Pharmacological Research 51 (2005) 79–84

Pharmacological research

www.elsevier.com/locate/yphrs

Trazodone addition for insomnia in venlafaxine-treated, depressed inpatients: a semi-naturalistic study

Gilles Bertschy[a,*], Emna Ragama-Pardos[a], Michel Muscionico[a], Abderrafi Aït-Ameur[b], Loraine Roth[a], Christian Osiek[a], François Ferrero[a]

[a] *Department of Psychiatry, University Hospital and University of Geneva, Geneva, Switzerland*
[b] *Miremont Psychiatric Clinic, Badens, France*

Accepted 11 June 2004

Abstract

In this paper, we present the results of a prospective semi-naturalistic study of the addition of trazodone for insomnia to a 4 week, 300 mg/day venlafaxine treatment in 50 depressed inpatients. The Montgomery and Asberg depression rating scale was used as a rating instrument. The study is designated as semi-naturalistic due to the fact that, although the venlafaxine treatment regimen was strictly defined, the timing of the trazodone introduction and the dosage were determined by the clinicians. The indication was based on the persistency of insomnia despite the use of authorized sedative co-medication (zopiclone as a hypnotic, clorazepate as an anxiolytic). Among the 42 patients who completed the study, 27 did not receive trazodone (G1) while 15 did (G2). Although the two groups were not clinically different at study entry, G2 patients showed less improvement than G1 patients during venlafaxine treatment alone, both in terms of insomnia (MADRS item 4) and inner tension (MADRS item 3). After trazodone introduction, insomnia improved and the median (interquartile range) of this item in G1 and G2 patients showed no statistically significant difference on Day 28 (G1:0 (0–1); G2:0 (0–2)). However, inner tension did not improve and the median (interquartile range) was higher on Day 28 in G2 patients (G1: 1 (0–2); G2: 2(1–4); $P < 0.05$). Thus, trazodone is probably used for patients who develop not only insomnia, but also inner tension/anxiety during venlafaxine treatment. However, it alleviates only the first symptom, not the second.

Keywords: Venlafaxine; Trazodone; Depression; Sleep; Anxiety

1. Introduction

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor antidepressant with a well-demonstrated clinical efficacy [1]. Higher daily doses (200–375 mg per day) are more effective and/or have a faster onset of action than lower daily doses (75–150 mg per day) [2–4].

Trazodone is an effective antidepressant [5] with a complex mechanism of action. Its therapeutic activity may be more closely linked to its anti5HT2 postsynaptic receptor action and the post-synaptic 5HT1 agonist action of its metabolite *m*-chlorophenylpiperazine than to its weak inhibition of serotonin reuptake [6]. In a comparative study with venlafaxine [7], both drugs were more effective than placebo, but venlafaxine produced a greater effect on cognitive disturbance and retardation factors while trazodone improved sleep disturbance, as rated by the Hamilton rating scale for depression. This beneficial profile of action on the sleep of depressed patients has led some authors to use trazodone in addition to other antidepressants, both SSRIs [8–10] and MAOIs [11–13], which have a less favourable profile of action on sleep. In the Nierenberg et al. study [9], patients with insomnia who were taking bupropion or fluoxetine reported an improvement with trazodone, but not with the placebo, as expressed by the total Pittsburgh sleep quality index scores. More recently, Kaynak et al. [10] used a double-blind crossover design to compare the effects of trazodone and placebo on 12 SSRI-treated patients. Final Pittsburgh sleep quality index scores showed similar improvement in

* Corresponding author. Service de Psychiatrie Adulte, 2 Chemin du Petit Bel-Air, 1225 Chêne-Bourg, Geneva, Switzerland. Tel.: +41 22 305 4701; fax: +41 22 305 4769.
E-mail address: gilles.bertschy@hcuge.ch (G. Bertschy).

