Alcohol & Alcoholism Vol. 36, No. 4, pp. 329–334, 2001

FLUPENTHIXOL DECANOATE AND RELAPSE PREVENTION IN ALCOHOLICS: RESULTS FROM A PLACEBO-CONTROLLED STUDY

GERHARD A. WIESBECK*, HEINZ-GERD WEIJERS, OTTO M. LESCH[1], THOMAS GLASER[2], PETER-JOACHIM TOENNES[2] and JOBST BOENING

Addiction Research Group, Department of Psychiatry, University of Wuerzburg, [1]Department of Psychiatry, University of Vienna, Austria and [2]Bayer Vital, Leverkusen, Germany

(*Received* 27 *March* 2000; *in revised form* 9 *January* 2001; *accepted* 6 *February* 2001)

Abstract — Flupenthixol, with its broad receptor profile, interacts with a variety of dopamine and serotonin binding sites which are important in the neurobiology of alcohol dependence. Its pharmacology, together with encouraging results from both animal studies and clinical trials with cocaine users, led us to postulate that flupenthixol would significantly prevent relapse in detoxified alcohol-dependent individuals. We conducted a prospective, randomized, double-blind, placebo-controlled, multi-centre trial with two parallel groups and appropriate statistical evaluation. Subjects met criteria for moderate to severe alcohol dependence (DSM-III-R), without any concomitant psychiatric disorder. After complete detoxification, 281 women and men received either 10 mg of flupenthixol decanoate or placebo as i.m. injection every second week for 6 months on an out-patient basis, followed by 6 months of follow-up. Efficacy was based on absolute abstinence, with relapse being defined as consumption of any alcohol after inclusion in the study. In contrast to the hypothesis, flupenthixol did not reduce, but was associated with more, relapses. Though well tolerated, relapse rates after 6 months of treatment were 85.2% (flupenthixol) versus 65.5% (placebo), a highly significant difference from the medication. Flupenthixol was also inferior to placebo with regard to other secondary criteria of efficacy (cumulative abstinence duration, relapse rate after 12 months). These results indicate that a 10 mg dose of flupenthixol decanoate does not have a beneficial effect on abstinence maintenance in alcohol-dependent individuals.

INTRODUCTION

Traditional alcohol treatment programmes reveal limited success. For example, Project MATCH Research Group (1997) reported abstinence rates ranging from 19% (out-patient treatment) to 35% (in-patient treatment) during a 12-month follow-up. Since relapse rates peak during the first months after cessation of drinking (Lesch *et al*., 1989; Feuerlein and Kuefner, 1989; Swift, 1999), a search has begun for pharmacological means to prevent relapse especially during this difficult period (Garbutt *et al*., 1999).

Flupenthixol, an established antipsychotic drug, is known for its mild antidepressant and anxiolytic activity, as well as for its minimal sedative effects at low doses (Budde, 1992). Flupenthixol antagonizes dopamine binding at a number of receptor subtypes, primarily at D1, D2, D3 and with less affinity at D4 receptors, and also affects serotonin binding at 5-HT_{2A} and 5-HT_{2C} receptors as well as noradrenaline binding at α1-adrenergic receptors (Glaser *et al*., 1998). With this non-selective, but rather broad, binding profile, flupenthixol seems to interact with a variety of important receptors which are involved in the neurobiology of craving and alcohol dependence (Robinson and Berridge, 1993; Erickson, 1996; De Witte, 1996; Noble, 1996). The drug's balanced interaction with both D1 and D2 receptors seems to be 'tailor-made' for binding sites believed to be crucial to the biology of alcohol reinforcement (Noble *et al*., 1991; McBride *et al*., 1993; Hietela *et al*., 1994; Lewis, 1996; Glaser *et al*., 1998; McBride and Li, 1998).

However, only a few and contradictory reports from both animal and human studies have been done on the usefulness of flupenthixol in treating drug and alcohol abuse or dependence (Schilkrut *et al*., 1988; Duvauchelle *et al*., 1992; King *et al*., 1994; Mansbach *et al*., 1994; Richardson *et al*., 1994; Soyka and Sand, 1995; Negus *et al*., 1996). In an animal model using rats specially bred for voluntary high alcohol consumption, flupenthixol at low dosages (0.1–1 mg/kg) reduced alcohol-intake in a dose-dependent manner (Sinclair *et al*., 1989). However, this effect appeared to be non-specific since food and water consumption decreased as well (Soyka and De Vry, 1998).

