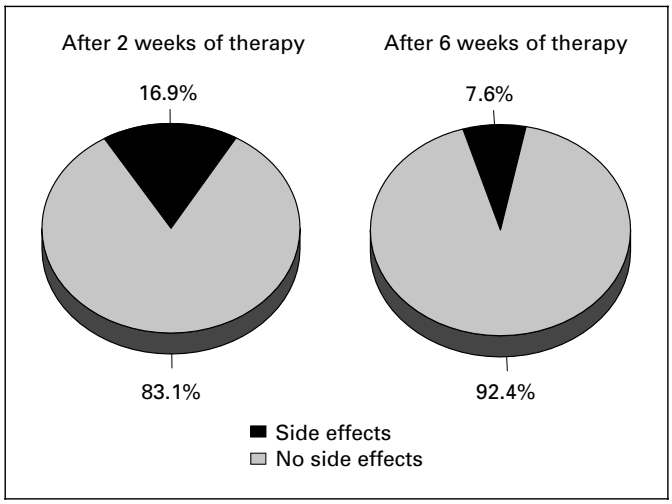

Fig. 8. Side effects after 2 and 6 weeks of therapy with trazodone CR. Side effects were reported by 16.9% of the patients at week 2, but only by 7.6% at week 6.

mouth and hypertension by 2 patients each. Other side effects were reported by 15 patients. After 6 weeks of treatment, daytime tiredness was reported by 16 patients, nausea by 4, vertigo and morning tiredness by 3, agitation, headache, menstruation problems, palpitations and sleep disturbances by 2 patients each. Other side effects were noted by 15 patients.

Global Rating

Global rating was based on a 5-point scale similar to the Austrian school-mark grading system (1 = very good, 2 = good, 3 = satisfactory, 4 = sufficient, 5 = insufficient) and was performed by the patients (n = 520) and doctors at the final consultation.

Patients' rating of satisfaction with trazodone CR yielded a mean value of 2.03 (fig. 9). Patients who had not received any other medication before were slightly more satisfied (mean: 1.94) than patients switched to trazodone (mean: 2.09). Patients' rating was consistent throughout all diagnostic subgroups (patients with bipolar affective disorder, currently depressed, 2.07; patients with depressive episodes 1.90; patients with recurrent depressive episodes 2.18; patients with persistent mood disorder 2.19). 40.4% of the patients described trazodone CR as 'good', only 3.5% found therapeutic success insufficient.

Doctors' rating of the efficacy of trazodone CR resulted in a mean value of 1.81 (fig. 10). In 43.7% of the patients therapeutic outcome was described as 'very good'. Newly treated patients showed a better therapeutic response (mean value: 1.75) than patients switched to trazodone CR (mean: 1.85). There were no relevant differences between the different diagnostic subgroups, with patients with depressive episodes faring best (1.68), followed by depressed patients with a bipolar affective disorder (1.86), patients with recurrent depressive disorders (1.92) and persistent mood disorder (1.96).

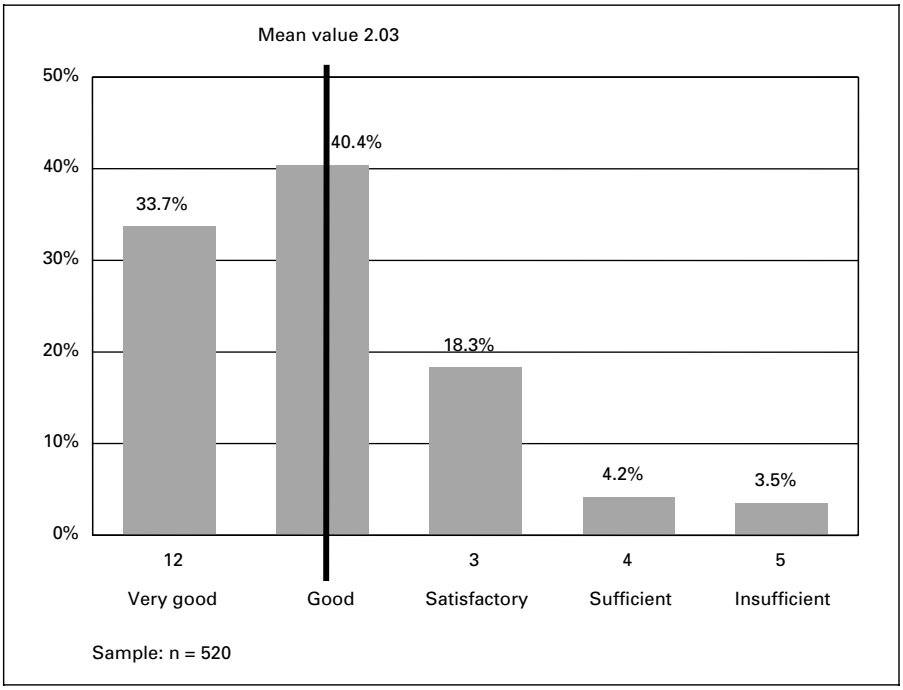

Fig. 9. Patients' rating of satisfaction with trazodone CR therapy, based on school marks.

