Clinical Neuropharmacology
Vol. 11, Suppl. 2, pp. S74–S82

Antidepressant and Anxiolytic Activities of Tianeptine: An Overview of Clinical Trials

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Summary: Tianeptine is a new antidepressant effective against anxiety accompanying mood disturbances. Its clinical properties have been assessed by double-blind controlled studies (versus imipramine, amitriptyline, nomifensine, viloxazine) in depressed patients fulfilling the diagnostic criteria of the DSM III: single recurrent major depressive episodes without melancholia or psychotic features, and dysthymic disorders. The authors have concluded that tianeptine is effective in depressive disorders as shown both by depression rating scales and subjective impressions of treated patients. This improvement increases regularly with time. Seventy-eight percent of patients were considered to be "responders" at the end of the treatment with tianeptine. Antidepressant activity of tianeptine is equally present in depressive states appearing after withdrawal from alcohol. In depressed patients with anxiety, the results also reveal the efficacy of tianeptine on anxiety symptoms. Tianeptine, in addition, shows a marked action on somatic complaints. These results have been confirmed by open long-term trials, particularly in the elderly. Tianeptine can be placed in a middle position in the bipolar classification, between the sedative and stimulant antidepressants. Its antidepressant and anxiolytic properties and its action on somatic complaints make the drug particularly suitable for the treatment of the entire range of depressive symptomatology. **Key Words:** Tianeptine—Antidepressant—Depressive disorders—Anxiety—Somatic complaints.

ANTIDEPRESSANT ACTIVITY

Methods

The antidepressant action of tianeptine has been evaluated in depressed patients fulfilling the diagnostic criteria of the DSM III for (a) major depression without melancholia and without psychotic features, or for (b) dysthymic disorders, whose depression was severe enough to justify the prescription of an antidepressant. The studies have either been controlled (Table 1) or open (Table 2).

Assessments were made by means of internationally validated rating scales, before treatment and at regular intervals during the studies. The depression scales used were

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TABLE 1. *Tianeptine controlled studies of 521 patients*

Reference drugs	Investigators
Amitriptyline	Lôo et al. (1)
	Pichot et al. (2)
Imipramine	Ostaptzeff (3)
Viloxazine	Buge (4)
Nomifensine	Weiss et al. (5)

the Hamilton Depression Rating Scale (HDRS), the Montgomery and Åsberg Depression Rating Scale (MADRS), and the Overall Depression Scale. General psychiatric scales included the Hopkins Symptom Checklist (HSCL; self-rating), Clinical Global Impressions (CGI), Beck Inventory (self-rating), and the Brief Psychiatric Rating Scale (BPRS).

The patients were selected on the basis of a minimum score on the depression scales. As shown by the scores before treatment, the depressive states included in the trials tended to be severe (Table 3). Of 937 patients included in studies where the MADRS was used, 285 (30%) had an initial global score equal to or greater than 35. In the controlled trials, the drug was given as single drug therapy in 64% of the cases.

TABLE 2. *Tianeptine open studies*[a]

Investigators	Aim of the study
Lôo, Briole, Castelnau, Charbonnier, Dachary, Danion, Darcourt, Dufour, Escande, Favre, Feline, Guelfi, Leger, Lemoine, Malka, Olie, de Praingy, Scharbach, Scotto, Tignol	Long-term study
Chapuy, Cuny, Delomier, Galley, Michel	Long-term study in the elderly
Guelfi	Study of tianeptine in 1,000 patients in general practice

[a] Studies currently underway.

TABLE 3. *Depression scales—Scores before treatment*

Scales	Inclusion threshold	Mean initial score (±S.E.M.)
HDRS[a]		
Guelfi et al. (10)	36	49.8 ± 1.1
Lôo et al. (9)	35	46.6 ± 1.1
MADRS		
Pichot, Guelfi (2)	20	30.8 ± 0.6
Lôo, Malka et al. (1)	20	30.0 ± 0.8
Lôo et al. (long-term study)[b]	25	32.7[c] ± 0.2
Chapuy, Cuny, Delomier, Galley, Michel[b]	25	32.1[c] ± 0.6

[a] Twenty-six items, the absence of symptom is rated as "1."
[b] Studies currently underway.
[c] Preliminary data.