More data on flupenthixol in humans come from cocaine users. In an open study with ten 'crack' cocaine smokers, an average 72% reduction of craving and a prolonged retention in an out-patient treatment programme were reported on 10–20 mg flupenthixol decanoate every 14 days (Gawin *et al*., 1989). Using a placebo-controlled double-blind design, Khalsa *et al*. (1994) reported a significant reduction of both craving and drug consumption, as well as a much better participation in psychotherapeutic treatment groups in cocaine users. Interestingly, a mean dose of 12 mg was well tolerated by patients who remained abstinent, whereas severe extrapyramidal

*Author to whom correspondence should be addressed at: Addiction Research Group, Psychiatric Clinic, University of Wuerzburg, Fuechsleinstr. 15, 97080 Wuerzburg, Germany.

Participating centres and investigators: Austria: Wien, Anton-Proksch-Institut, Kalksburg: O. Lesch, M. Saletu, A. Nimmerrichter, H. Walter, G. Zyhlarz, N. Benda, A. Leitner, B. Subasi; Germany: Angermuende, Krankenhaus, Abteilung für Psychiatrie: G. Richter, P. Rybarczyk, N. Morkel, I. Basler; Augsburg, Bezirkskrankenhaus, Klinik für Psychiatrie und Psychotherapie: M. Schmauss, M. Niederecker, M. Banszerus, L. Teufel; Bayreuth, Bezirkskrankenhaus, Klinik für Psychiatrie und Psychotherapie: C. Mattern, G. Rauch; Darmstadt, Elisabethenstift: U. Vorbach, W. Beck, T. Bracher; Ingolstadt, Psychiatrische Klinik: M. Lemke, A. Kagerbauer; Lohr, Krankenhaus für Psychiatrie und Neurologie des Bezirks Unterfranken: G. Jungkunz, H. Eckrich, M. Frey, P. Grampp, H. Münzel, K. Reitzle; Muenchen, Psychiatrische Universitätsklinik: M. Soyka, C. Aichmüller, G. Kotter, H. Rothenhäusler, C. Schütz; Offenbach, Praxis Dr Klinger: P. Klinger, A. Sapok; Regensburg, Bezirksklinikum Regensburg, Psychiatrische Universitätsklinik: H. Fleischmann, C. Wenig, C. Schäfer, A. Kirschteuer; Stuttgart, Bürgerhospital: K.-L. Täschner, J. Fischer, A. Menges; Werneck, Krankenhaus für Psychiatrie und Psychotherapie des Bezirks Unterfranken: H. Jansen, G. Zöller; Wuerzburg, Psychiatrische Universitätsklinik: J. Boening, N. Wodarz, C. Mauerer, M. Oelschläger, T. Kraus, G. A. Wiesbeck.

symptoms occurred in others after smoking cocaine again (Gawin *et al*., 1996). Preliminary results were also reported regarding the successful use of flupenthixol in schizophrenic cocaine users (Levin *et al*., 1998). However, studies were small and some were negative.

Based on the somewhat encouraging findings in cocaine users, our clinical study was initiated to elucidate the effectiveness of flupenthixol in alcohol dependence. Our hypothesis was that flupenthixol would be more effective than placebo in preventing relapse in abstinent alcoholics.

SUBJECTS AND METHODS

Patients

After written informed consent, 281 patients, women (n = 77; 27.4%) and men (n = 204; 72.6%) between the ages of 22 and 55 years, were enrolled through 13 alcohol treatment centres across Germany and Austria. Patients had to fulfil at least six DSM-III-R criteria (303.90) for moderate or severe alcohol dependence ascertained by clinical interview (American Psychiatric Association, 1987). Additionally, they had to reach a score of ≥11 according to the Munich Alcoholism Test (Feuerlein *et al*., 1980). The severity of the alcohol-dependence syndrome was rated with the 'Goettinger Dependence Scale' (GABS; Jacobi *et al*., 1987), which is the German version of the 'Severity of Alcohol Dependence Questionnaire' (SADQ; Stockwell *et al*., 1979). Further requirements were complete abstinence from alcohol consumption and any pharmacotherapy (as assessed by repetitive controls of liver enzymes, breath-alcohol analyses, and urine tests) for a minimum of 14 days and a maximum of 42 days and the absence of any withdrawal symptoms verified by a weighted score of <2 on the Withdrawal Syndrome Scale for alcohol and related psychoactive drugs (Bech *et al*., 1989). Co-morbidity (depression, anxiety) at the time of inclusion was controlled for by defining cut-off scores on the Hamilton Depression Rating Scale (HAMD score >18) (Hamilton, 1960) and on the Hamilton Anxiety Rating Scale (HAMA score >16) (Hamilton, 1959) as exclusion criteria. Further conditions for participation were: a negative urine test for psychoactive drugs, the absence of severe neurological and medical disorders, no psychiatric disorder requiring psychotropic medication or hospitalization, and the intention to remain abstinent.