1043-6618/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phrs.2004.06.007

both groups (the group that received trazodone before the placebo and the group that received the placebo before trazodone), suggesting a spillover effect. Yet, despite the similar subjective scores, polysomnographic recordings clearly showed the difference between the beneficial effects of trazodone and the absence of effects of the placebo, as compared with baseline. Patients treated with trazodone showed an increase in total sleep time, the percentage of stage 3 + 4 sleep, the sleep efficiency index, the sleep continuity index and a decrease in the percentage of stage 1 sleep, the number of awakenings and stage shifts. Such polysomnographic data coincide with those of the study of Saletu-Zyhlarz et al. [14] that examines the use of trazodone in untreated insomniac dysthymic patients.

In our clinic, depressive inpatients were first treated with a rapidly titrated, high dose (300 mg) venlafaxine regimen. The addition of benzodiazepines for anxiety and suicidal ideation and of hypnotics for insomnia was a standard procedure. Since this approach was not sufficient to control the sleep disorders of a minority of patients, we developed the use of trazodone addition. Trazodone was added to, but not substituted for, the benzodiazepine and/or hypnotics regimen for three reasons: (1) we needed to reduce the length of stay; (2) many patients had been taking benzodiazepines for a considerable length of time; and (3) many patients had also reported a significant level of anxiety or suicidal ideation.

In this paper, we present the results of a prospective semi-naturalistic study of the use of trazodone in addition to a high dose venlafaxine treatment for depressed inpatients. The study is designated as semi-naturalistic due to the fact that, although the venlafaxine treatment regimen was strictly defined, the timing of trazodone introduction and the dosage was determined by the clinicians, as in their usual practice. In so doing, the clinicians defined two subgroups of patients: one receiving trazodone in addition to venlafaxine and one not receiving this first drug. This study examines the efficacy of trazodone addition by: comparing these two subgroups in terms of pre-study variables (sociodemographic, clinical and biological) and pre-study therapeutic variables, comparing these two subgroups in terms of the evolution of depression (MADRS total score), sleep impairment (MADRS item 4), inner tension (MADRS item 3, an item that encompasses both inner tension and anxiety, which we thought could perhaps be related to sleep problems) and benzodiazepines/hypnotics prescription.

2. Method

2.1. Subjects

We recruited inpatients with an ICD10 depressive episode of moderate or high severity and a MADRS (Montgomery and Asberg depression rating scale [15]) global score of 25 or more for the study. Excluded from the study were patients with serious cardiac, hepatic, renal or brain disease; associated psychotic characteristics; schizophrenia or schizo-affective disorders; alcohol, drug or high dose benzodiazepine dependence in the preceding year as well as patients currently treated with neuroleptics or mood stabilizing drugs. Pregnant patients were also excluded. The study was approved by the medical ethical review board and patients were required to give their written, informed consent.

2.2. Procedure

Once included in the study, no wash-out period was considered necessary if patients were already receiving an antidepressant treatment. Most patients were being treated with a SSRI and a direct transition from a SSRI to a SNRI was not problematic. Patients started on Day 0 with a 75 mg dose of venlafaxine (extended-release form) at 8:00 p.m. The daily dose was then increased by 75 mg per day to reach a 300 mg daily dose (150 mg b.i.d.) on Day 3. Co-medications allowed for anxiety and insomnia were restricted to clorazepate and zopiclone (maximum daily doses allowed: 60 and 15 mg, respectively). In the case of extremely severe anxiety and suicidal risk, levomepromazine could be administered as a rescue medication for a maximum duration of 3 days.

Trazodone addition was a therapeutic option available to the clinician in charge of the patient. If sleep problems persisted after the use of standard co-medications (clorazepate and zopiclone), clinicians could then decide to introduce trazodone. It was recommended to introduce trazodone on Day 14, but the clinicians could introduce the drug before or after this day according to their own clinical appreciation of the therapeutic needs of the patient. The daily dose, which was taken at bedtime, was progressively adapted based on the clinical evolution of the patient.

Depressive symptomatology was evaluated using MADRS total score on Days 0, 4, 7, 11, 14, 21 and 28. Insomnia was rated using the item 4 score of the MADRS (sleep impairment), tension and anxiety by using the item 3 score (inner tension). MADRS raters (psychiatrists or clinical psychologists) underwent special training and were not involved in the treatment of the patients. On Day 0, morning blood samples were taken to measure plasma free T4, TSH and cortisol levels (as markers of the activity of the hypothalamic–pituitary–thyroid axis and the hypothalamic–pituitary–adrenal axis) and on Days 14 and 28, venlafaxine and *O*-desmethylvenlafaxine plasma levels were measured (both as routine monitoring procedure and as part of a study of the relationships between plasma levels and clinical response).