Table 3. Comparison of the percent improvement rates of baseline values in 20 Zung SAS items after 6-week therapy with trazodone CR

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	–	*	**		**	**	**		**	*	**	**	**	**	**	**	**	**		*
2		–					**		*		**	**	*	**	*	**	**	**		
3			–				**				**	**		**	**	**	**	**		
4				–			**		*		**	**	*	**	**	**	**	**		
5					–															
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19			**		**	**	**		**	*	**	**	**	**	**	**	**	**	–	**
20							*		*		**	*		**	*	**	**	**		–

SAS item 1 = anxious; 2 = feeling afraid; 3 = panicky; 4 = falling apart; 5 = pessimistic; 6 = shaking and trembling; 7 = head/neck/backache; 8 = weak and tired; 9 = restless; 10 = heart beating; 11 = dizzy spells; 12 = fainting spells; 13 = breathing difficulties; 14 = numbness and tingling; 15 = stomach ache; 16 = urinary urgency; 17 = hand sweating; 18 = blushing; 19 = sleep disturbed; 20 = nightmares. Rows: * $p < 0.01$; ** $p < 0.001$ improvement; columns: * $p < 0.01$; ** $p < 0.001$ deterioration (Wilcoxon).

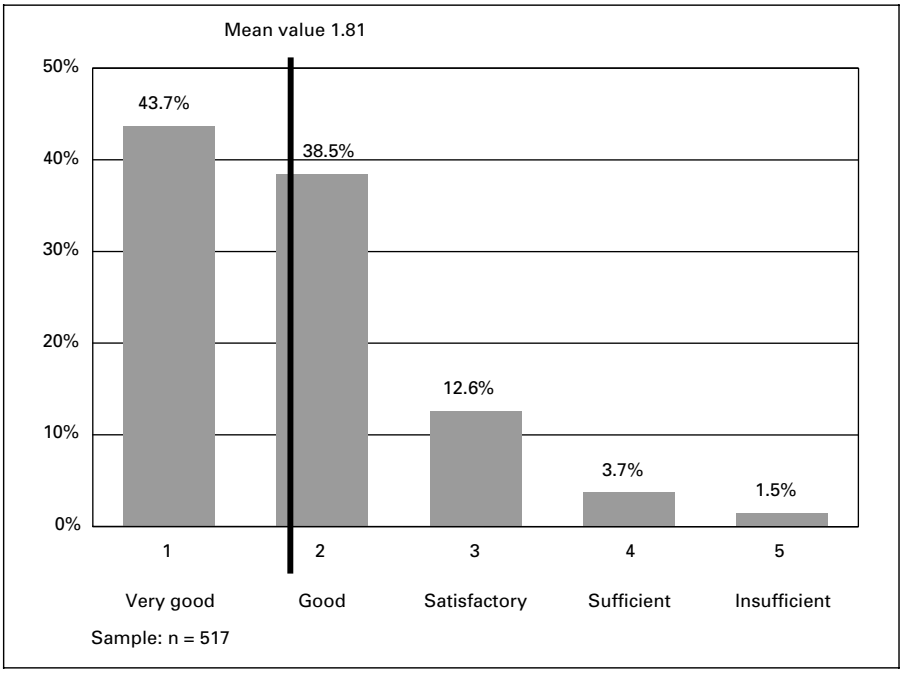

Fig. 10. Doctors' rating of the efficacy of trazodone CR, based on school marks.