Study design

This study was conducted between June 1994 and March 1998. It was designed as a prospective, randomized, double-blind, placebo-controlled, bi-national multi-centre trial. A difference in relapse rates between 70% in the placebo group and 50% in the flupenthixol group was regarded as clinically relevant. To confirm this difference with a type I error of alpha = 0.05 and a type II error of beta = 0.10, a total number of at least 268 patients (134 patients in each treatment group) was projected as estimated from *a priori* sample size calculations. Thirteen alcohol treatment centres in Austria and Germany participated. Each centre's ethics committee approved the protocol and consent procedures of the study which was conducted in accordance with the European Good Clinical Practice Guidelines and the current version of the Declaration of Helsinki.

Procedures

Patients were randomly assigned to either 10 mg flupenthixol decanoate or placebo, both applied every second week in identical forms as an i.m. injection, over a period of 6 months (treatment phase), succeeded by a medication-free 6-month follow-up period. Treatment practices in all centres were similar. Patients received supportive psychotherapy through either individual and/or group therapy, as appropiate to clinical need. Participation in self-help support groups, such as Alcoholics Anonymous, was recommended. The patients were seen by their investigator every second week during the first 6 months. Every 4 weeks a physical examination, venepuncture (for liver function tests, red and white blood cell counts, and prothrombin time) and extensive ratings were performed. During the medication-free second part of the trial (6-month follow-up period), visits took place every eighth week. When patients missed a visit or dropped out, they or their family were contacted to obtain reasons for absence. They were deemed to have relapsed for the missed visit (the worst-case scenario presumed for missing data).

Outcome measures related to efficacy and safety

Outcome variables were based on absolute abstinence, which was defined as no alcohol consumption. To be considered abstinent, the patient's self-report had to be in accordance with the investigator's clinical assessment and the result of a breath analyser. Additionally, relapse was recorded in spite of a patient's self-reported abstinence if his liver enzyme parameters increased over baseline [≥40% increase in γ-glutamyltransferase (GGT) or ≥60% increase in alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) values over baseline] according to the method of Irwin *et al*. (1988). Relapse did not necessarily lead to exclusion from the study unless it occurred as heavy drinking [i.e. the patient was not able to attend his scheduled follow-up appointment due to intoxication or if he revealed a breath alcohol concentration of ≥1‰ (100 mg/dl)] at a visit. The severity of relapses was rated by a physician as 'with' or 'without loss of control'.

The number of patients relapsed (i.e. consumed any alcohol) after 6 months of treatment was the primary parameter of efficacy. Secondary criteria were as follows: time to first relapse; relapse rate after 12 months; cumulative abstinence duration; changes in craving as assessed by a 100-mm visual analogue scale (VAS) that ranged from no desire (0) to an uncontrollable desire (100); changes in social functioning assessed by the Social Functioning Questionnaire (SFQ; Tyrer, 1990). All adverse events (AE) were categorized and documented according to the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guidelines for Clinical Safety Data Managements.

Statistical analysis

This trial was designed as a prospective study with a confirmatory statistical evaluation. The main analysis used was an intention-to-treat (ITT), procedure including any randomized patients who received at least one injection of the trial medication (Lehert, 1993). A per-protocol analysis was also performed including all patients without any major protocol violation. Missing data on abstinence were interpreted as relapse (worst-case scenario). The main comparisons of efficacy

were between the flupenthixol and the placebo groups. Cross-tabulations of drinking behaviour (abstinence/relapse) were tested by Fisher's exact test. Time-to-first drink (relapse) was analysed by the life-table method of Kaplan-Meier (survival analysis), censoring missing data (log rank test; Lee, 1980). All results were interpreted at the two-tailed 5% significance level.

RESULTS

Characteristics of the patients

A total of 281 patients received either flupenthixol ($n = 142$) or placebo ($n = 139$). Of these 281 patients (ITT), 244 entered the per-protocol analysis. The flupenthixol and the placebo group were well matched, since they did not differ significantly in sex, age, body weight, and a variety of variables characterizing drinking behaviour and the alcohol-dependence syndrome (Table 1).

Of 281 patients enrolled, 91 (32.4%) completed the trial (6 months treatment, 6 months follow-up). One hundred and nine patients who were receiving flupenthixol (76.8%) and 81 patients being treated with placebo (50.3%) were withdrawn ($\chi^2 = 19.1$; df = 1; $P < 0.0001$). However, for seven out of eight recorded reasons for drop-out, the difference between the two treatment groups was not statistically significant (Table 2). 'Relapse' was the only reason why flupenthixol-treated patients (24.7%) and placebo-treated patients (14.4%) differed significantly.