2.3. Statistics

Comparisons between groups were performed with non-parametric statistics for nominal variables (chi-square test) and quantitative variables (the Mann–Whitney *U*-test for comparison between groups and the Wilcoxon signed rank test for intra-group comparisons) using SPSS 9.0 for Win-

dows (1998). Quantitative results are presented as median (interquartile range).

3. Results

3.1. Study population

Fifty patients were included in the study. Only two patients received a single 25 mg dose of levomepromazine during the first days of their treatment for severe anxiety and suicidal ideation. There were eight drop-out cases, which were related to manic or mixed switches states ($n = 2$; drop-out dates: Days 11 and 13), treatment interruption by the patient ($n = 2$; Days 12 and 14), suicidal attempt ($n = 1$; Day 22), total insomnia in spite of trazodone addition ($n = 1$; Day 18; only case of drop-out during trazodone addition; the patient was excluded because the severity of the insomnia necessitated a change in the antidepressant treatment), major headaches in a context of pre-study non-opiate antalgics withdrawal ($n = 1$; Day 14), and major protocol violation due to the introduction of trazodone on Day 0 ($n = 1$; Day 0). The 42 remaining patients were included in the results of this study. Twenty-seven patients ended the study without needing trazodone addition (group 1: G1) and 15 required trazodone addition (group 2: G2). Characteristics of G1 and G2 patients are presented in Table 1. In G2, the median day of trazodone introduction was the 14th day with eight patients having received trazodone on Day 14, three before Day 14 (Days 7, 9, and 11), and four after Day 14 (Days 16, 21, 25, and 26). The median (interquartile range) dose of trazodone on Day 28 was 100 mg (100–200) with a range of 50–200 mg. Trazodone association was well tolerated without any serious side-effects, including specific, adverse sexual events such as priapism. Minor side effects were more frequent, but were limited to slight morning dizziness/drowsiness and moderate orthostatic hypotension, which both disappeared spontaneously or with dose adaptation.

Table 1
Sociodemographic and clinical characteristics of the patients without (G1) and with (G2) trazodone addition: a comparison with the Mann–Whitney *U*-test between G1 and G2 for quantitative variables and with the chi-square test for nominal variables

	G1	G2
Age	42 (32–48)	41 (36–48)
Gender (M/F)	10/17	7/8
Age of onset	40 (30–48)	34 (25–46)
Depression		
Bipolar	1	1
First episode	18	7
Recurrent	9	7
Anxious comorbidity (yes/no)	5/22	2/13
Personality disorders (yes/no)	7/20	6/9
Episode duration (months)	4 (2–8)	3 (2–4)
Antidepressant before study entry (yes/no)	10/17	4/11
Benzodiazepines before study entry (yes/no)	22/5	14/1

Quantitative variables are presented as median (interquartile range).

3.2. Comparison of pre-study variables between G1 and G2

There were no statistically significant differences ($P < 05$) in pre-study variables between G1 and G2, including sociodemographic (gender, age), clinical (duration of the present episode, polarity, recurrence, comorbidity, age at onset, severity as evaluated with Day 0 MADRS score and number of symptoms of the ICD10 somatic syndrome), and pre-study therapeutic variables (treatment with benzodiazepines, antidepressants). Concerning biological variables (morning free T4, TSH, cortisol plasma levels), no differences were found between G1 and G2.

3.3. Comparison of clinical evolution between G1 and G2

Given the scattered pattern of trazodone introduction between Days 7 and 26, we first compared the two groups during the initial phase of treatment before any trazodone introduction (Days 0, 4 and 7). Results for the two groups were also compared at the end of the study (Day 28). The results are presented in Table 2.

