hospitalised patients. Signs of increasing agitation must however be anticipated, and indicate prompt reassessment of the antidepressant treatment.

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Sirs,

Intermittent withdrawal program of neuroleptics with sulpiride in remitted schizophrenic outpatients

Long-term neuroleptic treatments are at high risk for neuroleptic-associated tardive syndromes. Furthermore, inadequate high dose treatment might prevent patients from returning to their former employment because of behavioral inactivity induced by neuroleptics. Consequently, there has been increasing interest in developing viable clinical management alternatives to long-term, high-dose neuroleptic drug maintenance and prophylaxis. One approach is the use of continuous medication at doses considerably below those traditionally viewed as therapeutic (Heresco-Levy *et al*., 1993). Others have attempted to reduce cumulative neuroleptic doses by administering medication only during episodes of symptom exacerbation (Herz *et al*., 1991). The present study was performed to explore the usefulness of a neuroleptic withdrawal program in remitted schizophrenics using gradual intermittent treatment with the selective D2 receptor blocker, sulpiride.

Forty-six remitted schizophrenic outpatients (their maintenance chlorpromazine equivalents: 265.6 ± 163.5 mg) were given gradual drug reduction and then switched to one tablet of sulpiride 200 mg/day at night. Twenty-two patients gave informed consent to participate in this intermittent neuroleptic withdrawal program (Trial group). Other patients continued to take sulpiride 200 mg/day (Continuous group). An abrupt withdrawal group (their maintenance chlorpromazine equivalents: 258.8 ± 186.2 mg) was used as a retrospective placebo group (Placebo group). Final number of patients on the Trial, Continuous and Placebo group was 19, 15 and 13, respectively. The three groups were virtually identical with respect to age and sex of the subjects, onset age, years after onset the disease, number of hospitalization and remission periods before the beginning of the trial (Table 1). The gradual intermittent withdrawal program consisted of five steps (drug intake every

Table 1. Background of Subjects. Values are expressed as the mean $\pm$ SD

	Number	Age	Sex		Onset age	Years after onset of the disease	Number of hospitalization	Remission period (years)
			Male	Female				
Trial group	19	42.3 ± 12.9	14	5	26.5 ± 9.7	15.7 ± 12.5	3.3 ± 3.1	3.0 ± 5.0
Continuous group	15	36.9 ± 12.3	11	4	24.8 ± 5.6	13.3 ± 8.7	2.5 ± 2.0	4.0 ± 5.6
Placebo group	13	39.4 ± 10.0	9	4	26.8 ± 6.9	13.9 ± 8.3	3.8 ± 2.4	7.7 ± 8.5

day; once every two days; once every three days; once every week and completely drug free) and each step lasted for six months. Serum prolactin levels in each patient were monitored in each step. Survival analyses for each treatment group were performed on the number of symptom-free days from the beginning of the trial until relapse symptoms appeared.

There was no significant difference in survival curves between the Trial group and the Continuous group analyzed over time with the generalized Wilcoxon test ($Z = 1.167$, $p > 0.05$). However a significant difference was obtained with the Kaplan–Meier test over 750 days ($p < 0.05$). At this time point, the relapse rate was 60.0% in the Continuous group and 89.2% in the Trial group. The Trial group exhibited significantly greater prophylaxis than the Placebo group analyzed over time with the generalized Wilcoxon test ($Z = 13.473$, $p < 0.01$). Moreover, a significant difference was obtained with the Kaplan–Meier test over 12 days ($p < 0.05$), and over 24 days ($p < 0.01$). Consequently, the intermittent withdrawal program with sulpiride was superior to an abrupt withdrawal of neuroleptics. Gradual intermittent treatment with sulpiride is a useful strategy for discontinuation of neuroleptics in remitted schizophrenic outpatients and intermittent treatment once every 3 days maintained dopaminergic inhibition of prolactin levels.

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Sirs,

Reduced expression of interleukin-6 receptor mRNA in the hypothalamus of restrained rat

Recent evidence indicates that neuronal and glial cells can synthesize interleukin-6 (IL-6) and contain IL-6 receptors (IL-6R). In addition, IL-6 may act as a neurotrophic factor (Maeda *et al*., 1994) and also stimulate adrenocorticotrophic hormone secretion (Akira *et al*., 1990). By means of a sensitive reverse transciptase-polymerase chain reaction (RT-PCR) technique, we investigated the expression of the IL-6R message in the hypothalamus of rats under stressful conditions.

Eight male Wistar rats (12–14 weeks old) were divided into two groups. One group ($n = 4$) acted as controls and the other ($n = 4$) was restrained by wrapping them in wire gauze for 4 h (09·00–13·00 h). The experimental rats and their controls were decapitated at the same time after the restraint stress. The hypothalami were dissected and frozen at −80°C. Total RNA in the hypothalamus was extracted according to the method of Chomczynski and Sacchi (1987).

The mRNA levels of IL-6R and glyceraldehyde 3-phosphate dehydrogenase (G3PDH) were determined by a semiquantitative RT-PCR method (Murphy *et al*., 1990). The PCR products were separated on polyacrylamide gel and analysed using electronic autoradiography (InstantImager, Packard, Meriden). The band intensity of IL-6R cDNA was compared with the band intensity of G3PDH and the results were expressed as the ratio to G3PDH.

The IL-6R message in the hypothalamus was significantly decreased in the restrained rats ($0{\cdot}566 \pm 0{\cdot}12$; mean ± standard error) compared with the control ($1{\cdot}000 \pm 0{\cdot}068$). Exposure to stress may induce the synthesis and release of IL-6 and as a result IL-6R may be downregulated, although to validate this the quantities of IL-6 should be measured.

Such changes in IL-6R may be related to the neuroendocrine changes in response to severe