TABLE 4. *Overall depression scale*

	D_0	D_{45}	Difference between drugs
Tianeptine n = 24	80.6 ± 5.0	56.1 ± 6.6[a]	p = 0.70 NS
Imipramine n = 23	79.7 ± 5.4	51.4 ± 6.0[a]	

From Ostaptzeff (3).
[a] $p < 0.01$.

Results

Results of Controlled Studies

In the various controlled studies, whatever the means of assessment used, tianeptine has demonstrated its antidepressant action. Comparing it with imipramine, Ostaptzeff (3) has shown that tianeptine has an antidepressant action equivalent to that of the reference drug (Table 4). In their study on 265 patients, 135 treated with tianeptine and 130 with amitriptyline, Pichot and Guelfi (2) have also demonstrated the antidepressant effect of tianeptine, quantified by the change in Clinical Global Impressions (CGI, Fig. 1). The change of MADRS scores was parallel to that observed with amitriptyline (Table 5). Gorceix (5) has also shown the antidepressant efficacy of tianeptine (Table 6), to be equal to that of nomifensine.

The effectiveness of tianeptine has been tested in alcoholics. A multicentre controlled study, comparing tianeptine to amitriptyline in the double-blind condition, was performed by Lôo et al. (1). The patients included in the study had the association of depression and alcoholism, using DSM III criteria for "alcohol abuse" or

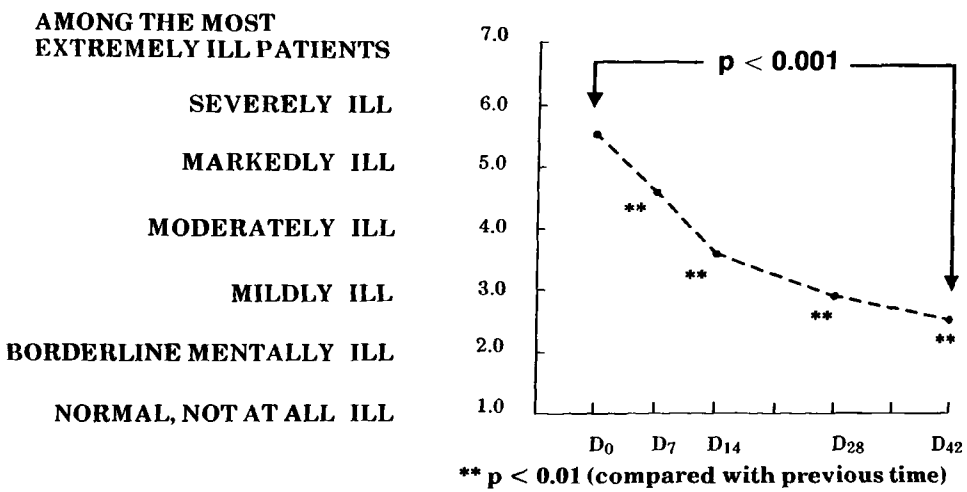

FIG. 1. Clinical Global Impression. Tianeptine–Amitriptyline (n = 265). From Pichot et al. (2).

TABLE 5. *MADRS*

	D_0	D_7	D_{14}	D_{28}	D_{42}
Tianeptine					
n = 103	30.8 ± 0.6	23.2 ± 0.6[a]	17.0 ± 0.7[a]	12.6 ± 0.7[a]	11.0 ± 0.8[b]
Amitriptyline					
n = 108	31.1 ± 0.6	23.3 ± 0.7[a]	15.6 ± 0.6[a]	11.8 ± 0.6[a]	9.6 ± 0.6[a]

From Pichot et al. (2).
[a] $p < 0.01$ (compared with previous time).
[b] $p < 0.05$ (compared with previous time).
Difference between drugs: $p = 0.240$ (NS).

