Imipramine and Sexual Dysfunction during the Long-term Treatment of Recurrent Depression

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Ninety patients in the maintenance therapy phase of the Pittsburgh Study of Maintenance Therapies in Recurrent Depression (Frank et al., 1990) were studied to determine possible relationships between the type of therapy (imipramine versus no drug) and the level of sexual functioning. The level of sexual functioning was determined by a composite subscale score of the Social Adjustment Scale which assessed (1) current level of enjoyment and interest in sex; (2) change in interest; (3) current frequency of sexual intercourse; (4) change in frequency; and (5) pain and/or difficulty reaching orgasm. Loss of libido was assessed by both the Hamilton Rating Scale for Depression and the SCL-90. Logistic regression analysis revealed no relationship between treatment with active imipramine and sexual functioning for the total group, or for females alone. Analysis of males alone revealed a decreased interest in sex among those treated with imipramine, but no significant differences in frequency or problems. The implications for maintenance pharmacotherapy and the cost/benefit ratio of unacceptable side effects versus drug efficacy are discussed. ***[Neuropsychopharmacology 11:21–27, 1994]***

KEY WORDS: *Imipramine; Sexual dysfunctions; Maintenance; Depression; Tricyclics*

Research examining the side-effects of antidepressants has effectively documented the potential negative effects such agents may have on patients suffering from acute major depression (Jefferson 1975; Cassem 1982; Rabkin et al. 1985; Pollack and Rosenbaum 1987; Frank et al. 1990). It would appear, however, that those enrolled in long-term maintenance therapy may experience fewer such effects, at least in the area of weight gain (Frank et al. 1992). Despite anecdotal evidence suggesting that sexual side effects are frequent and a common reason for drug discontinuation or noncompliance, the number of controlled studies of the effects of antidepressant medication on sexual function is limited.

Kolodny et al. (1979) state that approximately 5% of depressed patients treated with tricyclics experience a paradoxical sexual response involving a continued disruption of sexual function despite clinical amelioration of other symptoms of depression. A comprehensive review of the sexual side effects of psychiatric drugs (Segraves 1988) documents 33 case reports of sexual impairment due to antidepressant agents. Most of these descriptions (22 out of 33 patients) are men experiencing erectile dysfunction and ejaculatory failure as a result of tricyclic medications (Greenberg 1965; Simpson et al. 1965; Gross 1982; Schwarcz 1982; Yassa 1982; Nininger 1987; Price and Grunhaus 1990).

A double-blind study conducted by Harrison et al. (1985, 1986) examined the effects of imipramine and phenelzine on sexual function. Both drugs decreased the frequency of masturbation, and phenelzine de-

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creased the number of sexual thoughts. Kowalski and colleagues (1985) examined the effects of amitriptyline and mianserin on nocturnal penile tumescence. The results suggest that both compounds decrease the magnitude and the frequency of nocturnal erections. It should be noted, however, that the sample used was a nonpsychiatric population.

Only one placebo-controlled clinical trial has been identified that specifically evaluates the effect of a tricyclic (clomipramine) on the sexual functioning of women (Monteiro et al. 1987). The population studied were all seeking treatment for symptoms of obsessive–compulsive disorder, and not depression. Twenty-nine percent of the women in the clomipramine treatment group reported both decreased interest in sex (attributing to difficulty achieving orgasm) and problems with lubrication. Forty-three percent described reduced sexual sensation, and 71% were anorgasmic. The generalization of these findings for women being treated with depression is questionable because the neurological and affective differences between obsessive–compulsive disorder and major depression are marked.

Several case reports have documented sexual dysfunction in depressed women, due not to their affective illness, but due to their treatment with tricyclics. Price et al. (1986) describe a patient experiencing anorgasmia from treatment with imipramine. Quirk and Einarson (1982) report that two women (ages 24 and 30) both having depression and features of obsessive–compulsive disorder became completely anorgasmic upon treatment with clomipramine. Riley and Riley (1986) similarly describe two depressed women who became anorgasmic due to treatment with clomipramine, and one woman who experienced similar side effects resulting from treatment with imipramine. Sovner (1983) and Shen (1982) report anorgasmia in depressed women due to treatment with imipramine and amoxapine, respectively. Sovner (1984) also reported that nortriptyline, an antidepressant which affects serotonergic activity, produced anorgasmia.