No statistically significant differences were found for G1 and G2 at baseline for the global severity of their depressive states, for the specific items of insomnia and inner tension, or for the use of sedatives. This resemblance continued during the first week of treatment and extended to the prescription of hypnotics and minor tranquilizers as measured on Day 7 (although there was a trend for higher zopiclone use in G2: $P < 0.10$). Significant improvement of these three clinical variables was observed between Days 0 and 28 in each group (Wilcoxon signed ranks test; data not shown in Table 2) and on Day 28, G1 and G2 were not significantly different in terms of global MADRS score (although there was, in fact, a trend for better results in G1: $P < 0.07$) and insomnia, this last point corresponding to the hypnotics dose, for which there was no difference between the groups on Day 28. Yet a significant difference appeared on Day 28, showing less favourable results for G2 in terms of tension and anxiety as evaluated both directly by scores of the specific items and indirectly by the clorazepate daily dose. Such results suggested two hypotheses: (1) Patients needing trazodone addition during venlafaxine treatment (G2) were the patients for whom both insomnia and inner tension were either developed or aggravated during venlafaxine treatment. (2) For these patients, trazodone was more effective for insomnia than for inner tension. These hypotheses were difficult to test with our semi-naturalistic design and the freedom given the clinicians concerning the date of trazodone introduction. However, considering the results for these patients at the last evaluation before trazodone introduction (Day traz; for details about this day see previous section) we could observe two phenomena. First, insomnia

Table 2
clinical evolution of G1 (no trazodone addition, $n = 27$) and G2 (trazodone addition, $n = 15$): a comparison with Mann–Whitney U-test between G1 and G2 using the same variable on the same day: $^{***}P < 0.05$

	Day 0		Day 4		Day 7		Day 28	
	G1	G2	G1	G2	G1	G2	G1	G2
MADRS total score	38 (30–41)	36 (31–42)	24 (15–31)	29 (19–33)	23 (11–32)	19 (15–28)	7 (4–23)	16 (12–21)
Insomnia item	3 (1–5)	4 (3–5)	2 (0–4)	2 (2–2)	1 (0–3)	2 (0–3)	0 (0–1)	0 (0–2)
Inner tension item	3 (2–4)	4 (3–4)	2 (1–3)	2 (1–3)	2 (0–3)	2 (1–3)	1^{***} (0–2)	2^{***} (1–4)
Zopiclone (mg/day)	7.5 (7.5–7.5)	7.5 (7.5–7.5)	7.5 (7.5–7.5)	7.5 (7.5–15)	7.5 (0–15)	7.5 (7.5–15)	7.5 (0–7.5)	7.5 (0–15)
Clorazepate (mg/day)	30 (20–40)	20 (2.5–30)	30 (20–40)	20 (0–30)	30 (15–40)	15 (1.3–30)	15^{***} (0–20)	25^{***} (20–40)

Results are presented as median (interquartile range).

worsened after the first week of venlafaxine treatment (rising from 2 (0–3) on Day 7 to 4 (0–4) on Day traz) and then clearly improved with trazodone addition (0 (0–2) on Day 28). Second, inner tension remained constant throughout this period, 2 (1–3) on Day 7, 2 (2–3) on Day traz and 2 (1–4) on Day 28) showing no improvement despite trazodone addition. In contrast, in the G1 group the period between Days 7 and 28 was one of improvement: on Day 14, the scores of the insomnia item, 0 (0–1), and of the inner tension item, 2 (0–2), had already attained the levels that would be maintained until Day 28. If we compare the change of the insomnia item between Day 7 and Day traz in G2 with the same change between Days 7 and 14 in G2 the difference is significant: $P < 01$. Such results support the above-mentioned hypotheses: patients who received trazodone experienced both insomnia (which worsened during the venlafaxine phase of treatment) and inner tension (which did not improve during the venlafaxine phase of treatment) problems. Trazodone addition alleviated the first but not the second problem.