"alcohol dependence." The study involved 129 patients, withdrawn from chronic alcoholism at the time of the study. The results are summarized in Table 7.

Comparison of MADRS scores shows that tianeptine has an antidepressant activity equivalent to that of amitriptyline. Tianeptine was superior to amitriptyline, based on the subjective impressions of the patients expressed in the Hopkins Symp-

TABLE 6. *HDRS*

	D_0	D_{15}	D_{30}	Difference between drugs
Tianeptine				
n = 12	50.3 ± 2.5	35.8 ± 1.9[a]	34.3 ± 1.5 (NS)	p = 0.20 NS
Nomifensine				
n = 14	51.2 ± 2.0	38.9 ± 1.8[a]	39.6 ± 1.8 (NS)	

From Gorceix (5).
[a] $p < 0.001$ (compared with previous time).
NS, nonsignificant (compared with previous time).

TABLE 7. *Tianeptine, T—Amitriptyline, A*

	D_0	D_7	D_{14}	D_{28}	Difference between drugs
MADRS					
T (n = 56)	30.0 ± 0.8	21.9 ± 1.2[a]	16.9 ± 0.9[a]	12.9 ± 0.9[a]	p = 0.496
A (n = 56)	28.8 ± 0.7	22.1 ± 1.0[a]	17.2 ± 0.9[a]	13.7 ± 1.1[a]	
HSCL (global score)					
T (n = 51)	59.5 ± 3.9	36.1 ± 3.6[a]	27.9 ± 3.0[a]	22.7 ± 2.9[a]	p = 0.017
A (n = 51)	58.3 ± 4.4	42.4 ± 4.3[a]	38.2 ± 4.1 (NS)	32.7 ± 4.3 (NS)	
HSCL (depressed mood)					
T (n = 54)	14.9 ± 0.9	9.6 ± 0.8[a]	7.3 ± 0.7[a]	6.2 ± 0.8 (NS)	p = 0.006
A (n = 54)	14.0 ± 1.0	10.4 ± 1.0[a]	9.6 ± 1.0 (NS)	8.2 ± 1.0[b]	

From Lôo et al (1).
NS, nonsignificant.
[a] $p < 0.01$ (compared with previous time).
[b] $p < 0.05$ (compared with previous time).

TABLE 8. *HSCL—Composition of the "depressed mood" factor. Classification by decreasing order of saturation*

29	Feeling lonely
30	Feeling blue
31	Worrying or stewing about things
57	Feeling tense or keyed up
54	Feeling hopeless about the future
28	Feeling blocked or stymied in getting things done
3	Being unable to get rid of bad thoughts or ideas
2	Nervousness or shakiness inside
26	Blaming yourself for things

From Lôo et al. (1).

tom Checklist. Multivariate analysis of the HSCL singled out a "depressed mood" factor, grouping nine items of the checklist (Table 8). For this factor, the difference in time course of the two drugs was statistically significant ($p = 0.006$), the observed improvement being greater in the tianeptine group. These results confirm the efficacy of tianeptine on the various components of the withdrawal syndrome in chronic alcoholics, previously reported by Grivois et al. (6). Furthermore, it has been established that pharmacokinetics of tianeptine are not influenced by alcohol intake (7). This property, along with the antidepressant action of tianeptine, make the drug particularly suitable in depressive states of the alcoholic patient.

In summary, results of the various controlled studies demonstrate the antidepressant action of tianeptine. The overall course reveals regular symptomatic improvement with time, proven by a significant decrease in global scores of the depression scales ($p < 0.001$). Statistical analysis shows that improvement is already significant by the seventh day of treatment. Improvement is significant at each time of evaluation, compared with previous time, until the 28th and 42nd days of treatment. Thus, the effect of the drug is regularly progressive with time. The decrease in global depression scores during treatment ranges from 64 to 68%, depending on the study. Considering individual results and taking, as do other authors (8), an improvement of 50% in the MADRS global score to be a positive response to treatment, 78% of the patients were considered "responders" at the end of the treatment with tianeptine.