These potential negative side-effects of treatment with tricyclics may increase the wariness of men and women experiencing depression with regard to the efficacy of these medications, and this may diminish the adherence to prescribed treatment regimens. This increased wariness may also reduce the willingness of a patient to continue treatment with maintenance pharmacotherapy, even though this has been found to significantly reduce the chance of recurrence (Frank et al. 1990; Kupfer et al. 1992; Frank et al. 1993). Therefore, a better understanding of the impact of maintenance tricyclic therapy on sexual function is clearly warranted. The present report focuses on ongoing sexual difficulties in patients randomly assigned to maintenance treatment with imipramine in the range of 200 mg in comparison to those assigned to placebo or to non pill conditions.

METHODS

The patients included in the present report were receiving treatment in the Pittsburgh Study of Maintenance Therapies in Recurrent Depression (Frank et al. 1990). All subjects were between ages 21 and 65, and entered the program in their third or greater episode of definite major depressive disorder, according to Research Diagnostic Criteria (RDC) (Spitzer et al. 1978). In addition, all patients were required to have had at least one other major depressive episode during the prior 2.5 years, one additional lifetime major depressive episode, and at least a 10-week period of remission between the index episode and the immediately previous episode. These criteria for patient selection were utilized to yield a study group at high risk for recurrence. All previous episodes must have required psychiatric treatment or must have resulted in significant functional impairment. Patients with a recent history of nonaffective Axis I psychiatric disorder were excluded, as were those who had significant medical histories. Patients meeting full RDC for borderline or antisocial personality disorder were also excluded from the study, although patients with other Axis II disorders were not. Following a minimum two-week drug-free wash-out period, each patient underwent a comprehensive independent assessment to reevaluate the severity of depression. A Raskin Severity of Depression score (Raskin et al. 1969) of seven or greater, and a Hamilton Rating Scale for Depression (HRSD) score (Hamilton 1960) of 15 or greater constituted the severity criteria for inclusion in this protocol.

All subjects then received the same short-term treatment regimen consisting of a combination of imipramine hydrochloride (150 mg to 300 mg) and interpersonal psychotherapy (IPT) (Klerman et al. 1984). Treatment sessions were scheduled weekly for 12 weeks, then biweekly for 8 weeks, and then monthly. At whatever point in this short-term treatment regimen the patient maintained an HRSD score of less than or equal to five for three consecutive weeks, a second biological and psychosocial evaluation was completed. Patients then continued to receive combined treatment for an additional 17 weeks, during which both HRSD and Raskin scores, and imipramine dosages were required to remain stable. A third evaluation was then conducted. After that, patients were randomly assigned to one of the five maintenance treatments: (1) a maintenance form of IPT (IPT-M; Frank 1991) offered alone; (2) IPT-M with active imipramine therapy continued at the acute treatment dosage; (3) IPT-M with placebo; (4)

Table 1. Demographic and Illness-History Characteristics

	Total Group (n = 90)				
	Drug		No-Drug		KW,
Variable	Mean	SD	Mean	SD	p Value
Gender	35F/9M		36F/10M		
Age at entry	38.93	11.18	40.67	11.42	0.49, NS
Duration of index episode (weeks)	22.89	18.20	21.26	18.03	0.46, NS
Number of previous episodes	7.55	8.23	6.72	6.47	1.16, NS
Baseline HRSD (17-item)	21.57	4.86	21.89	4.64	0.07, NS

medication clinic visits with active imipramine therapy; and (5) medication clinic visits with placebo.

One hundred twenty-eight subjects entered the maintenance phase of the study. Of these, 90 completed at least six months of maintenance therapy, 44 in one of the two active drug conditions, and 46 in one of the three placebo or nonpill conditions. Demographic and clinical characteristics of the study population are presented in Table 1. It is this group who is included in the current analyses. Of the 38 subjects who did not survive to the six-month point, 30 experienced a recurrence of depressive illness, and either were terminated from the protocol for other reasons. Among the early terminations, none left due to intolerable side effects.

