Mirtazapine Substitution in SSRI-Induced Sexual Dysfunction

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Background: Sexual side effects are a common and bothersome reaction to selective serotonin reuptake inhibitors (SSRIs), frequently leading to cessation of treatment. Mirtazapine, an α_2-adrenoceptor and serotonin-2/3 receptor antagonist, appears to cause few sexual problems.

Method: Nineteen patients (12 women and 7 men), with SSRI-induced sexual dysfunction who were in remission from major depressive disorder (total Hamilton Rating Scale for Depression [HAM-D] score ≤ 10), were switched to open-label mirtazapine for up to 6 weeks. Mirtazapine was titrated from 7.5 mg to 45 mg daily, as tolerated. Sexual functioning was measured weekly with the Arizona Sexual Experiences Scale (ASEX), and depression was measured weekly with the HAM-D.

Results: Eleven patients (58%) had a return of normal sexual functioning (mean ± SD ASEX score = 12 ± 3), and another 2 (11%) reported significant improvement in sexual functioning (mean ASEX score reduced from 24 ± 1 to 20 ± 0). All nineteen patients maintained their antidepressant response (HAM-D score after 6 weeks of mirtazapine = 6 ± 3). The most commonly reported side effects (using moderate/severe rating on a symptom checklist) were initial sedation (N = 3), irritability (N = 6), and muscle soreness and stiffness (N = 3). Weight gain of 10 to 20 lb (4.5–9 kg) was seen in 3 patients (2 women and 1 man).

Conclusion: Mirtazapine is an effective antidepressant for many patients experiencing SSRI-induced sexual dysfunction.

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Antidepressant-induced sexual dysfunction is one of the most common side effects of selective serotonin reuptake inhibitors (SSRIs), probably affecting more than half of patients who take them.[1] Both men and women frequently experience delayed orgasm and diminished libido.[1]

While no antidote for antidepressant-induced sexual dysfunction has been well studied, case reports suggest that the α_2-adrenoceptor antagonist yohimbine may be effective.[2] The new antidepressant mirtazapine is an α_2-adrenoceptor antagonist, as well as an antagonist of serotonin-2 (5-HT_2) and 5-HT_3 receptors. This pharmacologic profile and preliminary data from phase 3 studies suggest that the incidence of mirtazapine-induced sexual dysfunction may be low. In fact, safety data on mirtazapine that combined results from many different studies found that 5% of 359 patients who took mirtazapine reported sexual dysfunction compared with 10% of 328 patients who took placebo.[3] The only kind of sexual dysfunction reported by mirtazapine-treated patients was decreased libido in both men and women. In an open-label study, 11 depressed patients who had experienced sexual dysfunction while taking an SSRI were switched to mirtazapine.[4] None reported sexual adverse effects while taking mirtazapine.

We conducted an open-label pilot study of mirtazapine as a substitute for an SSRI in patients who had achieved remission from major depression during treatment with an SSRI, but were experiencing sexual dysfunction.

METHOD

Subjects

Through advertising and clinic referral, we enrolled 19 men and women, aged 22 to 65 years, who had achieved remission from an acute episode of DSM-IV major de-

pressive disorder diagnosed by a Structured Clinical Interview for DSM-IV interview (total Hamilton Rating Scale for Depression [HAM-D][5] score ≤ 10) during treatment with fluoxetine, sertraline, or paroxetine. These patients complained of treatment-emergent sexual dysfunction sufficient to request a change in antidepressant medication. (None had comorbid psychiatric conditions.) Exclusion criteria included failing to meet the above requirements; having any serious medical problem, such as diabetes, severe high blood pressure, or seizures, that might impair sexual function; and being a woman of childbearing potential unwilling to use a reliable form of birth control. Nine patients (47%) enrolled were taking fluoxetine (mean ± SD dose = 34 ± 19 mg), 7 (37%) were taking sertraline (mean ± SD dose = 107 ± 34 mg), and 3 (16%) were taking paroxetine (mean ± SD dose = 23 ± 6 mg). No significant differences were found between men and women in type or dose of prior antidepressants.

Following a screening assessment, the SSRI was tapered over 1 to 2 weeks. After a washout period of 1 to 2 more weeks, during which time patients were drug free to assess both mood and sexual functioning, mirtazapine was started at a daily dose of 7.5 mg h.s. and raised as high as 45 mg daily over 3 to 6 weeks as tolerated. Depression was measured weekly on the HAM-D, and sexual function was measured weekly with the Arizona Sexual Experiences Scale (ASEX)[6] (Appendix 1). Patients were allowed to continue concomitant stable medication regimens, which included estrogen replacement, analgesics, antihistamines, antibiotics, antihypertensives, and lipid-lowering agents.