Table 1. Main features of the trial sample

Parameter	Flupenthixol ($n = 142$)	Placebo ($n = 139$)
Male: no. (%)	107 (75)	97 (70)
Female: no. (%)	35 (25)	42 (30)
Age (years)	41.7 (8.0)	41.8 (7.7)
Body weight (kg)	75.3 (14.3)	73.5 (12.9)
DSM-III-R criteria for dependence	8.0 (1.0)	8.1 (1.0)
Munich Alcoholism Test, MALT (score)	33.3 (6.0)	33.6 (5.6)
Goettinger Dependence Scale, GABS (score)	58.4 (17.3)	57.5 (18.4)
Mean corpuscular volume, MCV (fl)	94.1 (5.67)	94.7 (5.24)
γ-Glutamyltransferase (GGT) (IU/l)	65.8 (82.8)	47.9 (57.1)
Alcohol intake before detoxification (g/day)	257 (136)	263 (168)
Craving (VAS) (mm)	14.3 (21.2)	13.1 (22.4)
Social functioning (SFQ) (score)	14.7 (3.9)	14.9 (3.9)

Values are means ± SD, unless stated otherwise. Differences between groups were not significant.
VAS, visual analogue scale.

Efficacy

After 6 months of treatment, more flupenthixol-medicated than placebo-treated patients had relapsed. The difference proved highly significant in both worst-case ITT analysis (i.e. cases not retrievable were counted as relapse) and ITT analysis which took only documented relapses into consideration. The difference between the two groups remained highly significant until the end of the 12-month trial (Fig. 1). The per-protocol (PP) analysis revealed similar results: during 6 months of treatment 97/126 (77.0%) patients in the flupenthixol group and 69/118 (58.5%) patients in the placebo group relapsed ($P \leq 0.002$; Fisher's exact probability test). At the end of the 12 months treatment, only 34 (23.9%) flupenthixol-treated patients, compared with 58 (41.7%) placebo-treated patients, had been continuously abstinent (worst case analysis; $P = 0.002$). The survival curve is shown in Fig. 2.

During the first 6 months, the mean time to first relapse, a secondary outcome measure, was 48 ± 39 days for patients on flupenthixol and 48 ± 40 days for patients on placebo, respectively (Fig. 3).

Since the above parameters do not reflect abstinent periods after a first relapse, the total number of abstinent days was calculated as the 'cumulative abstinence duration' (CAD). During the first 6 months of treatment, the mean (± SD) CAD in the flupenthixol-treated group was 100 ± 62 days or 56% days abstinent. This was significantly less than 122 ± 66 days or 67% days abstinent in the placebo-treated group ($P = 0.0015$; Wilcoxon test). 'Loss of control' occurred in 33/101 (32.7%) of flupenthixol-treated patients compared to 19/75 (25.3%) of placebo-treated participants. This difference did not reach statistical significance ($\chi^2 = 1.14$; df = 1; $P = 0.32$).

Other outcome measures

Craving (VAS scores) decreased over time in placebo-treated patients independently of whether they relapsed or not,

Table 2. Reasons for drop-out

Termination status	No. (%) of patients: Flupenthixol	Placebo	Statistical comparison (χ^2)
Main reason for early termination			
Severe relapse	35 (24.7)	20 (14.4)	$P < 0.001$
Non-compliance	21(14.8)	23 (16.5)	n.s.
Deterioration of health	18 (12.7)	11 (7.9)	n.s.
No reason documented	12 (8.5)	10 (7.2)	n.s.
Withdrawal of consent	11(7.7)	10 (7.2)	n.s.
Protocol violations	8 (5.6)	4 (2.8)	n.s.
Adverse clinical drug event	3(2.1)	2 (1.4)	n.s.
Abnormal laboratory values	1(0.7)	1 (0.7)	n.s.
Subtotal of drop-outs	109 (76.8)	81 (58.3)	$P < 0.00001$
Patients with normal termination	33 (33.2)	58 (41.7)	$P < 0.00001$
Total	142 (100)	139 (100)	

n.s., not significant.

