Flesinoxan was well tolerated. The incidence of treatment-emergent adverse events with the 0.4 mg/day dose was comparable to that with placebo (46% vs 47%); doses of 1.2 and 4.0 mg/day were associated with an increasing incidence of adverse events (53% and 59%, respectively). Most frequently reported side effects that were more frequent than placebo were dizziness and nausea, especially at the highest dose.

The highest incidence of adverse events occurred with imipramine (79%), whilst the incidence with alprazolam (45%) was similar to that reported with flesinoxan 0.4 mg and placebo. The incidence of withdrawals due to adverse events with flesinoxan 0.4 mg (3%) and 1.2 mg (4%) was similar to that with placebo (4%). Serious adverse events occurred in 9, 5, 6 and 5 patients given placebo or flesinoxan 0.4, 1.2 or 4.0 mg, respectively. Flesinoxan had no effect on vital signs or laboratory parameters.

In conclusion, flesinoxan is well tolerated at doses of up to 4.0 mg/day in patients with major depressive disorder or GAD.

P.5.014 Pharmacological treatment of social phobia: A controlled study with alprozolam and buspirone

V.I. Krylov. *Department of Psychiatry, Pavlov Medical University, Obvodnoy Chanal 13, St. Petersburg, Russia*

In a double-blind, parallel group trial, 66 subjects with social phobia received alprozolam, buspiron, or placebo. After 8 weeks, both active drugs were clinically statistically significantly more effective than placebo, as assessed by rating scales. There was some further improvement between weeks 8 and 12, particularly in alprozolam group: at weeks 12, 72.7% of the alprozalam and 63.3% of buspirone-treated patients were almoust asymptomatic. Patients withdrawn from active drugs had relapsed by week 24, providing additional support for the efficacy of the active drugs.

P.5.015 Flesinoxan treatment of Generalized Anxiety Disorder: A fixed dose, placebo-controlled trial

F. Noël, G. Stevens, D. Bradford. *Solvay Duphar B.V., Weesp, The Netherlands*

Flesinoxan, in three fixed doses, was compared with placebo and alprazolam in patients with Generalized Anxiety Disorder (DSM III-R criteria with the modification of a minimum two months duration of symptoms). The multi-center study was conducted in Germany in out-patients of at least moderate severity (score on HAM-A at baseline $\geq$ 18). Alprazolam was given in a daily dose of 1.5 mg (divided in three doses); flesinoxan was given in two divided daily doses (blinded by a placebo capsule for the midday dose) of 0.4, 1.2 and 4.0 mg daily. The study design consisted of a 1-week single-blind placebo run-in phase, a 4-week treatment period and a 1-week taper-off phase. During the first week of the double-blind treatment phase, the two highest doses of flesinoxan and alprazolam were tapered on. During the taper-off phase, all flesinoxan treatment patients received (double-blind) placebo, and alprazolam was tapered off over 5 days.

A total of 393 patients were entered into the double-blind phase. Although the six-month duration criterion of the DSM III-R was not a requirement for entrance to the study, 75% of the patients had been ill longer than 6 months. In total, 54 (14%) of the patients terminated treatment early.

Of the treatment arms, 0.4 mg and 1.2 mg flesinoxan and alprazolam were statistically and clinically superior to placebo. Alprazolam showed a typical response of an early onset of action by Day 7, but by Day 14 treatment with flesinoxan showed effects on important key symptoms, and was not different from alprazolam by the end of the trial. The final assessment showed a rapid return of symptoms in the alprazolam group, while the flesinoxan-treated groups maintained the amelioration of symptoms attained during the treatment period. Although a dose-response relationship for flesinoxan was not evident in the efficacy results, the tolerance to the drug was clearly dose related. The most common signs and symptoms reported were headache and dizziness (flesinoxan) and somnolence (alprazolam).

In conclusion, flesinoxan is effective and safe in patients with GAD in the dose range of 0.4–1.2 mg/day.

P.5.016 Correlates and course of irritability and disinhibition during alprazolam treatment of panic disorder

Vladan Starcevic, Katarina Kelin. *Institute of Mental Health, Palmoticeva 37, 11000 Belgrade, Yugoslavia*

The purpose of this study was to examine demographic and clinical correlates and course of irritability and/or disinhibition (defined as poor control over aggressive impulses in a person who did not exhibit such behaviour previously) in a sample of panic disorder (PD) patients during their short-term treatment with alprazolam.

