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Compulsive personality as predictor of response to serotoninergic antidepressants

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A large body of evidence suggests that serotoninergic antidepressants such as clomipramine, fluvoxamine, and fluoxetine are the most effective pharmacological treatments of obsessive-compulsive disorders.[1] The classic biochemical theory of major depression hypothesises disturbances in serotoninergic or catecholaminergic neurotransmission, or both. Until now, however, no specific symptoms have been clearly shown to orient with a selective antidepressant.[2] In addition to the depressive disorder, the underlying personality may be assessed as a possible aid to the therapeutic decision. Compulsive personality usually pre-exists in patients developing obsessive-compulsive disorder.[3]

We hypothesised that patients with a major depressive episode and an underlying compulsive personality would preferentially have serotoninergic depression and hence respond to a serotoninergic antidepressant such as fluvoxamine.[4]

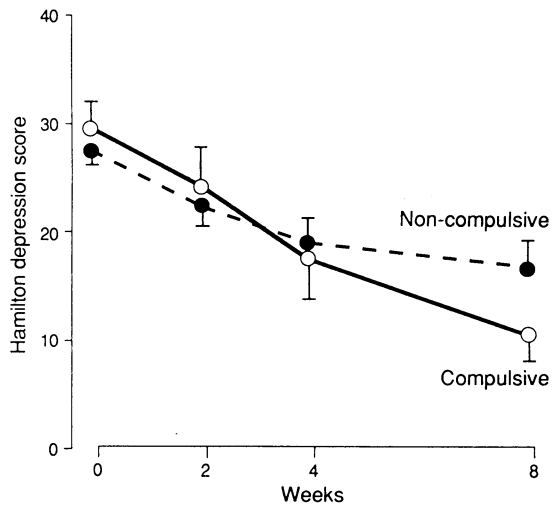
Patients, methods, and results

We studied 46 outpatients who fulfilled DSM-III criteria (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*) for a major depressive episode[3] and who also scored higher than 17 on the first 17 items of the Hamilton depression scale. The patients were among consecutive referrals to our department from general practitioners. Twenty two of the 46 patients had an underlying compulsive personality (DSM-III criteria)[3] as manifested by at least four of the following five features: restricted ability to express warm and tender emotions; perfectionism; insistence that others must submit to his or her way of doing things; excessive devotion to work and productivity; indecisiveness. The other 24 patients did not have a compulsive personality (only one or no compulsive feature).

The two study groups did not differ significantly in age (mean 46·8 years (range 28-63) *v* 41·3 years (22-64)), sex (12 men, 10 women *v* 12 men, 12 women), weight, duration of current depressive episode, previous treatment, medical or psychiatric history, or baseline level of depressive symptoms. The study lasted eight weeks and included assessments at baseline and after two, four, and eight weeks of treatment with the 24 item Hamilton depression scale and a subscale for endogenomorphic depression.[5] All side effects were recorded. The initial dose of fluvoxamine was 100 mg at bedtime, which could be increased to 200 mg from the third week. Other psychotropic drugs were excluded except for a low dose benzodiazepine anxiolytic or hypnotic, or both, if needed. The protocol was approved by the ethics committee of the university medical school and all patients gave informed consent.

Statistical analysis was by χ^2 test with the Yates correction for small samples, one way analysis of variance, and two way analysis of variance (compulsive *v* non-compulsive, four replications) with repeated measures. End point data in drop outs did not change the conclusions and are not reported.

Ten patients dropped out of the study because of lack of efficacy of the treatment or side effects (three patients in the compulsive group, seven in the non-compulsive group; $\chi^2=0{\cdot}84$, $p=0{\cdot}36$). To see whether completing the study could be prognostic an analysis of variance was performed on the basal Hamilton total score. This two way analysis (completer *v* non-completer, compulsive *v* non-compulsive) showed no significant effect or interaction. The same analysis of variance was performed on age, and this model also did not reach significance.



Changes over time in Hamilton depression scores with fluvoxamine in patients with major depressive episode with or without underlying compulsive personality. Bars are 95% confidence intervals

Comparison of changes in Hamilton depression scores over time showed significantly greater improvement in the compulsive group after eight weeks of treatment (F (3,32) = 10·65; $p=0{\cdot}0001$) (figure). This difference was even more pronounced on the subscale for endogenomorphic depression (F (3,32) = 7·09; $p=0{\cdot}0009$), which had already shown a significant difference between the groups after four weeks ($p=0{\cdot}05$). There was no significant difference between the groups in the number of reported side effects (mainly gastrointestinal; 12 patients in the compulsive group, 12 in the non-compulsive group; $\chi^2=0{\cdot}01$, df=1, $p=0{\cdot}92$). The mean final dose of fluvoxamine was 168·4 (SD 50·6) mg in the compulsive group and 179·4 (39·8) mg in the non-compulsive group ($F=0{\cdot}52$; $p=0{\cdot}48$).