Analytical Procedures

The primary study goal was to achieve satisfactory sexual response to mirtazapine treatment, defined as ASEX total score < 19, no individual item with a score > 4, and no more than 2 individual items with a score of 4. Those patients who met the above criteria were categorized as responders, and those who did not were categorized as nonresponders. Prior studies suggest that these criteria lead to excellent positive and negative predictive values (88% and 85%, respectively), sensitivity (82%), and specificity (90%).[7] It was also found that women reported significantly higher levels of sexual dysfunction than men (for patients, $F = 5.22$, $df = 1,56$; $p = .026$; for controls, $F = 5.05$, $df = 1,35$; $p = .031$).[7]

Progress notes from patient charts were reviewed retrospectively by raters blind to the outcome to determine presence of relationship problems (with spouse, family members, or significant other). The presence of side effects was determined by review of weekly patient progress reports and by items reported on a symptom checklist.[8]

Descriptive statistics were performed at each timepoint (screening through week 6 of mirtazapine treatment) to determine the mean HAM-D, total ASEX, and individual ASEX item scores for male and female responders and nonresponders, as well as for all patient groups combined. Repeated-measures analyses of variance were performed to determine any significant change over time in HAM-D, total ASEX, and individual ASEX item scores among the patients, as well as any significant between-group differences. If significant time, gender, or responder effects were revealed, post hoc Tukey tests were performed to determine where the differences occurred.

Table 1. Mirtazapine Substitution: Patient Characteristics

Patient	Gender	Age (y)	Prior Drug	Prior Dose (mg/d)	Duration (mo)	Mirtazapine Dose at 6 wk (mg/d)
1	F	62	Sertraline	150	36	30
2	F	61	Fluoxetine	40	76	30
3	F	50	Fluoxetine	20	4	22.5
4	F	46	Fluoxetine	20	12	15
5	F	32	Sertraline	100	36	45
6	F	41	Paroxetine	20	5	22.5
7	F	49	Sertraline	50	12	45
8	F	52	Fluoxetine	80	48	45
9	F	49	Paroxetine	20	30	30
10	F	38	Sertraline	100	8	45
11	F	38	Fluoxetine	30	36	37.5
12	F	40	Sertraline	100	8	45
13	M	65	Sertraline	100	12	30
14	M	41	Fluoxetine	20	25	30
15	M	53	Fluoxetine	40	48	45
16	M	47	Paroxetine	30	6	15
17	M	49	Sertraline	150	31	45
18	M	54	Fluoxetine	40	48	45
19	M	22	Fluoxetine	20	4	30

RESULTS

A total of 40 subjects were screened, of whom 22 met study criteria. Three patients, all men, dropped out before completing 2 weeks of mirtazapine treatment owing to drowsiness/tiredness (N = 1), irritability (N = 1), and scheduling problems (N = 1). When subjects did not answer all 5 ASEX items, their data were not used in the analysis of total ASEX score. However, their data were used in analyses of any and all of the individual ASEX items they did answer. Therefore, the ASEX data gathered from 1 female subject were omitted from analyses of total ASEX score owing to incompleteness of her weekly ASEX measures. The final subject sample consisted of 12 women and 7 men (mean ± SD age in years was 47 ± 11). The mean daily dose of mirtazapine achieved at 6 weeks was 32 ± 13 mg/day. Table 1 lists characteristics of the patients and their treatments. Results from data analyses are listed in Table 2 and Figures 1–3.

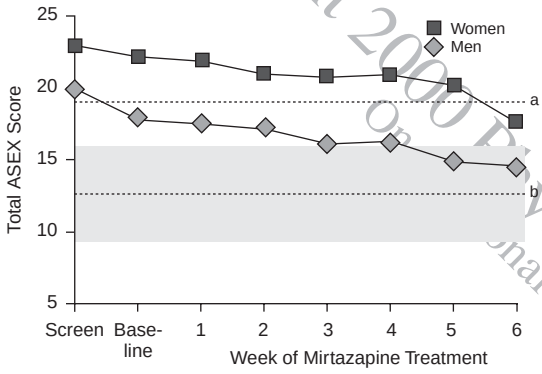
The mean HAM-D score for all patients at screening was 6 ± 2 and the mean total ASEX score was 22 ± 3 with no significant gender differences. However, there was a near-significant trend ($t = 1.9$, $p = .07$) for

Table 2. Hamilton Rating Scale for Depression (HAM-D) and Arizona Sexual Experiences Scale (ASEX) Scores: Screen vs. Week 6[a]

	Women						Men						Paired t Tests			Both										
	Screen			Week 6			Screen			Week 6			Screen to Wk 6			Screen			Gender Significance			Week 6			Gender Significance		
Measure	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	t	df	p	N	Mean	SD	F	df	p	N	Mean	SD	F	df	p
ASEX																											
1	12	5	1	12	4	1	7	4	1	7	3	1	–3.52	18	.002	19	5	1	0.511	1,17	.48	19	3	1	.958	1,17	.34
2	12	4	1	11	3	1	7	4	1	7	3	1	–5.13	17	.001	19	4	1	1.1	1,17	.31	18	3	1	.369	1,16	.552
3	12	4	1	11	3	1	7	4	1	7	3	1	–2.96	17	.009	19	4	1	.013	1,17	.91	18	3	1	.820	1,16	.38
4	12	5	1	11	4	2	7	5	1	7	3	1	–4.64	17	.001	19	5	1	1.85	1,17	.19	18	4	1	1.67	1,16	.21
5	12	4	1	11	4	2	7	3	1	7	3	1	–2.95	17	.009	19	4	1	4.64	1,17	.05	8	3	1	2.13	1,16	.16
Total																											
ASEX	12	23	3	12	16	7	7	20	3	7	14	4	–5.47	18	.001	19	22	3	3.55	1,17	.08	19	16	6	.471	1,17	.50
HAM-D	12	6	2	12	7	2	7	5	4	7	7	2	…	…	…	19	6	2	1.2	17	.29	19	6	3	1.5	17	.23