The study was conducted in 57 PD patients (36 women, 21 men) who were treated with alprazolam (mean dose = 3.8 mg/day) for 8 weeks. The Structured Clinical Interview for DSM-III-R (SCID) was used for the purpose of diagnosing PD and comorbid psychiatric disorders. The Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and Tridimensional Personality Questionnaire (TPQ) were used in order to make personality disorder diagnoses and examine relevant personality dimensions. The patients' condition was assessed weekly by the means of the panic diary, self-report instruments and clinician-rated scales, including the Clinical Global Impressions (CGI) Scale and CGI-Change Scale.

Twenty-six (45.6%) patients exhibited irritability and/or disinhibition during treatment. PD patients who developed this side effect differed significantly from those who did not, in the following: they were more often men (57.7% vs. 19.4%), younger (mean age of 28.6 years vs. 37.9 years), less often married (38.5% vs. 77.4%), more often had a history of alcohol abuse (53.8% vs. 12.9%), and scored higher on the novelty seeking scale of the TPQ (21.6 vs. 14.2). The two groups did not differ significantly in terms of the associated personality disorder diagnoses.

As for 26 patients with irritability and/or disinhibition, the following was noted in terms of the course of this side effect: it first appeared during the first four weeks of treatment (that is, during the dose escalation) in 21 (80.8%) patients, and lasted for a mean of 4.4 weeks. The course of irritability and/or disinhibition was continuous in 24 (92.3%) patients, its greatest intensity was judged as severe in 7 (26.9%) and moderate in 13 (50%) patients, and it interfered significantly with functioning in 17 (65.4%) patients. Alprazolam had to be discontinued in 2 (7.7%) patients, and the dose reduced in 9 (34.6%) patients, mainly because of this side effect. Despite this, 20 (76.9%) patients with irritability and/or disinhibition (vs. 25 [80.6%] of patients without irritability and/or disinhibition) were rated as much improved or very much improved on the CGI-Change Scale after 8 weeks of treatment.

Although most patients may be willing to tolerate irritability and/or disinhibition, and although this side effect may not ultimately diminish the therapeutic effect of alprazolam, social dysfunction caused by it can be serious. Hence, risks and benefits of alprazolam treatment should be carefully weighed in patients who may be likely to develop irritability and/or disinhibition, especially in those with a history of alcohol abuse.

References

[1] O'Sullivan G.H., Noshirvani H., Basoglu M., et al. (1994) Safety and side-effects of alprazolam: controlled study in agoraphobia with panic disorder. British Journal of Psychiatry 165, 79–86.

[2] Rosenbaum J.F., Woods S.W., Groves J.E., et al. (1984) Emergence of hostility during alprazolam treatment. American Journal of Psychiatry 141, 792–793.

P.5.017 Fluvoxamine for children and adolescents with Obsessive Compulsive Disorder: A controlled multicenter trial

Mark A. Riddle [1], J. Claghorn [2], G. Gaffney [2], J. Greist [2], D. Holland [2], R. Landbloom [2], B. McConville [2], T. Piggott [2], M. Pravetz [2], J. Walkup [1], Yaryura-Tobias [2], V. Houser [3]. [1] *Division of Child and Adolescent Psychiatry, Johns Hopkins Medical Institutions, Baltimore, MD 21056;* [2] *Solvay Pediatric OCD Research Group, Marietta, GA 30062; Solvay Pharmaceuticals, Marietta, GA 30062*

Introduction: Over the past decade there has been an emerging clinical literature supporting the efficacy of both pharmacological and behavioral treatments for children and adolescents with OCD, but few of the trials have been controlled. Fluvoxamine, a monocyclic SSRI, has been ex-

tensively studied throughout the world for the treatment of adults with depression, panic disorder and OCD.. The purpose of the study is to evaluate the effects of fluvoxamine in children and adolescents with OCD in a controlled, multicenter treatment trial.