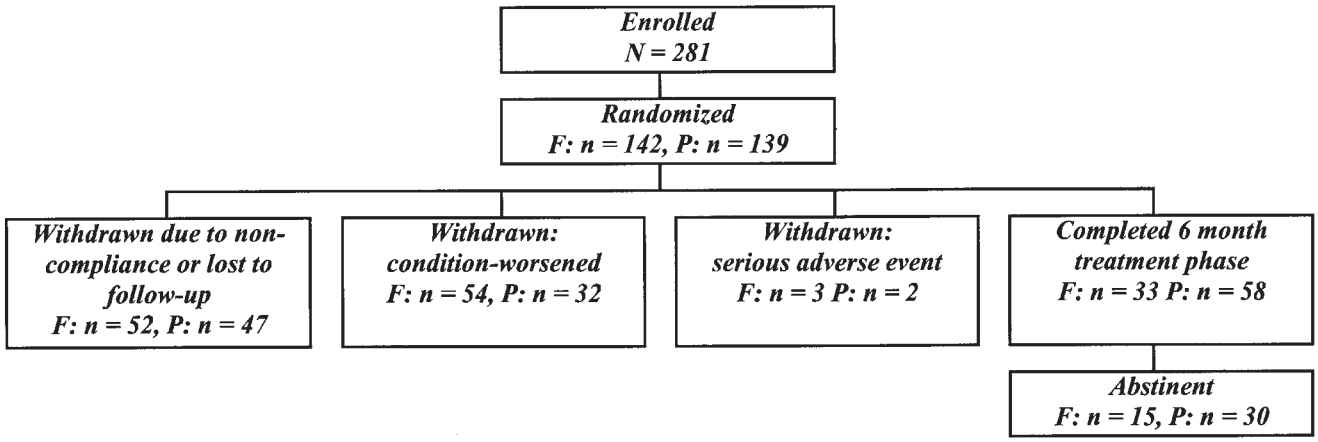

Fig. 1. Enrolment, randomization and follow-up in a controlled study of flupenthixol (F) versus placebo (P) for alcohol dependence.

but craving scores increased in those flupenthixol-treated subjects who relapsed. Therefore, data on craving were subjected to an ANOVA repeated measure model with 'group' (flupenthixol/placebo), 'outcome' (relapse/no relapse) and 'time' (at baseline/last value before relapse or premature termination or after 6 months) as factors. This ANOVA revealed significant effects for 'group' (df = 1; F = 4.56; P = 0.035) and 'time' (df = 1; F = 3.95; P = 0.049). The interaction for 'group × outcome × time' revealed a tendency but failed statistical significance (df = 1; F = 3.43; P = 0.067).

The same ANOVA procedure for the analysis of SFQ-scores revealed a significant main effect only for 'time' (df = 1; F = 9.67; P = 0.002): scores decreased between first and last rating (i.e. improvement of social functioning).

Logistic regression analysis

A logistic regression analysis was performed to calculate the effect of every main baseline feature (Table 1) on the primary parameter of efficacy (i.e. relapse rate after 6 months in a worst-case analysis). The model identified one variable, that is GGT, as having a statistically significant effect (P = 0.02) on outcome. To further check the relevance of this finding, we calculated an ANOVA with 'treatment' (flupenthixol vs placebo) and 'GGT' (dichotomized at the median) as factors and with 'relapse rate' being the dependent variable. This yielded a highly significant main effect for 'treatment group' (P < 0.001) but no significant main effect for GGT or for the interaction 'treatment × GGT'.

Adverse events

The total number of adverse events was less on flupenthixol (n = 211) than on placebo (n = 268). At least one adverse event was reported by 59 (41.5%) flupenthixol-treated patients and by 69 (49.6%) placebo-treated patients (χ^2 = 1.85; df = 1; P = 0.19). The most common adverse events were incidents of intercurrent diseases of minor severity or of non-specific complaints. Adverse events were rated according to their severity: 'serious' adverse events occurred in only four (2.8%) patients on flupenthixol (renal colic, suicide, abortion during the 12th week of unknown pregnancy, fracture of lower leg due to accident), but in six (4.3%) patients on placebo (suspected breast

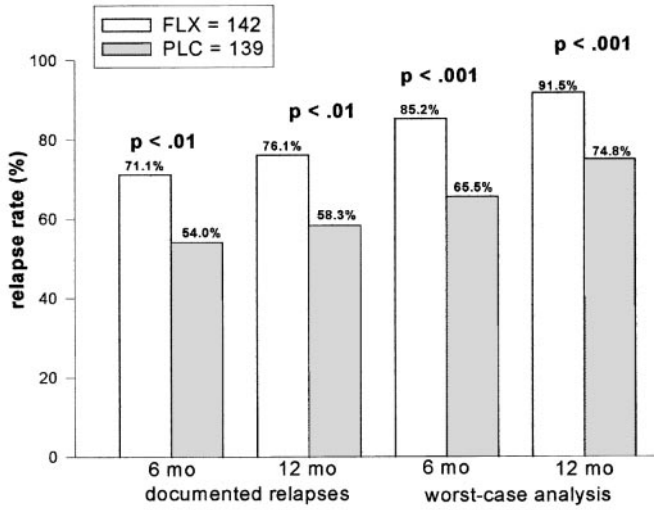

Fig. 2. Relapse rates (intention-to-treat analysis) after 6 and 12 months of treatment.
FLX, flupenthixol; PLC, placebo.