Results of Open Studies

In an open long-term (1 year) study directed by Lôo et al., preliminary results confirm the efficacy of tianeptine. The 650 patients included are 19–87 years old and suffer from major depression (63%) or dysthymic disorder (37%). The results in the first 300 patients, who were treated for at least 3 months, can be seen in Table 9 for

TABLE 9. *MADRS—Long-term study (preliminary data on 300 patients with 3 months of treatment)*

D_0	D_{14}	M_1	M_3
32.7 ± 0.3	22.8 ± 0.6^a	17.1 ± 0.5^a	14.7 ± 0.6^a

From Lôo et al. (1).
[a] $p < 0.01$ (compared with previous time).

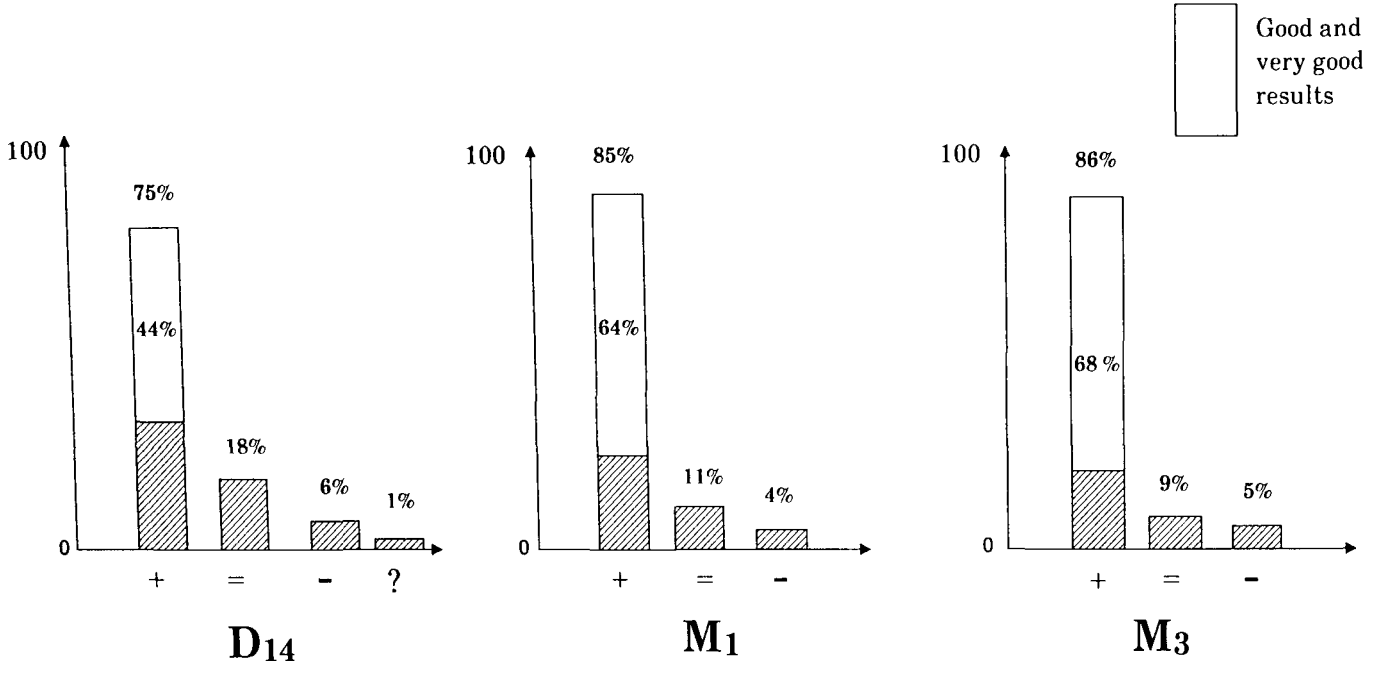

FIG. 2. Clinical Global Impression Item 2—course of the illness (% of cases). +, improvement; =, no modification; −, worsening; ?, uninterpretable. From Lôo et al. (1).

the MADRS and in Fig. 2 for the CGI. They show a reinforcement of the antidepressant effect of the drug all along the course of treatment.