Methods: Subjects 8–17 years old with a minimum six month history of OCD (DSM-IIIR) were recruited at 17 investigative sites throughout the United States. Exclusion criteria included significant medical or psychiatric co-morbidity, or a past history of not responding to an adequate trial of another serotonin reuptake inhibitor. A 7–14 day single-blind, placebo washout/screening period occurred prior to randomization. To be randomized subjects were required to have a baseline score $\geq$ 15 on the 10-item Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and $\geq$ 7 on the NIMH Global Obsessive Compulsive Scale. Subjects who had not responded by week 6 of the 10 week trial could terminate the double-blind portion of the study and enter a long-term open trial of fluvoxamine. Outcome comparison of fluvoxamine vs. placebo used the intent-to-treat, last-observation-carried-forward method of analysis.

Results: Of the 120 subjects randomized, 74 subjects (38 fluvoxamine, 36 placebo) completed the 10-week trial. The fluvoxamine and placebo groups were similar demographically. Each group had nearly equal number of boys and girls. About a third of the subjects had been on other medicines. Very few subjects had other co-morbid conditions. Most of the 44 subjects who terminated early, (22 placebo, 9 fluvoxamine) did so due to lack of improvement at week 6. Only 4 subjects (3 fluvoxamine, 1 placebo) discontinued due to side effects, none of which were considered serious; 9 subjects discontinued for "other" reasons. The primary efficacy variable, CY-BOCS, showed significant differences from placebo (N = 120; $p < 0.05$) for the intent-to-treat, last-observation-carried-forward analysis at weeks 1–6 and week 10, with a trend toward significance at week 8. This finding was also supported by significant differences in the 3 secondary outcome measures. Side effects more common on fluvoxamine included insomnia, agitation, hyperkinesia, somnolence and dyspepsia. There were no clinically significant changes in laboratory or EKG parameters during short-term fluvoxamine treatment.

Conclusions: Fluvoxamine is rapidly effective and appears safe for the short-term treatment of OCD in children and adolescents as young as age 8. Improvement in OCD symptoms were uniformly identified by clinicians, parents as well as the children. The design, subjects and results of this study will be compared with those of other published, controlled, medication trials for OCD in children and adolescents.

References

[1] De Veaugh-Geiss J, Moroz G, Biederman J et al.: Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder – a multicenter trial. J Am Acad Child Adolesc Psychiatry 1992, 31 (1), 45–49.

[2] Riddle MA, Scahill L, King R et al.: Double-blind crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 1992, 31 (6), 1062–1069.

P.5.018 Discrimination between the 5-HT$_1$ receptor agonists flesinoxan and eltoprazine

J. Gommans [1], T.H. Hijzen [1], R.A. Maes [2], B. Olivier [1]. [1] *Department of Psychopharmacology, Faculty of Pharmacy, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands;* [2] *Department of Toxicology, Faculty of Pharmacy, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands*

Flesinoxan and eltoprazine bind with high affinity to 5-HT$_1$ receptors, flesinoxan in particular to 5-HT$_{1A}$ receptors, and eltoprazine to 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors. In previous operant, two lever, drug-vehicle discrimination experiments, flesinoxan and eltoprazine partially cross-generalized to each other (59.9% and 49.4% respectively). The flesinoxan cue could be antagonized by the specific 5-HT$_{1A}$ receptor antagonist WAY-100635. The eltoprazine cue could not (Gommans et al., 1995; Gommans et al., submitted). Thus, despite the fact that there is considerable overlap between the mechanism of action of the two drugs, there are also salient differences. Therefore we investigated whether rats could learn to discriminate between flesinoxan and eltoprazine.

Rats were trained to discriminate flesinoxan (1.0 mg/kg p.o.) from eltoprazine (1.5 mg/kg p.o.), using a two lever operant procedure with a FR 10 schedule of reinforcement. All rats learned the discrimination readily. Saline administration resulted in approximately 50% lever presses on both levers; response rates were reduced and the latency to initiate lever pressing was increased. This indicates that the saline "cue" (or lack there of) is incompatable with both training cues. Dose response curves were obtained with both training drugs, the prototypical 5-HT$_{1A}$ receptor agonist 8-OH-DPAT, the 5-HT$_{1B}$ receptor agonist anpirtoline, and the 5-HT$_{2A/2C}$ receptor antagonist mianserin. Flesinoxan (dose range tested: 0.125–1.5 mg/kg p.o.) and 8-OH-DPAT (0.01–0.1 mg/kg s.c.) substituted completely for flesinoxan. Eltoprazine (0.125–1.5 mg/kg) and anpirtoline (0.063–0.25 mg/kg s.c.) substituted completely for eltoprazine. These results show that the cue of flesinoxan is mediated by activation of 5-HT$_{1A}$ receptors and the cue of eltoprazine by activation of 5-HT$_{1B}$ receptors. Mianserin (1.0–12.0 mg/kg p.o.) yielded no more than 65% lever presses on either lever, i.e. was more comparable to saline than to one of the training drugs.

