Long Term Efficacy and Clinical Safety of Tianeptine in Depressed Alcoholic Patients after Alcohol Withdrawal

R. Malka,1 H. Loo,2 H. Ganry,3 C. Marey3 and A. Kamoun3
1 Centre Gilbert Raby, Meulan et Institut de Psychiatrie La Rochefoucault, Paris, France
2 Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique, Hôpital Sainte-Anne, Paris, France
3 IRIS, Courbevoie, France

Summary

A multicentre study was designed to treat patients presenting with a major depressive episode, single or recurrent, or dysthmic disorder with tianeptine for 1 year. 22% of these patients had a concurrent diagnosis of alcoholism. This intermediate analysis presents results obtained with the first 122 depressed alcoholic patients included, of which 63 were treated for 1 year. The results allow the evaluation of the long term efficacy and tolerability of tianeptine.

The antidepressant activity of tianeptine was confirmed by an almost 50% reduction of initial Montgomery-Asberg depression rating scale scores after 1 month of treatment. Total scores and subscores of the Hamilton anxiety rating scale and Hopkins symptom checklist self-ratings improved concomitantly. Single item and factor scores of the checklist for assessment of somatic symptoms indicated improvement in complaints present at the beginning of the study and an absence of notable adverse effects, particularly of the anticholinergic type. Three patients took massive doses of tianeptine; despite the association with alcohol, these patients did not show marked adverse effects.

These results indicate the potential of tianeptine as an antidepressant in alcoholic patients after withdrawal of alcohol, its long term efficacy, and its good tolerability in patients who are particularly susceptible to the adverse effects of psychotropic drugs. The drug does not provoke orthostatic hypotension or weight change.

Alcoholism and depression are often associated in psychiatric patients (Malka 1988). Many alcoholic patients have symptoms of depression (Weissman & Myers 1980). This association has led to the hypothesis of a common aetiology between alcoholism and depression (Winokur 1979). However, it is difficult to distinguish respective functions of genetic, biological, psychopathological and cultural factors, which is why the relationship is not confirmed by all authors (Merikangask et al. 1985). Nevertheless, some patients do develop genuine depression after prolonged alcohol intoxication (primary alcoholism). Conversely, alcohol (by its psychotropic properties) can complicate pre-existing depression (secondary alcoholism) [Malka et al. 1986]. Alcohol withdrawal could unmask the underlying depression, necessitating prescription of an antidepressant.

The importance of prolonged antidepressant treatment has already been stressed (Loo & Olié
1984; Prien 1987; Zarifian & Loo 1982). Our open multicentre trial aimed to treat more than 300 patients for 1 year had 2 objectives; to confirm the antidepressant activity, and to evaluate the tolerability, of the drug in long term treatment. The study is unique (Galinowski et al. 1988; Olie et al. 1984) for its organisation of data collection, its course and its results.

Tianeptine is a new antidepressant with a tricyclic structure (Labrid et al. 1988). Its principal action involves an increase in serotonin (5-hydroxytryptamine) reuptake (Fillion 1989; Hamon et al. 1989; Kato & Weitsch 1988; Lejeune et al. 1988). Ex vivo, tianeptine induces this activity in hippocampal and cortical synaptosomes (Mennini et al. 1987), and has been confirmed in animals (Weitsch et al. 1986) and humans (Renaud et al. 1988) by an increase in platelet serotonin after long term administration. The clinical antidepressant activity of tianeptine has been confirmed in several double-blind controlled trials against reference drugs (Defrance et al. 1988; Grivois et al. 1981; Guelfi et al. 1989; OstaptzetT 1981). Its good clinical tolerability has also been confirmed (Delalleau et al. 1988).

The interest in tianeptine for the treatment of depression after alcohol withdrawal (Loo et al. 1988b; Malka et al. 1989) lies firstly in its central position among other antidepressants – its therapeutic profile appears to be neither stimulant nor sedative – (Loo & Deniker 1988a; Loo et al. 1981) and secondly, in its biochemical mechanism of action. Alcohol influences serotonin metabolism in animals (Badawy et al. 1980) and humans (Ballenger et al. 1979; Davis et al. 1967), therefore the use of antidepressants with a serotonergic mechanism of action seems feasible. The rarity of anticholinergic adverse effects (Delalleau et al. 1981) during treatment with tianeptine facilitates its prescription in patients with a diminished somatic state and a higher sensitivity to the adverse effects of psychotropic drugs, such as alcoholism (Malka et al. 1986; Malka & Loo 1988).

This report presents the results of an intermediate analysis of 63 depressed patients included in the study after alcohol withdrawal following treatment with tianeptine for 1 year. Complete data were available for 51 of these patients. The purpose of the study was to treat depression occurring after alcohol withdrawal. As the risk of relapse is very high after short term treatment in depression, and probably still higher in depressed alcoholic patients, long term treatment over 1 year was investigated.

**Patients and Methods**

Male and female subjects, aged 18 years or older, treated as outpatients (or could be hospitalised initially) were included. In addition to the DSM III (American Psychiatric Association 1980) diagnosis of alcoholism [alcohol dependence (303.9x) or alcohol abuse (305.0x)] patients had to fulfil DSM III criteria for either major depressive episode, single (296.22) or recurrent (296.32) without melancholia or psychotic features, or dysthymic disorder (300.40). A minimum Montgomery-Asberg depression rating scale (MADRS) [Montgomery & Åsberg 1979] score of 25 was required, as well as a clinical indication for antidepressant treatment and patients’ informed consent.

Exclusion criteria were as follows: melancholia and depression with psychotic features; severe organic disease; patients treated with monoamine oxidase inhibitors (MAOI) who could not have their treatment withdrawn at least 15 days before entry; treatment with barbiturates, mood-regulating drugs (lithium, valpromide, carbamazepine) or triazolobenzodiazepines (alprazolam, triazolam, estazolam). Women liable to become pregnant, pregnant or lactating women, and patients unable to accept long term treatment were also excluded. Prescription of anxiolytics or hypnotics (other than triazolobenzodiazepines), and low doses of sedative neuroleptics were permitted during the trial.

Treatment was open after a placebo washout of 4 to 7 days to exclude early placebo responders. Non-MAOI antidepressants prescribed before entering the trial were withdrawn at least 7 days before inclusion. The daily dosage of tianeptine was 37.5mg (3 tablets) per day, with the option of titrating the dose between 25 and 50mg daily. Patients with renal failure and those older than 70