Preliminary results in other open studies, either French or international, confirm the effectiveness of tianeptine, particularly in elderly patients. In drug addicts with depression after drug withdrawal, Lôo et al. (9) have shown the effectiveness of tianeptine during four-week treatments. This is illustrated by the change in HDRS results (Table 10).

Occurrence of Mania and Hypomania

Twelve cases of typical acute mania or hypomania were reported during the various clinical trials in patients who, except in two cases, had not had personal antecedents of manic disorders.

ANXIOLYTIC ACTIVITY

Methods

The anxiolytic activity of tianeptine was studied by Pichot and Guelfi (2) in a series of depressed and anxious patients who fulfilled the depression criteria of the DSM III and also the anxiety criteria of the Food and Drug Administration for the evaluation of anxiolytic agents. The patients had a minimum of 20 on the Hamilton Anxiety Rating Scale (HARS), and were treated by single drug therapy after elimination of "placebo-responder" patients by pretreatment with placebo for 3–14 days. The remaining patients were representative of the population of depressed and anxious patients, since typical results were obtained in this series with amitriptyline, which is known to have antianxiety properties.

Results

The time course of the HARS overall score shows significant improvement in anxiety level with tianeptine. This effect occurs from the seventh day of treatment onwards and concerns both psychological and somatic anxiety. Multivariate analysis of HSCL singled out an "Anxiety" factor including eight items of the self-rating checklist (Table 11). With tianeptine, there is an obvious improvement in the "Anxiety" factor of the HSCL, parallel to that observed with amitriptyline (Table 12).

This action of tianeptine on signs of anxiety associated with depression is confirmed by the results of other studies. It is equivalent to that of amitriptyline or

TABLE 10. *HDRS—Evolution of global score (n = 27)*

D_0	D_{14}	M_1
46.6 ± 1.1	39.6 ± 1.1[a]	36.9 ± 1.3[b]

From Lôo et al. (9).
[a] $p < 0.01$ (compared with previous time).
[b] $p < 0.05$ (compared with previous time).

TABLE 11. *HSCL—Composition of the "anxiety" factor. Classification by decreasing order of saturation*

23	Suddenly scared for no reason
33	Feeling fearful
50	Having to avoid certain places or activities because they frighten you
18	Feeling confused
48	Trouble getting your breath
17	Trembling
22	A feeling of being trapped or caught
4	Faintness or dizziness

From Pichot et al. (2).

tetrabamate. It is not accompanied by effects of sedation such as psychomotor retardation or diurnal drowsiness. Aggravation of anxiety symptoms was observed in only 5% of cases, early in the course of treatment.

ACTION ON SOMATIC COMPLAINTS

The action of tianeptine on somatic complaints was evaluated using the Checklist for Evaluation in Somatic Symptoms (CHESS) of Guelfi and Pull.

In the controlled study versus amitriptyline of Pichot and Guelfi (2), the change in the overall CHESS score shows a significant ($p < 0.01$) regression in the intensity of somatic complaints (Table 13).

Item and factor analysis of the CHESS showed the kind of complaints which particularly improve in clinical trials: sleep disturbances, digestive disorders, cardiorespiratory manifestations, autonomic disturbances, miscellaneous pain, and reduced libido.

CONCLUSION

Clinical properties of tianeptine were evaluated in open and controlled double-blind studies, using internationally validated rating scales, in patients with depression defined according to the DSM III diagnostic criteria: (a) major depression, single episode or recurrent, without melancholia, without psychotic features; and (b) dysthymic disorders, associated or not with alcohol abuse or alcohol dependence in chronic alcoholics.