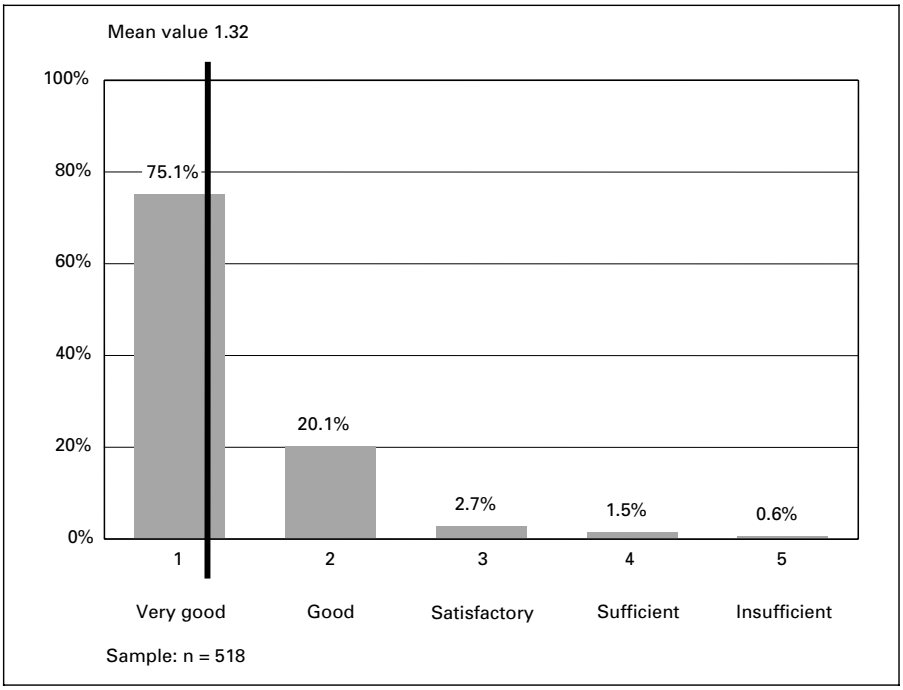

Fig. 11. Doctors' rating of the safety of trazodone CR, based on school marks.

Doctors' ratings of safety yielded a mean value of 1.32, with 75.1% of the patients receiving the mark 'very good' (fig. 11). There were no relevant differences between newly treated patients and those switched to trazodone, nor between patients belonging to different diagnostic subgroups.

CGI based on the CGI item 2 was found very much improved by 40.5% of the patients, much improved by 37.8%, while only in 2.3% a lack of change was documented, and in 1.3% a slight worsening (fig. 12). Newly treated patients fared better than patients switched to trazodone CR (fig. 13).

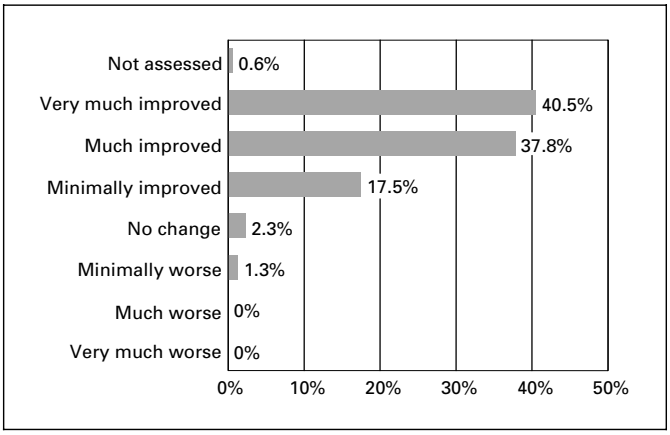

Fig. 12. CGI after 6 weeks of therapy based on the CGI item 2 ('global improvement') as compared with baseline.

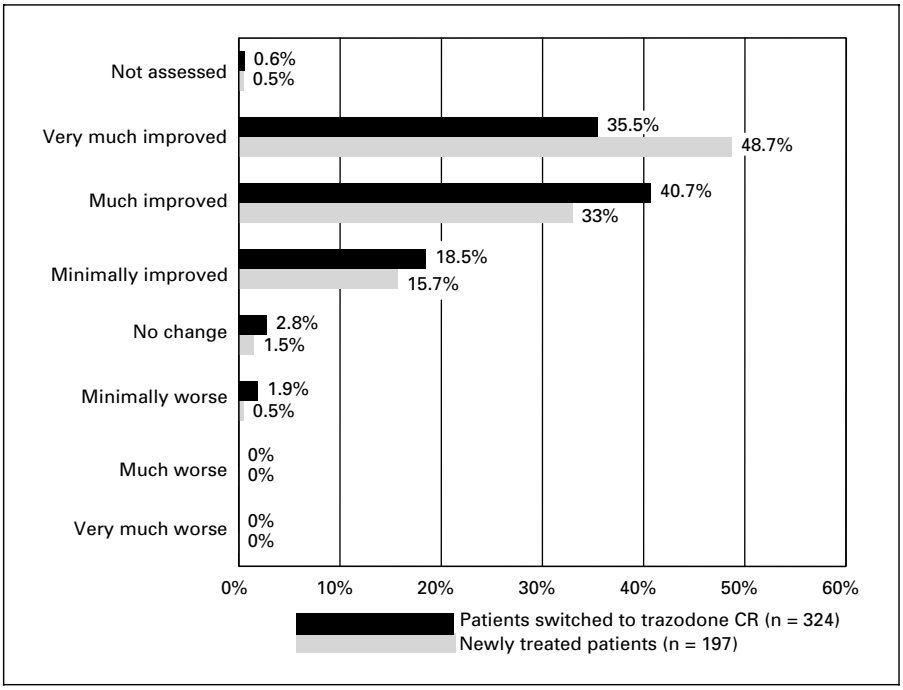

Fig. 13. CGI after 6 weeks of therapy with trazodone CR based on the CGI item 'global improvement' in switched vs. newly treated patients as compared with baseline.