Measures

The level of sexual functioning and the relative enjoyment of and interest in sex were not assessed by a single comprehensive instrument, but rather by analyzing specific questions and subscales of two interview measures obtained by an independent clinical evaluator and by two different self-report measures. The interview measures were the HRSD (Hamilton 1960) and the Social Adjustment Scale (SAS) (Weissman and Bothwell 1976). The HRSD was administered at admission to the protocol and prior to each treatment session throughout the acute, continuation, and maintenance phases of the protocol. When the relationship between HRSD score and sexual functioning was examined, we used a 16-item total (the 17-item score minus the score for loss of libido). The SAS was administered at baseline, at the beginning and at the end of continuation therapy, and every three months during maintenance treatment. Loss of libido was recorded by the HRSD. The SAS assessed: (1) current level of interest and enjoyment in sex, (2) change in interest, (3) current frequency of sexual intercourse, (4) change in frequency of intercourse, and (5) pain on intercourse and/or difficulty reaching orgasm. Each of these items was rated on a one to five scale, with one representing the highest level of functioning. Independent clinical evaluators were trained to a criterion interrater agreement level of 0.85 on both the HRSD and the SAS. Ongoing monitoring of interrater agreement was conducted every six months throughout the protocol.

The self-report measures included the Beck Depression Inventory (BDI) (Beck et al. 1961), which assessed the patient's change in interest in sex, and the Hopkins Symptom Checklist (SCL-90) (Derogatis et al. 1974). The SCL-90 included items assessing whether a loss of sexual interest or pleasure was bothersome to the subject. Both self-reports were completed upon protocol entry and at each subsequent evaluation. For the logistic regression analysis reported below, a single summary score intended to represent overall sexual function as assessed by the SAS was used. This score represented the average of the SAS items, assessing interest, frequency, and sexual problems. No transformations were performed because each variable used in this average ranged from one to five. Mean scores on relevant variables at 6 months of maintenance treatment are presented in Table 2.

Statistical Methods

Ordinal logistic regression analysis was used to determine if sexual difficulties during maintenance treatment were related either to being on active medication or to experiencing subsyndromal symptoms of depression. Analysis was conducted to determine if (1) an association existed between treatment with imipramine and the level of sexual functioning as determined by the SAS composite score and (2) an association existed between HRSD-16-item total (measured at six months into maintenance) and the level of sexual functioning as determined by the SAS composite score.

Pearson correlations were used to test the association between the Hamilton loss-of-libido item score and the score for the remaining 16 items of the HRSD score.

Table 2. Sexual Functioning and Depression in Drug-Treated and Non-Drug-Treated Patients after 6 Months of Maintenance Therapy

	Treatment Group				
	Drug		No-Drug		KW,
Variable	Mean	SD	Mean	SD	p Value
Total group (n = 90)					
Loss of libido (SCL-90)	0.61	0.97	0.64	1.03	0.05, NS
Loss of libido (HRSD)	0.26	0.44	0.39	0.58	1.10, NS
Change in interest (Beck)	0.39	0.64	0.41	0.62	0.03, NS
SAS subscales					
Level of sexual interest	1.71	0.90	1.91	1.19	0.08, NS
Change in sexual interest	2.13	0.61	2.20	0.59	1.33, NS
Frequency of sex	2.76	1.46	2.73	1.40	0.00, NS
Change in frequency	2.35	0.58	2.36	0.69	0.07, NS
Sexual problems	1.63	1.19	1.77	1.42	0.19, NS
Females (n = 71)					
Loss of libido (SCL-90)	0.58	1.03	0.69	1.11	0.31, NS
Loss of libido (HRSD)	0.23	0.43	0.44	0.61	2.42, NS
Change in interest (Beck)	0.35	0.66	0.47	0.66	0.86, NS
SAS subscales					
Level of sexual interest	1.68	0.94	2.12	1.27	1.76, NS
Change in sexual interest	2.09	0.58	2.33	0.60	2.00, NS
Frequency of sex	2.77	1.45	2.67	1.37	0.05, NS
Change in frequency	2.33	0.60	2.41	0.67	0.38, NS
Sexual problems	1.72	1.28	1.96	1.56	0.50, NS
Males (n = 19)					
Loss of libido (SCL-90)	0.71	0.76	0.50	0.71	0.42, NS
Loss of libido (HRSD)	0.38	0.52	0.20	0.42	0.64, NS
Change in interest (Beck)	0.57	0.53	0.20	0.42	2.34, NS
SAS subscales					
Level of sexual interest	1.86	0.69	1.20	0.42	4.55, $p < 0.03$
Change in sexual interest	2.29	0.76	2.10	0.57	0.44, NS
Frequency of sex	2.71	1.60	2.90	1.52	0.04, NS
Change in frequency	2.43	0.53	2.20	0.79	0.29, NS
Sexual problems	1.20	0.45	1.13	0.35	0.12, NS