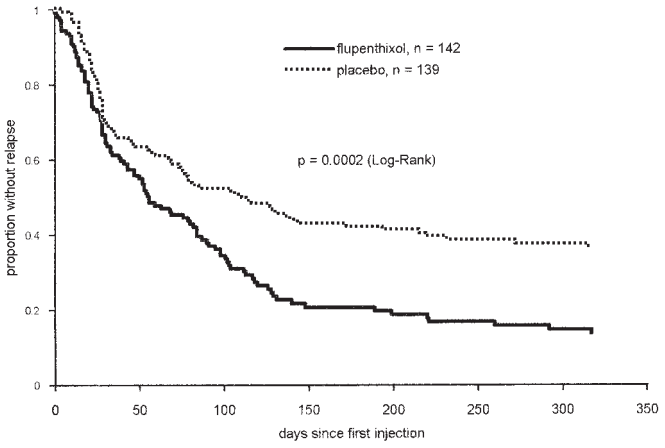

Fig. 3. Time to first relapse (Kaplan-Meier survival analysis).

cancer, adrenal cyst, attempted suicide, psychotic episode, removal of stent due to oesophageal stenosis, blood loss). One patient in the flupenthixol group committed suicide during the 6-month medication-free follow-up period. None of these serious events was assessed as causally related to the study drug. Adverse events as a reason for premature termination were reported in only three (2.1%) patients on flupenthixol and in two (1.4%) patients on placebo (Table 2).

DISCUSSION

We conducted a rigorous trial evaluating the effectiveness of a 10 mg dose of flupenthixol decanoate injection in preventing relapse in alcohol-dependent individuals. Previous studies focused on alcohol consumption in animals, on cocaine or drug dependent humans. They were retrospective, non-randomized, unblinded or just single-case reports. None of them had a prospective design. Therefore, to the best of our knowledge, there has been no study similar to ours so far.

The results of this trial did not support our originally formulated hypothesis. Since flupenthixol-medicated patients and placebo-treated patients were well matched in age, sex, alcohol consumption and severity of dependence, our data suggest that flupenthixol is able to significantly reduce an alcoholic's chance of remaining abstinent. Additionally, flupenthixol-treated patients revealed a 'cumulative abstinence duration' less than that of placebo-treated subjects, indicating that this medication does increase not only the number, but also the duration, of relapses, compared to placebo. Additional support for this interpretation is provided by the design of the study. Multi-centre trials like ours usually decrease the risk of bias in the selection of patients. Although such a biasing influence cannot be completely excluded, a tendency that favoured flupenthixol was observed in only one out of 13 centres. In other words, the negative effect of flupenthixol on abstinence maintenance did not depend on a few outliers, but was reflected by the data of almost every centre. However, in the two major centres with a combined total of 119 patients, the difference in the relapse rates between the treatment groups was pronounced, thus contributing substantially to the overall result.

For the sake of internal consistency, we checked the influence of every main baseline characteristic on outcome, finding that 'GGT' was the only parameter revealing a significant effect on relapse. Since GGT levels were higher (but not significantly) in the flupenthixol group, this may possibly indicate a tendency for alcoholism to be more severe in flupenthixol-treated patients, which might cause their worse outcome. However, this speculation was not supported by an ANOVA which revealed no effect of GGT on relapse independently of the treatment groups.

Flupenthixol decanoate given in a dosage of 10 mg every second week was well tolerated and safe. Both numbers and severity ratings of adverse events were higher, though not significantly, in the placebo-treated group; thus making it unlikely that flupenthixol-treated patients drank alcohol to cope with medication-related adverse effects. This is in accordance with the report of Gawin *et al*. (1989), who came to a similar conclusion regarding cocaine users.

Craving decreased over time in placebo-treated patients, independently of whether they relapsed or not, but craving scores increased in those flupenthixol-treated subjects who relapsed. Therefore, it seems justified to ask whether flupenthixol might be able to induce craving for alcohol — a speculation totally in contrast to our original hypothesis. The analysis of variance calculated to test this possibility revealed a tendency which did not statistically ($P < 0.10$) confirm this supposition. Nevertheless, it is well known that patients' characteristics may influence the outcome of pharmacological alcohol relapse prevention studies. It might be that certain types of alcohol dependence (see Lesch and Walter, 1996) are more susceptible to the apparent adverse effects of flupenthixol that we have demonstrated.

The results of the present trial are generally in line with those recently reported with other dopaminergic substances such as lisuride or bromocriptine (Naranjo *et al*., 1997; Schmidt *et al*., 1997). Thus, it seems that a modulation of dopaminergic pathways by dopamine D1 and/or D2 receptor agonists or antagonists has no beneficial effect on relapse prevention in alcohol dependence.