Discussion

549 outpatients (62% females) of all age groups and different subtypes of depression (52% depressive episode, 26% recurrent depressive disorder, 16% dysthymia, 5.4% bipolar affective disorder – depression, 1.2% other affective disorder) participated in the multicenter, open clinical postmarketing study on the therapeutic effects, safety and target symptoms of trazodone CR at 80 offices of Austrian neuropsychiatrists.

The CR formulation of trazodone, which was introduced into the Austrian market in July 2000, avoids the relatively high peak plasma concentrations of the conventional formulation that may cause side effects. The practice of administering single doses of 100/150 mg proved successful in cases where anxiety and insomnia were dominant [9, 10, 49]. The development of a CR formulation for daily use in clinical depression is therefore a highly important achievement.

At the beginning of the present study, 62% of the patients were switched to trazodone CR from other medications, 38% were treated for the first time. After a 2-week fixed dose-titration regimen and a 4-week adjustment period to the optimal dose, 66% of the patients remained on 150 mg Trittico® retard, 20% increased (mainly to 300 mg) and 11% decreased (mainly to 100 mg) the dose.

Only 3.7% discontinued treatment (mainly for insufficient improvement).

At the beginning of the study 57% were receiving concomitant medication, 49% in week 2 and in week 6 only 44%. This was due to the fact that the sleep-promoting effects of trazodone CR no longer made anxiolytic sedatives or hypnotics necessary. On the other hand, the high percentage of patients receiving concomitant SSRI medication could be explained by antidepressant-associated insomnia being a special indication for trazodone, as has been described by Jacobsen [50], Nierenberg et al. [20] and Nierenberg and Keck [51]. It might, however, also have been due to the necessity to give vigilance-promoting SSRIs in the morning.

Neuropsychiatrists' ratings based on the CGI showed very much to much improvement in 78.3%, while only 3.6% remained unchanged or were found deteriorated.

Observer rating based on the HAMD revealed a statistically significant improvement from a baseline score of 21 to 14 after 2 weeks, and a normalization to a score of 8 after 6 weeks. Therapeutic effects seen in the HAMD were similar in the five different subgroups as well as in patients with or without comedication.

Patients' rating based on the Zung SDS and SAS also showed a significant improvement in the 2nd and 6th week of therapy.

Our findings confirm previous controlled trials in both Europe and the US, showing the antidepressant efficacy of trazodone to be superior to that of placebo and equivalent to that of conventional tricyclics. However, fewer anticholinergic side effects were reported [52–54].

Evaluation of the target symptoms of trazodone by ranking the most improved symptoms in percent of the baseline values identified *insomnia* as the most improved psychopathological item in all three scales, with the effects mostly seen already in the 2nd week of treatment (80% in the HAMD, 35% in the SDS, and 32% in the SAS). While in the observer ratings also *suicidal tendencies* and *weight loss* were found to be much improved, in the self-rated Zung SDS the 2nd and 3rd most improved items were *sadness* and *loss of drive*, and in the self-rated Zung SAS *anxiety* and the *feeling of falling apart*. Thus, the present clinical postmarketing study confirmed earlier predictions based on neurophysiological findings concerning the therapeutic effects of trazodone on its target symptoms such as depressed mood, anxiety and insomnia [8–10, 18].

Tolerability was very good. In the 2nd week only 16.9% and in the 6th week only 7.6% of the patients reported side effects, mostly characterized by tiredness and only slight nausea and vertigo. Thus, the side effect profile of the CR formulation is similar to that of the standard formulation known for its low toxicity and benign profile in overdose [55, 56]. The dropout rate was extremely low (3.7% over 6 weeks). In an earlier 6-week study comparing the conventional and the CR formulation of trazodone 150 mg/day, the combined dropout rate was 22.2%, with the CR formulation being superior to the direct-release tablet [57]. In the present study we did not observe the muscle weakness or soreness, skin swelling or urinary complaints that were reported in another postmarketing comparative study of conventionally formulated trazodone [58]. In particular, there appeared to be no undesirable interaction with other medications frequently given together with trazodone, including SSRIs such as fluoxetine, which are known to increase plasma concentrations of the active trazodone metabolite, *m*-CPP [59]. The absence of interactions of trazodone or *m*-CPP with benzodiazepines has already been reported [42].

In the 5-step school-mark grading system patients gave Trittico 150 mg retard an overall performance mark of 2.03 (good), while doctors rated its efficacy with 1.8 and safety with 1.3 (very good). The present clinical study confirms previous investigations that found trazodone to be an effective and safe antidepressant with beneficial effects, specifically on its target symptoms insomnia, depression and anxiety. Moreover, it confirms our own earlier predictions based on neurophysiological investigations concerning the mode of action of the drug.

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