Correlations were also used to examine the relationships between the SAS loss of libido item and the total Hamilton score.

Analyses were conducted on the entire sample of ninety subjects and separately on the group of female (n = 71) and male (n = 19) patients. Kruskal-Wallis analysis of the individual variables of the sexual functioning composite score, and the other measures of sexual functioning were performed for the total group, and for the two subgroups.

RESULTS

Total Group

Logistic regression analysis failed to show any statistically significant relationship between active imipramine treatment and the level of sexual functioning (n = 90, p = .75). Similarly, no association was found among drug treatment, level of depression, and level of sexual functioning (p = .18). As can be noted in Table 2, Kruskal-Wallis analysis revealed no differences between the drug group and the non-drug group for the individual sexual functioning variables.

Pearson correlation analysis showed a significant relationship between the SCL-90 loss-of-libido item and a higher score on the HRSD-16 for the group not treated with active antidepressant (r = 0.30, $p < .04$) as well as for the group treated with imipramine (r = 0.43, $p < .006$).

A significant correlation was discovered between the Hamilton loss-of-libido item and the remaining 16 Hamilton scale items among those subjects not treated with medication (r = 0.42, $p < .003$); however, no relationship was discovered between these two variables for those patients in the active drug group (r = 0.17, p = .28).

Females

Logistic regression analysis revealed no association between treatment with imipramine and the level of sexual functioning in female patients (n = 71, p = .50). Similarly, no relationship was found between drug

Table 3. Range of SAS Composite Scores

SAS Summary Score*	Imipramine Group				No Imipramine Group			
	Male		Female		Male		Female	
	n	Cum. %	*n*	Cum. %	*n*	Cum. %	*n*	Cum. %
1.00–1.99	5	71.4	15	71.4	6	60.0	11	33.3
2.00–2.99	0	71.4	9	75.0	2	80.0	13	72.7
3.00–3.99	1	85.7	5	90.6	2	80.0	5	87.9
4.00–4.99	1	100.0	3	100.0	0	100.0	4	100.0

* SAS scores unavailable for six females and for two males.

treatment, the 16-item HRSD scores, and a decreased level of sexual functioning. Table 3 lists the range of composite SAS scores for female subjects. As can be noted in Table 2, Kruskal-Wallis analysis discovered no differences between the drug and the non-drug group for the other variables of sexual functioning.

Similar to the analysis of the entire sample, there was a statistically significant correlation for both the drug ($r = 0.360$, $p < .05$) and the non-drug ($r = 0.409$, $p < .02$) groups between the loss-of-libido question on the SCL-90, and a higher Hamilton score.

A relationship was also found between the Hamilton loss-of-libido question and the 16-item Hamilton score for the nondrug group ($r = 0.478$, $p < .003$). Again, no relationship was found between these two variables for the imipramine-treated patients ($r = 0.005$, $p < .976$).

Males

Logistic regression analysis found no relationship between imipramine treatment and the overall level of sexual functioning in the male subjects. Similarly, no relationship was found between the HRSD-16 scores of those men treated with medication and the level of sexual functioning. Table 3 lists the range of composite SAS scores for the male subjects.

Kruskal-Wallis analysis of the relatively small number ($n = 19$) of male patients revealed a significant difference between those treated with imipramine hydrochloride and those in the non-drug group for the level of sexual interest at the six-month point as measured by the SAS. Men treated with imipramine had an average score of 1.86 (0.69) on the interest subscale while men in the non-drug group had a mean score of 1.20 (0.42) (KW = 4.55, $p < .03$). The higher score of the group treated with imipramine indicates a lower level of sexual interest than among the non-drug group. No significant differences were observed with the other four SAS variables (interest change, frequency, frequency change, and problems), nor on the SAS composite score.

