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Letters to the editor

Venlafaxine–clomipramine combination

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Venlafaxine was combined with clomipramine in two patients: while the first one presented severe side effects suggesting a metabolic interaction, the second one presented no side effects and no metabolic interaction between venlafaxine and clomipramine.

A 24-year-old man suffered a 6-year history of panic disorder, social phobia, obsessive-compulsive disorder, and recurrent major depressive disorder. He was treated with clomipramine (300 mg/day) for three months, with moderate improvement. He had sexual difficulties, and anticholinergic effects of moderate severity: dysuria, dry mouth, and constipation. Clomipramine was reduced to 150 mg/day, and augmented with sertraline (50 mg/day), and later with citalopram (20 mg/day). He did not improve further, but anticholinergic effects were mild and tolerable. Clomipramine (150 mg/day) was later augmented with venlafaxine (300 mg/day) for two months. The clinical picture remained stable, but the patient suffered more severe anticholinergic side effects than with clomipramine monotherapy at 300 mg/day (dysuria, dry mouth, and constipation). In addition, tremor of the hands developed. Venlafaxine was discontinued, and clomipramine (75 mg/day) was continued. Anticholinergic side effects improved significantly during the following two weeks.

A 70-year-old woman suffered from a psychotic depression and a systemic lupus erythematosus (SLE). SLE had caused mild renal impairment, and for many months it had been treated with methylprednisolone 4 mg/day, hydroxychloroquine 200 mg/day, and ticlopidine 500 mg/day. After many psychopharmacological trials, the psychotic depression finally improved with a combination of venlafaxine 225 mg/day, clomipramine 125 mg/day, alprazolam 0.5 mg/day, valproate 400 mg/day, and haloperidol 0.3 mg/day.

After two months on this combination without side effects, clomipramine plus desmethylclomipramine serum level (assessed at 7.30 a.m. with a Fluorescent Polarized Immune Assay) resulted 167 ng/ml. Then, venlafaxine was discontinued in a week, whereas the other psychoactive drugs were kept at the same doses. Eight days after venlafaxine discontinuation, clomipramine plus desmethylclomipramine serum level (reassessed at 7.30 a.m.) resulted 179 ng/ml.

The anticholinergic side effects reported by the first patient were more severe with the clomipramine (150 mg/day) – venlafaxine (300 mg/day) combination than with clomipramine alone at 300 mg/day. Since venlafaxine has negligible anticholinergic effects (Baldessarini 1996), their worsening with the addition of venlafaxine to clomipramine could have been the result of a metabolic interaction (but no serum clomipramine level was available).

In the second patient, clomipramine serum levels did not change on and off venlafaxine. Clomipramine has multiple metabolic pathways (cytochromes P450 1A2, 2C, 2D6, 3A4) (Nemeroff et al 1996; Ereshefsky 1996) If venlafaxine had metabolically inhibited clomipramine, clomipramine level would have fallen after its discontinuation, because venlafaxine and its active metabolite were not present during the second assessment of clomipramine level, due to their short elimination half-lives (Physicians' Desk Reference 1996; Preskorn 1993). In vitro studies have shown that venlafaxine has low to minimal inhibitory effects on the metabolism of substrates of cytochromes P450 1A2, 2C, 2D6, and 3A (Nemeroff et al 1996; Preskorn 1996). A few in vivo studies have shown a weak inhibitory effect on P450 2D6, and no effects on P450 3A (Ereshefsky 1996). In three recent case reports, the combination of venlafaxine with other psychoactive drugs was associated with severe side effects, suggesting significant inhibition of their metabolism by venlafaxine (Benazzi 1997; Benazzi submitted for publication, a; Benazzi submitted for publication, b). In vivo metabolic inhibitory potency of venlafaxine remains to be clarified. Variance between the first and the second patient's response to venlafaxine-clomipramine combination may be related to several factors: metabolizer status, dose of venlafaxine, associated drugs, age, sex, and sensitivity to side effects. A MEDLINE search did not find similar reports.

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Measurement of anhedonia: additional remarks

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D'haenen (1996) presents a useful review of the instruments developed to measure anhedonia and their psychometric properties. Moreover, the author used the Rash model to test the homogeneity and transferability of a Dutch translation of the Fawcett Clark Pleasure Capacity Scale (FCPCS). The results have shown that the original scale did not fit the model but that a 14-item subscale did. In this letter to the editor we would like first to present our work concerning the development of a short scale extracted from the FCPCS and second to quote some other pleasure scales not referred to in the D'haenen review.

Because we have found insufficient discriminant validity of the French version of the FCPCS (Loas et al, 1992) we have built up a shortened version of that scale containing 12 items assessing only sensorial and physical features of pleasure (Loas et al, 1994). We have shown that the subscale had satisfactory validity and reliability (Loas and Boyer, 1995). It is interesting to note that six items out of our 12-item subscale are common with the 14-item subscale proposed by D'haenen (1996).

Moreover, there are three other pleasure scales which have satisfactory validity and fidelity. In 1984, Dworkin and Saczynski described the development and validation of three scales rating hedonic capacity. One scale consisted of 33 Minnesota Multiphasic Personality Inventory (MMPI) items, a second consisted of 24 California Psychological Inventory (CPI) items, and the third combined 48 items from both inventories. For the MMPI/CPI hedonic capacity scale the Cronbach alpha were, respectively, in three groups of normal subjects (undergraduates and twins) 0.89, 0.86 and 0.86. In a group of 44 twins the correlations between the MMPI/CPI hedonic capacity scale and the Chapman Anhedonia Scales (Physical Anhedonia Scale and Social Anhedonia Scale) were, respectively, – 0.37 ($P < 0.05$) and – 0.57 ($P < 0.001$). In 1989, Kazdin proposed the Pleasure Scale for Children to assess anhedonia in school-age children. The scale is a 3-point Likert scale containing 39 items. In a group of 232 child psychiatric inpatient children the Cronbach alpha coefficient was 0.96. The factorial analysis showed that the scale appears to be accounted for adequately by a single dimension. Moreover the scale correlated positively and significantly with other measures of pleasurable affect. Recently, Snaith et al (1995) have proposed a new scale, the Snaith-Hamilton Pleasure Scale (SHAPS), to assess anhedonia. The authors have shown satisfactory validity and reliability in the general population and psychiatric patients. The Kuder-Richardson formula 20 (KR 20) was 0.85 in 46 psychiatric patients. The French version of that scale have good concurrent validity and reliability (Loas et al, 1997).

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Clozapine: an accidental overdose

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Clozapine with its atypical antipsychotic profile has become a mainstay in the management of treatment resistant schizophrenia. Prescription and dispensing of Clozapine is strictly monitored to minimise the risk of agranulocytosis, and, as a result, cases of overdose have been reported infrequently (Mack, 1993). Where overdose has occurred the rapid rise in plasma levels of Clozapine and it's metabolites has tended to increase the adverse effects of seizures (Toth et al, 1994), sedation, hypotension, tachycardia (Marinkovic et al, 1994), pronounced agranulocytosis (Krupp et al, 1992) and may result in the demise of the patient (Meeker et al, 1992).