4. Discussion

This study suggests that trazodone addition was useful for the treatment of zopiclone-resistant insomnia in a group of depressed patients treated with high doses of venlafaxine. At study entry, no significant differences were found between the group of trazodone patients (G2) and the group of patients not needing trazodone (G1) for any of the clinical variables, including insomnia score and co-medication. It was only during the venlafaxine treatment phase that the insomnia of G2 proved to be more persistent than that of G1. After trazodone introduction the sleep of G2 improved, with scores similar to those of the G1 group at study end. However, if less improvement was observed in inner tension and sleep disorders in G2 than in G1 during venlafaxine treatment, after trazodone introduction, G2 tension, in contrast to G2 insomnia, remained stable and was significantly higher at study end in G2 than in G1. Stated simply, a subgroup of patients developed both insomnia and tension/anxiety problems during venlafaxine treatment, and trazodone alleviated the first problem, but not the second.

Comments concerning methodological shortcomings are required. This was, of course, a semi-naturalistic study [16]; thus it has all the limitations of an uncontrolled trial, in particular the lack of randomisation. This last point and the short duration of the study (4 weeks), make it difficult to know whether the insomnia seen in G2 would have improved similarly over time without trazodone addition. Furthermore, in order to have more representative data of our clinical routine, our study exposed itself to several specific shortcomings. Firstly, the subjectivity of the clinicians' decisions concerning if and when to introduce trazodone resulted in complications in interpreting the data. Interestingly, we observed that the clinicians rapidly asked for more autonomy than initially planned. The relatively large dispersion of the timing of trazodone introduction created a higher complexity of presentation and interpretation of the data. Secondly, the ratings of the specific symptoms relied on two individual items of the MADRS [15]. Particularly for insomnia, a self-report instrument, or even better, polysomnographia, could have produced useful information. This is particularly debatable for item 3, which mixes two related, but dissimilar, concepts of tension and anxiety, meaning that it probably lacks construct validity. However, using individual items of a rating scale is not unusual [17]. Thirdly, there were only 42 patients in the study. And lastly, due to the need to reduce the lengths of stay and to the fact that 85% of the patients were already receiving a benzodiazepine at study entry, we started by adding trazodone and only reduced hypnotics when the patient's insomnia improved. The same constraints affected the administration of benzodiazepines for tension/anxiety. Such situations of polypharmacia are routine, but mixing the effects of several therapeutic variables renders the interpretation of the results more difficult.

Other shortcomings are related to the statistical analysis and interpretation of the data. Serial non-parametric comparison does not take into account that, at baseline, patients in G2 tended to have higher scores for insomnia and inner tension, although this difference is not statistically significant (with a larger group it could have become significant). Finally, our results analysis is limited to the patients that completed the study. Exclusion of dropout cases may have biased the results. However, performing an end point analysis using the last observation carried forward for all the patients included

in the study ($n = 50$) does not change the final results ($P < 0.05$ for inner tension item and clorazepate daily dose and a similar trend, $P < 0.07$, for global improvement on Day 28).

With these methodological remarks in mind, we will now comment briefly on our results. Concerning the effectiveness of trazodone addition to control insomnia during venlafaxine treatment, our results confirm previous trials with other potentially stimulating antidepressants such as SSRIs [8–10] or MAOIs [11–13]. Although trazodone was added to sedatives in our inpatient context, it could probably be considered alone and offer an alternative, with little or no risk of dependence, to agents acting on the benzodiazepine receptors [18]. The dissociation of the evolution of inner tension and sleep impairment was not described in the above-mentioned studies about trazodone association with other antidepressants. Perhaps this dissociation was specifically related to an activating effect of venlafaxine, but in this case, it is interesting to note that no differences were found between venlafaxine and *O*-desmethylvenlafaxine plasma levels between G1 and G2 patients. These clinical aspects may have been largely ignored until now. We should mention that our group was unaware of this problem until we saw the figures, although we had the feeling that clinical management of patients needing trazodone addition was more complex than for patients who did not need trazodone. Should such results be confirmed, it seems reasonable to conceive that the stimulating effects of venlafaxine are counteracted by the sedating and anxiolytic effects of trazodone in a subgroup of patients; however, the effects of this latter drug are of short duration, and when taken at bedtime, it exerts an active effect during the night (improving sleep) that wears off before the following day.