Pearson correlation analysis showed a significant relationship between loss-of-libido as measured by the SCL-90 and a higher score on the HRSD-16 for the group of males treated with active imipramine ($r = 0.894$, $p < .007$). No relationship was discovered between these two variables for the non-drug group ($r = 0.00$, $p = 1.00$).

Correlation analyses also failed to prove a relationship between the Hamilton loss-of-libido question and the Hamilton measure either for males treated with active imipramine ($r = 0.629$, $p < .094$), or for those in the non-drug group ($r = 0.471$, $p < .170$).

DISCUSSION

The present investigation of sexual problems associated with long-term, antidepressant, maintenance treatment in remitted, recurrent, unipolar patients is limited by the lack of a comprehensive instrument aimed exclusively at the assessment of sexual functioning. We would argue, however, that the assessment made by independent clinical evaluators using the SAS interview represents an acceptable alternative and may have certain advantages over a measure focused exclusively on sexual functioning. In completing the SAS, evaluators were required to explore other aspects of the subjects' marital or romantic relationships, and, thus, had the advantage of being able to assess sexual functioning in those contexts. This provides an informal validity check on the information being obtained regarding sexual functioning.

A second limitation of the present investigation is its focus on assessment of sexual function at a single point rather than throughout the maintenance phase. The decision was made to examine a single time point six months after random assignment to the various maintenance treatment conditions in order to maximize the number of subjects in both drug and nondrug groups available for analysis, while still allowing sufficient time for any effects of prior acute and continuation drug treatment to dissipate. Had we examined data later in the maintenance phase (e.g., at one year or 18 months), power would have been markedly reduced and the groups would have become much more un-

balanced as a result of the number of recurrences in the nonmedication conditions.

Regardless of these limitations, we believe that these results demonstrate the relatively benign effects of long-term antidepressant therapy with respect to sexual difficulties. In the analysis of the total group, while logistic regression failed to find a relationship between either drug treatment status or level of depression and sexual functioning, correlational analysis suggested a relationship between the level of depression and the loss of libido. The relationship appeared to be more consistent in those patients treated without medication, appearing for both the SCL-90 and the Hamilton loss-of-libido items. As females comprised the majority of the study population, it is not surprising that the findings for the female-only group parallel those for the total group.

Interpretation of the data on the males is problematic because of the relatively small number of subjects. Logistic regression failed to prove a relationship between drug treatment and composite SAS score. The power for this analysis, however, was low. A Kruskal-Wallis test revealed a difference between drug-treated and nondrug-treated males only regarding sexual interest among the five SAS variables analyzed. This suggests that, like the females, the males were relatively unaffected by imipramine treatment. Those effects observed were regarding interest, rather than frequency of intercourse, or problems with ejaculation. None of the instruments, however, specifically inquired about difficulty achieving or maintaining an erection, the more typical complaint of males receiving acute tricyclic treatment. The relationship between loss of libido as measured by the SCL-90, and higher HRSD-16 scores for the men treated with imipramine, further supports the notion that the correlation between decreased interest in sex may not be a result of a drug-related physiological response, but instead a result of subclinical symptoms of depression. Note that the average age of the men was 40 with a standard deviation of 11 years. This leaves few over the age of 50 in the analysis. It is possible that older men may experience greater sexual dysfunction; however, we speculate that in a larger sample of comparably aged men, a similar response may be observed in those not treated with imipramine.

In contrast to previous findings regarding the acute effect of tricyclic antidepressants on sexual functioning, our analysis suggests that imipramine maintenance therapy may not adversely affect the level of sexual interest or pleasure. If anything, it would appear that it is the presence of low-grade depressive symptoms, irrespective of method of treatment, which is associated with diminished libido or decreased sexual pleasure. Given the very substantial benefit observed in the overall trial for maintenance pharmacotherapy (see Frank et al. 1990), we conclude that the cost/benefit ratio of impaired sexual functioning and pleasure versus the efficacy of maintenance therapy should alleviate fears and misconceptions about the prolonged use of tricyclic antidepressant medications.

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