Results from an animal study, which were not available at the beginning of this trial, agree with our findings. Wolffgramm and Heyne (1995) developed a behaviour-dependent animal model for drug and alcohol addiction, in which the oral administration of flupenthixol (1 mg/kg/day) significantly increased voluntary alcohol intake in alcohol-dependent rats (J. Wolffgramm and A. Heyne, personal communication).

In conclusion, our trial demonstrated that abstinence in alcohol-dependent patients can be adversely affected by a pharmacological intervention, flupenthixol.

Acknowledgements — This study was sponsored by the Bayer Company, Leverkusen, Germany. The statistical analysis was performed by the 'Institut für numerische Statistik' (IFNS), Cologne, Germany. We are indebted to Claudio A. Naranjo, MD, University of Toronto, for his helpful comments in reviewing the manuscript.

REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. American Psychiatric Asssociation, Washington, DC.

Bech, P., Rasmussen, S., Dahl, A. and Lauritsen, B. (1989) The Withdrawal Syndrome Scale for alcohol and related psychoactive drugs: interobserver reliability and construct validity. *Nordisk Psykiatrisk Tidsskrift* **43**, 291–294.

Budde, G. (1992) Efficacy and tolerability of flupenthixol decanoate in the treatment of depression and psychosomatic disorders: A multicenter trial in fenoral practice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **16**, 677–689.

De Witte, P. (1996) The role of neurotransmitters in alcohol dependence: animal research. *Alcohol and Alcoholism* **31** (Suppl. 1), 13–16.

Duvauchelle, C. L., Levitin, M., MacConell, L. A., Lee, L. K. and Ettenberg, A. (1992) Opposite effects of prefrontal cortex and nucleus accumbens infusions of flupenthixol on stimulant-induced locomotion and brain stimulation reward. *Brain Research* **576**, 104–110.

Erickson, C. K. (1996) Review of neurotransmitters and their role in alcoholism treatment. *Alcohol and Alcoholism* **31** (Suppl 1), 5–11.

Feuerlein, W. and Kuefner, H. (1989) A prospective multicenter study on inpatient treatment for alcoholics: 15- and 48-months follow-up (Munich Evaluation for Alcoholism Treatment, MEAT). *European Archives of Psychiatry and Neurological Sciences* **239**, 144–157.

Feuerlein, W., Ringer, C., Kuefner, H. and Antons, K. (1980) Diagnosis of alcoholism: The Munich Alcoholism Test (MALT). In *Currents of Alcoholism*, Galanter, M. ed., vol. 7, pp. 137–147. Grune & Stratton, New York.

Garbutt, J. C., West, S. L., Carey, T. S., Lohr, K. N. and Crews, F. T. (1999) Pharmacological treatment of alcohol dependence — a review of the evidence. *Journal of the American Medical Association* **281**, 1318–1325.

Gawin, F. H., Allen, D. and Humblestone, B. (1989) Outpatient treatment of 'crack' cocaine smoking with flupenthixol decanoate: a preliminary report. *Archives of General Psychiatry* **46**, 322–325.

Gawin, F. H., Khalsa-Denison, M. E. and Jatlow, P. (1996) Flupentixol-induced aversion to crack cocaine. [Letter.] *New England Journal of Medicine* **334**, 1340–1341.

Glaser, T., Fassbender, M. and Mauler, F. (1998) Receptor binding of flupenthixol and other neuroleptics. PT06004, XXIst CINP Congress, Glasgow.

Hamilton, M. (1959) The assessment of anxiety states by rating. *British Journal of Medical Psychology* **32**, 50–55.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Hietela, J., West, C. and Syvalahti, E. (1994) Striatal D-2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. *Psychopharmacology* **116**, 285–290.

Irwin, M., Baird, S., Smith, T. L. and Schuckit, M. (1988) Use of laboratory tests to monitor heavy drinking by alcoholic men discharged from a treatment program. *American Journal of Psychiatry* **145**, 595–599.

Jacobi, C., Brand-Jacobi, J. and Marquardt, F. (1987) The 'Goettinger Abhaengigkeitsskala' (GABS). An instrument for the differential assessment of the severity of alcohol dependence. *Suchtgefahren* **33**, 23–26.

Khalsa, M. E., Jatlow, P. and Gawin, F. H. (1994) Flupenthixol and desipramine treatment of crack users: double-blind results. In *NIDA Research Monograph 141. CPDD Problems of Drug Dependence*, Department of Health and Human Services 438 (NIH publication no. 94–3749), Washington, DC.

King, G. R., Joyner, C. and Ellinwood, E. H., Jr (1994) Continuous or intermittent cocaine administration: effects of flupenthixol treatment during withdrawal. *Pharmacology, Biochemistry and Behavior* **49**, 883–889.

Lee, E. (1980) *Statistical Methods for Survival Data Analysis*, 2nd edn. John Wiley, New York.

