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Does Viloxazine Really Improve Sex Drive? A Double-Blind Controlled Study

The action of viloxazine on libido and sex drive was evaluated with a randomised controlled double-blind trial against placebo on a population of 26 male out-patients affected by primary depression (DSM III). Modifications in the sexual sphere were assessed by the ad hoc inclusion of a series of items in the Zung Self-Rating Depression Scale. Thus modified, the scale was administered at the beginning and the end of a four-week trial period. Viloxazine proved to have a considerable disinhibiting effect, whose principal expression level was a return to pre-depression levels of frequency in sexual relations.

Disorders of sexual function are frequently observed in the course of depressive diseases (De Leo & Magni, 1983). The antidepressants now available are generally efficacious in the treatment of these sexual symptoms, as well as of the other somatic ones, but it has been shown that these drugs may themselves sometimes be responsible for the onset of alterations in libido and in sexual drive (De Leo & Magni, 1983). These iatrogenic phenomena may constitute a serious hindrance to recovery from the depressive episode, especially when their importance is underestimated by the doctor, or when the patient does not reveal their onset.

Almost all the commercially available antidepressants have been associated with the development of sexual side-effects; however, viloxazine – an atypical antidepressant (Pinder *et al*, 1977) – showed a stimulating effect on the sexual sphere in a previous open trial (De Leo *et al*, 1983). In fact, it produced significantly greater improvements in sexual symptoms than it did in other features of depression. The present study investigates the effect of this drug on sexual function with a randomised double-blind trial against placebo in patients suffering from primary depression (DSM III).

Method

Twenty-six male out-patients, age-range 29 to 62 years, were included; 24 were married, and two separated but cohabiting with new partners. All were diagnosed as having primary depression and included: ten cases of major depression (four in their first episode); two of bipolar depressive disorder, and 14 dysthymic disorder. All were motivated for out-patient treatment with psychotropic drugs, and all observed a period of wash-out (except from benzodiazepines) lasting seven days. Patients with schizophrenia, drug abuse, alcoholism, cerebral lesions, convulsions, or major organic diseases were excluded. All subjects defined their sex-life during euthymic periods as satisfying.

Viloxazine and placebo were randomly assigned for a period of four weeks: during the first, the subjects took two tablets (200 mg of the drug), while a third tablet was added at the beginning of the second week. A benzodiazepine drug – lorazepam (max. daily dose 7.5 mg) or oxazepam (max. daily dose 90 mg) – was added in all cases. Depressive symptoms were evaluated at the beginning and end of the trial with the Zung Self-Rating Depression Scale (SDS) (Zung, 1965), with the modifications described elsewhere (Magni *et al*, 1981). Four additional items were included in the SDS: 'I have trouble achieving erection; Since I've been feeling down, my sexual activities have fallen off; It seems to take me longer than usual to achieve climax; Ejaculation is difficult or takes longer.' This expanded version of the Zung scale was tested on a group of 60 psychiatric patients, 40 surgical patients, and 40 healthy subjects, all in an age-range of 20–65 years. The internal consistency of the modified SDS, measured with alpha coefficient, proved to be almost identical to that of the original SDS (0.86 vs 0.87). The new items showed high stability on test-retest, with correlations varying between 0.85 and 0.92 and retest times ranging from one week (surgical patients), through 15 days (psychiatric patients), to one month (psychiatric patients and normal subjects). Each patient was also submitted to a clinical global impression scale (CGI) before and after the trial.

Results

On opening the code, it was found that the viloxazine and placebo groups contained the same number of subjects (13 each); the mean ages of the two groups were respectively 46.42 (SD 11.29) and 48.66 (SD 10.15). There were two drop-outs, both cases of dysthymic disorders: the first, in the viloxazine group, complained of nausea and the second, in the placebo group, was injured in a road accident. The subjects treated with viloxazine spontaneously reported the following side-effects: nausea, loss of appetite, headache (1); nausea and loss of appetite (3); loss of appetite and heartburn (1); headache (1);

TABLE

Mean Scores at the SDS and at the Sex Drive (SD) Items

	viloxazine ($n=12$)		*placebo* ($n=12$)	
	SDS	*SD*	*SDS*	*SD*
1st evaluation	57.25 (SD 8.34) *T=6.5	8.33 (SD 1.37) **T=0	55.25 (SD 6.59) *T=2	8.17 (SD 1.59) ***T=15
2nd evaluation	49.91 (SD 5.76)	6.33 (SD 1.83)	51.75 (SD 6.69)	7.50 (SD 2.75)

Wilcoxon Matched-Pairs Signed-Ranks Test, two tailed: *$P<0.01$; **$P<0.001$; ***P N.S.

dizziness and dry mouth (1). The scores obtained on the SDS and on the items definable as sexual drive (SD) are shown in the Table.