Finally, there was a non-significant trend for better results concerning depression in G1, in agreement with the above-mentioned impression that patients needing trazodone addition showed a less satisfying response to antidepressant treatment (they also needed to pursue higher doses of benzodiazepine treatment). Thus, trazodone probably did not work as an augmentation treatment for depression. Moreover, this was not our hypothesis. We write “probably” because we do not have a placebo-controlled, double-blind design. Yet, Kaynak et al. [10], using such a design, observed no differences for the depression score after 1 week of trazodone versus placebo addition in SSRI-treated patients. As they did, we stress the fact that trazodone is used at higher doses (150–600 mg) when an antidepressant effect is desired than in their study (100 mg) or in our study (50–200 mg).

5. Conclusion

Our study suggests that trazodone may be useful for the treatment of hypnotic-resistant insomnia in patients undergoing high dose venlafaxine treatment. It also suggests that insomnia could be associated with inner tension and anxiety, but that trazodone at bedtime is probably of no help for the daytime symptoms. We are aware that this study has some methodological shortcomings and that the hypothesis of a dissociation between insomnia improvement and inner tension improvement requires confirmation by a controlled, randomized trial using more specific tools to evaluate insomnia and inner tension/anxiety. Yet, these semi-naturalistic results may help us understand some of the difficulties faced by clinicians in their daily practice with antidepressant treatments.

Acknowledgements

This work was partially supported by a grant of Wyeth, Switzerland. The authors would like to thank K. Harrison and S. Ter Pelle for their editorial assistance and M. Gex-Fabry, Ph.D. for her statistical assistance.

References

[1] Burnett FE, Dinan TG. Venlafaxine pharmacology and therapeutic potential in the treatment of depression. Hum Psychopharmacol 1998;13:153–62.
[2] Khan A, Upton GV, Rudolph RL, Entsuah R, Leventer SM. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose–response study.Venlafaxine Investigator Study Group. J Clin Psychopharmacol 1998;18:19–25.
[3] Rudolph RL, Fabre LF, Feighner JP, Rickels K, Entsuah R, Derivan AT. A randomized, placebo-controlled, dose–response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatr 1998;59:116–22.
[4] Schweizer E, Weise C, Clary C, Fox I, Rickels K. Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol 1991;11:233–6.
[5] Schatzberg AF. Trazodone: a 5-year review of antidepressant efficacy. Psychopathology 1987;20(Suppl 1):48–56.
[6] Marek GJ, McDougle CJ, Price LH, Seiden LS. A comparison of trazodone and fluoxetine: implications for a serotonergic mechanism of antidepressant action. Psychopharmacology (Berlin) 1992;109:2–11.
[7] Cunningham LA, Borison RL, Carman JS, Chouinard G, Crowder JE, Diamond BI, et al. A comparison of venlafaxine, trazodone, and placebo in major depression. J Clin Psychopharmacol 1994;14:99–106.
[8] Metz A, Shader RI. Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. Int Clin Psychopharmacol 1990;5:191–4.
[9] Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. Am J Psychiatr 1994;151:1069–72.
[10] Kaynak H, Kaynak D, Gozukirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. Sleep Med 2004;5:15–20.
[11] Haffmans PM, Vos MS. The effects of trazodone on sleep disturbances induced by brofaromine. Eur Psychiatr 1999;14:167–71.
[12] Jacobsen FM. Low-dose trazodone as a hypnotic in patients treated with MAOIs and other psychotropics: a pilot study. J Clin Psychiatr 1990;51:298–302.
[13] Nierenberg AA, Keck Jr PE. Management of monoamine oxidase inhibitor-associated insomnia with trazodone. J Clin Psychopharmacol 1989;9:42–5.
[14] Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, Semler B, Decker K, Parapatics S, et al. Insomnia related to dysthymia: polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. Neuropsychobiology 2001;44:139–49.

[15] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatr 1979;134:382–9.
[16] Blacker CVR, Mortimore C. Randomized controlled trials and naturalistic data: time for a change? Hum Psychopharmacol 1996;11:353–63.
[17] Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47:55–62.
[18] Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. Psychopharmacology (Berlin) 1999;144:220–33.