Lehert, P. (1993) Review and discussion of statistical analysis of controlled clinical trials in alcoholism. *Alcohol and Alcoholism* **28** (Suppl. 2), 157–163.

Lesch, O. M. and Walter, H. (1996) Subtypes of alcoholism and their role in therapy. *Alcohol and Alcoholism* **31** (Suppl. 1), 63–67.

Lesch, O. M., Dietzel, M., Musalek, M., Walter, H. and Zeiler, K. (1989) The course of alcoholism. Long-term prognosis in different types. *Forensic Science International* **36**, 121–138.

Levin, F. R., Evans, S. M., Coomaraswammy, S., Collins, E. D., Regent, N. and Kleber, H. D. (1998) Flupenthixol treatment of cocaine abusers with schizophrenia: a pilot study. *American Journal of Drug Alcohol Abuse* **24**, 343–360.

Lewis, M. J. (1996) Alcohol reinforcement and neuropharmacological therapeutics. *Alcohol and Alcoholism* **31** (Suppl. 1), 17–25.

Mansbach, R. S., Jortani, S. A. and Balster, R. L. (1994) Antagonism of cocaine's reinforcing and discriminative stimulus effects by α-flupenthixol. *Experimental and Clinical Psychopharmacology* **2**, 3–12.

McBride, W. J. and Li, T.-K. (1998) Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. *Critical Reviews in Neurobiology* **12**, 339–369.

McBride, W. J., Chernet, E., Dyr, W., Lumeng, L. and Li, T.-K. (1993) Densities of dopamine D-2 receptors are reduced in CNS regions of alcohol-preferring P rats. *Alcohol* **10**, 387–390.

Naranjo, C. A., Dongier, M. and Bremner, K. E. (1997) Long-acting injectable bromocriptine does not reduce relapse in alcoholics. *Addiction* **92**, 969–978.

Negus, S. S., Mello, N. K., Lamas, X. and Mendelson, J. H. (1996) Acute and chronic effects of flupenthixol on the discriminative stimulus and reinforcing effect of cocaine in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics* **278**, 879–890.

Noble, E. P. (1996) Alcoholism and the dopaminergic system: a review. *Addiction Biology* **1**, 333–348.

Noble, E. P., Blum, K. T., Ritchie, T., Montgomery, A. and Sheridan, P. J. (1991) Allelic association of the D-2 dopamine receptor gene with receptor binding characteristics in alcoholism. *Archives of General Psychiatry* **48**, 648–654.

Project MATCH Research Group (1997) Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* **58**, 7–29.

Richardson, N. R., Smith, A. M. and Roberts, D. C. (1994) A single injection of either flupenthixol decanoate or haloperidol decanoate produces long-term changes in cocaine self-administration in rats. *Drugs and Alcohol Dependence* **36**, 23–25.

Robinson, T. E. and Berridge, K. C. (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews* **18**, 247–291.

Schilkrut, R., Cabrera, J., Morales, E. and Herrera, L. (1988) Neuroleptics in the treatment of drug dependence in schizophrenics. *Psychopharmacology* **96** (Suppl.), 342.

Schmidt, L. G., Kuhn, S. and Rommelspacher, H. (1997) Pharmacological effects of lisuride shorten expectations to receive the drug and prolong the latency of relapse in cleaned alcoholics. *Pharmacopsychiatry* **30**, 219.

Sinclair, J. D., Le, A. D. and Kiianmaa, K. (1989) The AA and ANA rat lines selected for differences in voluntary alcohol consumption. *Experientia* **45**, 798–805.

Soyka, M. and De Vry, J. (1998) Flupentixol in der Therapie bei Suchterkrankungen. In *Flupentixol — Typisches oder atypisches Wirkspektrum*, Glaser, T. and Soyka, M. eds, pp. 117–130. Steinkopff, Darmstadt.

Soyka, M. and Sand, P. (1995) Successful treatment with flupenthixol decanoate of a patient with both schizophrenia and alcoholism. *Pharmacopsychiatry* **28**, 64–65.

Stockwell, T., Hodgson, R., Edward, G., Taylor, C. and Rankin, H. (1979) The development of a questionnaire to measure severity of alcohol dependence. *British Journal of Addiction* **74**, 79–87.

Swift, R. M. (1999) Drug therapy for alcohol dependence. *New England Journal of Medicine* **340**, 1482–1490.

Tyrer, P. (1990) Personality disorder and social functioning. In *Measuring Human Problems, A Practical Guide*, Peck, D. F. and Shapiro, C. M. (eds), pp. 119–142. John Wiley, Chichester.

Wolffgramm, J. and Heyne, A. (1995) From controlled intake to loss of control: the irreversible development of drug addiction in the rat. *Behavioral Brain Research* **70**, 77–94.