We conclude that rats can easily learn to discriminate between the 5-HT receptor agonists flesinoxan and eltoprazine, and that the cues are mediated by 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors respectively.

References

Gommans, J., Hijzen, T.H., Maes, R.A., Mos, J. and Olivier, B. (1995) Discriminative stimulus properties of flesinoxan: effects of enantiomers, (S)-UH301 and WAY-100635. Eur. J. Pharmacol. 284, 135–140.

Gommans, J., Hijzen, T.H., Maes, R.A and Olivier, B. Discriminative stimulus properties of eltoprazine. Submitted.

P.5.019 Anxiolytic effects found in the fear-potentiated startle response paradigm are not due to a non-specific disruption of startle behavior

R.J.E. Joordens, T.H. Hijzen, B. Olivier. *Department of Psychopharmacology, Faculty of Pharmacy, Rudolf Magnus Institute of Neurosciences, Utrecht University, Sorbonnelaan 16, 3584 CA, Utrecht, NL*

The startle response can be augmented by presenting the startle-eliciting noise in the presence of a stimulus that has previously been paired with an electric shock. The augmented startle response is called fear-potentiated startle response (FPS) and is considered to be a measure of a central state of fear (Davis et al. 1993). Clinically effective anxiolytic drugs usually reduce FPS, while anxiogenic drugs increase FPS (Davis et al. 1993, Hijzen et al. 1995). The startle response can also be potentiated by a strychnine injection (SPS). Because no fear-conditioning takes place in SPS, no central state of fear exists. When anxiolytic drugs reduce FPS, but not SPS, the decrease in FPS after anxiolytic drugs can be attributed to the anxiolytic properties of the drug.

In this study, the effects of the anxiolytic benzodiazepine alprazolam, the (putative) anxiolytic 5-HT$_{1A}$ receptor agonist flesinoxan and the anti-psychotic D$_2$ receptor antagonist haloperidol on both the FPS and the SPS were investigated. Both fear-conditioning and strychnine injection significantly potentiate the startle response (see table 1: main effect Potentiation). As expected, the anxiolytic drugs alprazolam and flesinoxan dose-dependently reduce FPS without affecting SPS (see table 1: Potentiation $\times$ Dose interaction effect). On the other hand, the neuroleptic drug haloperidol is supposed to exert no effect on FPS, although anxiolytic effects of haloperidol have occasionally been reported.

The findings of this study suggest that the dose-dependent reduction of the fear-potentiated startle response can be attributed to the anxiolytic properties of drugs and does not reflect a "non-specific" disruption of startle behavior.

Table 1: Summary of the main effects and interaction effect of alprazolam (ip), flesinoxan (po) and haloperidol (ip) on the FPS and SPS (* $P < 0.05$).

	Drug (dose in mg/kg)	Main effect Potentiation	Main effect Dose	Potentiation $\times$ Dose
FPS	Alprazolam (0, 1, 2, 3)	$F(1, 11) = 41.4^*$	$F(3, 9) = 20.9^*$	$F(3, 9) = 10.4^*$
	Flesinoxan (0, 1, 3, 10)	$F(1, 11) = 33.2^*$	$F(3, 9) = 1.9$	$F(3, 9) = 10.3^*$
	Haloperidol (0, 0.06, 0.12, 0.24)	$F(1, 11) = 44.3^*$	$F(3, 9) = 14.1^*$	$F(3, 9) = 8.2^*$
SPS	Alprazolam (0, 1.5, 3)	$F(1, 11) = 33.8^*$	$F(2, 10) = 14.4^*$	$F(2, 10) = 0.6$
	Flesinoxan (0, 10)	$F(1, 22) = 7.0^*$	$F(1, 22) = 0.0$	$F(1, 22) = 0.6$
	Haloperidol (0, 0.08, 0.24)	$F(1, 11) = 21.5^*$	$F(2, 10) = 3.2$	$F(2, 10) = 0.6$