Comment

These results suggest that depressive patients with an underlying compulsive personality respond better

to a serotoninergic antidepressant such as fluvoxamine than do depressive patients without an underlying compulsive personality. This is important as the personality of a depressive patient can easily be assessed for orientation with a selective type of compound. In the past many studies have tried to predict treatment response to selective antidepressants by using biological markers such as the concentration of neurotransmitter metabolites in urine or cerebrospinal fluid, with controversial results.[2] Moreover, these methods entail elaborate techniques for collecting body fluids and for assay.

Finally, our finding that depressive patients with a compulsive personality respond better to a serotoninergic antidepressant suggests some biochemical similarity in central serotonin disturbance between this subtype of depression and obsessive-compulsive disorder.

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Doctors and drops

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Nasal drops are a popular method of drug delivery to the mucocolumnar epithelium of the nose. Drugs from sympathomimetics to steroids have been given in this way. Though insufflation by a metered spray has become available, nasal drops properly applied in the head down and forward position (Moffat's position) have proved more effective in treating disease arising in the osteomeatal complex.[1] As our understanding of the key role of this complex in sinus disease increases,[2] so the rationale for using nasal drops has been re-asserted.

Treatment regimens usually prescribe a set number of drops to each nostril, to be self administered by the patient. The assumption is that a standard dose of the drug will thus be delivered. Many patients, however, have difficulty in sensing how many drops have entered the nose. Clearly, if the therapeutic margin of the drug is narrow safety margins may be exceeded.

Betamethasone sodium phosphate is a steroid preparation used in nasal disease. It is normally prescribed as two drops twice or three times daily in each nostril with the patient in Moffat's position. The proprietary product Betnesol (Glaxo Pharmaceuticals) utilises a standard dropper nozzle mechanism that is common to all current dropper products. It is designed to provide a constant size drop. To assess the accuracy of this system we recruited a group of healthy well informed doctors as volunteers.

Subjects, methods, and results

Ten asymptomatic doctors took part. All knew of the potential side effects of betamethasone and agreed to be rigorous in the application of the drops. A preweighed proprietary bottle of the drug (Betnesol) was given to each volunteer with the instructions to instil two drops into each nostril twice a day while adopting Moffat's position. Each administration was recorded. After 14 days the records were checked, the bottles reweighed, and the total weight of drug used by each volunteer thus calculated.

Manufacturer's data describe a standard drop weight of 0·025 mg betamethasone solution. To corroborate this 10 drops formed under gravity from each of five proprietary bottles were weighed, and the average weight of the 50 drops was indeed 0·025 mg. Using these data we calculated the notional average drops used daily by each volunteer (table). All 10 volunteers overused the drug, by a range of 41-338% (mean 132%). Seven volunteers reported difficulties in sensing the number of drops entering the nose.

To help further explain the overuse we examined the mechanism of drop formation. Whereas first drops under gravity formed promptly, second drops took up to three minutes to form and the tendency was to squeeze the bottle. When 50 drops from five bottles were formed by gentle squeezing the average weight was 0·033 mg, an increase over gravity drops of 32%.

Total weight of drug used and average number of drops used daily by 10 volunteers using betamethasone nasal drops for 14 days

Volunteer No	Total weight of drug used (mg) (notional=2·8 mg)	Average No of drops daily (notional=8)
1	7·98	20·4
2	10·14	25·8
3	6·37	16·2
4	13·75	35·1
5	4·43	11·3
6	5·74	14·6
7	6·56	18·7
8	6·16	15·7
9	5·05	12·9
10	5·92	15·1

Comment

Given a well informed, asymptomatic group of medical volunteers, drug overuse was the rule. As there was no bias towards overuse to alleviate symptoms the variability of results can be attributed to the mechanism of drug delivery. It was clear from the comments of the participants that accurate sensory assessment of the number of drops instilled was difficult. The inclination was to continue in the delivery position until drops were felt in the nose. In addition, the tendency to squeeze the bottle can greatly increase the dose delivered. When properly administered in Moffat's position drop solutions are still superior to other methods of drug delivery in the treatment of nasal disease. Nevertheless, if the drug delivery system of a systemically active drug can be so insensitive and variable, then development of a more accurate system seems desirable.

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