There were no significant differences between the two groups in age, SDS scores, or SD scores, and no significant correlations in either group between age and SDS scores or age and SD scores, at either test or retest. The treatment with viloxazine gave rise to a significant improvement in depressive symptoms. The CGI confirmed improvements in eight of the subjects who received the drug (three very much improved, three moderately improved, and two slightly improved), while only four subjects in the placebo group had improved (three moderately and one slightly). The difference between the two groups was significant ($P=0.005$, Fisher's Exact Probability Test). The most significant difference by the Wilcoxon test relates to the improvement in sex drive obtained with viloxazine. Separate examination of the individual items of the SD pool reveals a statistically significant difference for only one item in the viloxazine group. No. 10 ('Since I've been feeling down, my sexual activities have fallen off').

The SD scores at the beginning of the trial were approximately the same in both groups, and the greatest degree of impairment was this in item (10), with the same score in the two groups (3.00). One may therefore surmise that viloxazine acts on this level in particular, exerting an effect of disinhibition and favouring the recuperation of the subject's sexual activity. The fact that the answers to one item ('I still enjoy sex') did not undergo any significant modification during the trial may be considered to lend indirect support to the hypothesis formulated above: as libido remains more or less constant (the foregoing item evaluates libido), the intensification of sexual activity may rather be due to an effect of disinhibition exerted by the drug.

Comparing the scores on sexual items and those of the Zung scale as clustered by Blumenthal (1975) and then by Steuer *et al* (1980), there were, by the Wilcoxon test, significant improvements in the sex drive items ($P<0.001$), total Zung scale ($P<0.01$), depressed mood ($P<0.05$), somatic symptoms ($P<0.01$), and other somatic symptoms ($P<0.02$). There was no difference between test and retest of all other clusters (well-being, optimism, and items not included in the clusters).

The responses to viloxazine also differed according to diagnostic categories; none of the scores for the five subjects with dysthmic disorders showed significant change at retest, while only the Optimism Index and the Depressed Mood Index did not change significantly in the major affective disorder group.

Discussion

Although differences in methodology and sampling prevent a direct summation of the findings of this trial with those of the previous one (De Leo *et al*, 1983), the present results partially confirm those obtained in open conditions. Our double-blind control provides further evidence for the ability of viloxazine to act specifically on sex drive; it seems to promote the recovery of sexual activity, probably by means of disinhibitory stimuli, more than by provoking a substantial increase in libido, or modifying other areas of sexual function. While the possibility that this particular sexual disinhibition might be non-specific cannot be completely excluded, as far as we are aware there have been no studies supporting the restoration of sexual activity as a consequence of treatment with antidepressants, without a contemporaneous restoration of libido.

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Grade Scores of the Montgomery–Åsberg Depression and the Clinical Anxiety Scales

Two recent observer rating scales for mood disorder are the Montgomery-Åsberg Depression Rating Scale, MADRS (Montgomery & Åsberg, 1979) and the Clinical Anxiety Scale, CAS (Snaith *et al*, 1982). These two scales have been developed from item analysis of longer instruments, and have the considerable advantage of brevity and therefore ease of administration. Unlike many scales, a further advantage is that both incorporate clear instruction about the allotment of grade scores on the individual items and both the scales avoid a major emphasis on somatic symptomatology, thus recommending their use in the assessment of mood disorder in the setting of physical illness. Whereas many rating scales have poor specificity for the disorder they are designed to assess, e.g. an anxiety scale containing a large proportion of items referring to symptoms of depressed mood and vice versa, inspection of the items comprising the MADRS and the CAS shows that there is little overlap (one of the ten items of the MADRS does refer to psychic anxiety, but this reflects the fact that anxiety is a frequent accompaniment of depressive states); despite this small overlap, the two scales have been shown to tap essentially different dimensions of mood disturbance (Snaith & Taylor, 1985a).

A major drawback to the practical use of both the MADRS and the CAS is that, neither in the original publications nor subsequently, have score ranges indicating different grades of severity of the mood disorder been presented. The present study has been conducted to rectify this deficit.

Method

The study to establish score ranges indicating different levels of severity of the mood disorders was carried out in a psychiatric department; this was necessary, since although the ranges of scores are intended as a guide to other clinicians, it is important to establish these on the basis of the requirement for treatment as usually recommended by psychiatrists. Thus, the 'recovered/absent' grade indicates no need for treatment, the 'moderate' grade a probable need for treatment, and the 'severe' grade an undoubted need for treatment of the mood disorder. Therefore, the data were collected from patients who were in-patients or out-patients at the adult psychiatric unit of St James's University Hospital. The data for the MADRS were based on ratings of patients whose diagnosis was depressive illness (Major Depressive Episode by the criteria of DSM III) and patients at all levels of severity were included, from very severely ill requiring urgent treatment, to the fully recovered. However, no patients were included who suffered from concurrent severe physical illness, schizophrenia, or organic disorder. About half were males and half females, and the age-range was 20 to 70 years. The data for the CAS were based on ratings of patients whose diagnosis was anxiety neurosis (both General Anxiety