TABLE 12. *HSCL—"Anxiety" factor*

	D_0	D_{14}	D_{42}	Difference between drugs
Tianeptine n = 97	12.7 ± 0.7	6.1 ± 0.5[a]	4.3 ± 0.4[a]	p = 0.894 (NS)
Amitriptyline n = 106	13.1 ± 0.7	6.1 ± 0.5[a]	4.3 ± 0.4[a]	

From Pichot et al. (2).
NS, nonsignificant.
[a] $p < 0.01$ (compared with previous time).

TABLE 13. *CHESS 82—Change of global score (n = 103)*

D_0	D_7	D_{14}	D_{28}	D_{42}
38.4 ± 1.5	23.5 ± 1.2[a]	18.3 ± 1.2[a]	13.2 ± 0.9[a]	12.6 ± 1.1 NS

From Pichot et al. (2).
NS: nonsignificant (compared with previous time).
[a] $p < 0.01$ (compared with previous time).

These studies bring out the following conclusions concerning tianeptine: antidepressant efficacy; effectiveness on anxiety linked to the mood disorders, without overall sedation; and efficacy on somatic complaints expressed by the patient.

These results, validated by those obtained with reference antidepressants, show that tianeptine, in the recommended indications, is an effective antidepressant which can be placed in a middle position in the bipolar classification, between the sedative and stimulant antidepressants.

REFERENCES

1. Lôo H, Malka R, Defrance R, et al. Tianeptine and amitriptyline: controlled double-blind trial in depressed alcoholic patients. *Neuropsychobiology* (in press).
2. Pichot P, Guelfi JD. Etude multicentrique contrôlée à double insu contre amitriptyline de l'efficacité de la tianeptine dans le traitement des depressions avec composante anxieuse. Expert report.
3. Ostaptzeff G. Etude contrôlée à double insu versus imipramine de l'efficacité de la tianeptine dans les états dépresifs non psychotiques. In: *Biological Psychiatry 1981. Proceedings of the 3rd World Congress of Biological Psychiatry,* Stockholm; Elsevier/North-Holland, 1981:597–600.
4. Buge A. Etude comparée de l'activité et de l'acceptabilité de la tianeptine et de la viloxazine dans les dépressions déficitaires liées à une pathologie vasculaire du sujet agé et de la maladie de Parkinson. Expert report.
5. Weiss C, Gorceix A, Kindynis S, Dimitriu M. Etude contrôlée à double insu versus nomifensine de l'activité et du délai d'action d'un nouvel antidépresseur la tianeptine. In: *Biological Psychiatry 1981. Proceedings of the 3rd World Congress of Biological Psychiatry,* Stockholm; Elsevier/North-Holland, 1981:593–6.
6. Grivois H, Niox H, Kamoun A. Etude contrôlée à double insu de l'intérêt thérapeutique de la tianeptine dans les états dépressifs des alcooliques hospitalisés pour cure de sevrage. In: *Biological Psychiatry 1981. Proceedings of the 3rd World Congress of Biological Psychiatry,* Stockholm; Elsevier/North-Holland, 1981:601–4.
7. Royer RJ, Albin H, Barrucand D, Salvadori-Failler C, Kamoun A. Pharmacokinetic and metabolic parameters of tianeptine in healthy volunteers and in populations with risk factors. *Clin Neuropharmacol* 1988;11(suppl 1):S90–6.
8. Rickels K, Feighner JP, Smith WT. Alprazolam, amitriptyline, doxepin and placebo in the treatment of depression. *Arch Gen Psychiatry* 1985;42:134–41.
9. Lôo H, Hantzberg P, Defrance R, Kamoun A, Deniker P. Traitement par la tianeptine des syndromes dépressifs des toxicomanes sevrés. Appréciation de l'efficacité et recherche de dépendance. *Encephale* 1987;13:295–9.
10. Guelfi JD, Dreyfus JF, Lacassin J, Pichot P. Etude contrôlée à double insu comparant tianeptine et sulpiride. In: *Biological Psychiatry 1981. Proceedings of the 3rd World Congress of Biological Psychiatry,* Stockholm; Elsevier/North-Holland, 1981:605–8.