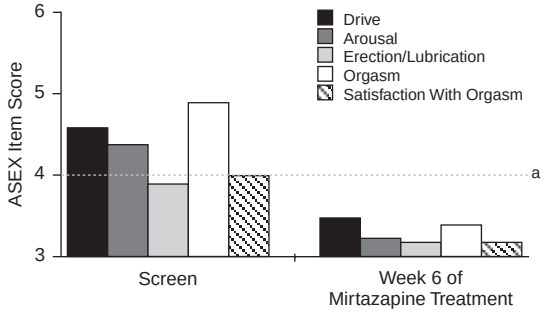
[a]Abbreviations: ASEX 1 = Drive, ASEX 2 = Arousal, ASEX 3 = Erection/Lubrication, ASEX 4 = Orgasm, ASEX 5 = Satisfaction With Orgasm.

Figure 1. Total Arizona Sexual Experiences Scale (ASEX) Score Over Time



[a]Score at or above this point indicates definite sexual dysfunction.
[b]Mean ± SD for healthy subjects = 12 ± 4.

Figure 2. Mirtazapine Substitution: Individual Arizona Sexual Experiences Scale (ASEX) Item Scores



[a]Score at or above this point indicates definite sexual dysfunction.

women to have higher total ASEX scores at screening (mean ± SD = 23 ± 3) than men (mean ± SD = 20 ± 3).

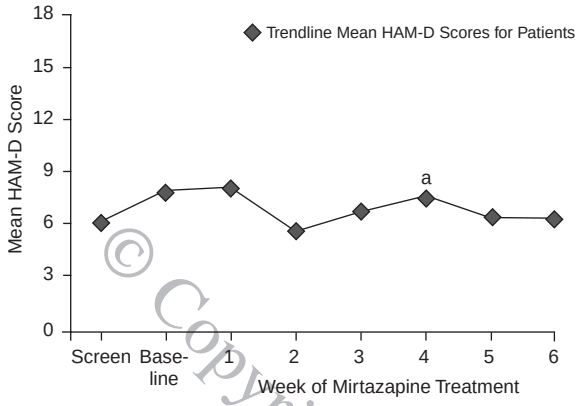
Mirtazapine treatment led to a significant reduction in total ASEX score ($F = 4.856$, $df = 7,16$; $p < .001$) (mean ± SD total ASEX score after 6 weeks = 16 ± 6) and in all individual ASEX items (with the exception of ASEX item Satisfaction With Orgasm, where $F = 1.449$, $df = 7,17$; $p = .19$) in both men and women (see Table 2 and Figures 1 and 2). Individual ASEX item scores decreased by a mean of 1 point, and total ASEX scores were decreased by a mean of 6 points. Although women consistently scored a mean of 4 points higher than men in total ASEX score and a mean of 1 point higher in individual ASEX item scores during the course of the study, these differences were not significant.

When satisfactory sexual response (an ASEX total score < 19, no individual item with a score > 4, and no more than 2 individual items with a score of 4) was used to categorize sexual functioning, 11 (58%) of 19 patients (responders) had a return of normal sexual functioning (mean ± SD total ASEX score after 6 weeks of mirtazapine = 12 ± 3), and another 2 reported improvement in sexual functioning (mean total ASEX score at screening = 24 ± 1, mean total ASEX score at week 6 = 20 ± 0). A higher percentage of men had sexual functioning that returned to normal during mirtazapine treatment (71%, mean total ASEX score = 12 ± 3) than women (50%, mean total ASEX score = 12 ± 3), although the Fisher exact test ($p = .633$) was not significant.

No significant differences were found in HAM-D scores between those who had a return of sexual functioning (responders) and those who did not (nonresponders) during the course of the study. The mean HAM-D score at screening for responders was 6 ± 2, and for nonresponders it was 7 ± 2. After 6 weeks of mirtazapine treatment, the mean HAM-D score for responders was 6 ± 4, and for nonresponders it was 7 ± 2. Three of 8 nonresponders had relationship problems (with spouse, family members, or significant other, determined through progress notes and patient self-report). Whereas more nonresponders had relationship problems (37.5% [3 of 8 patients]) than responders (9% [1 of 11 patients]), the Fisher exact test ($p = .26$) was not significant.

In summary, of 22 patients starting mirtazapine, the 19 patients for whom data were available maintained their antidepressant response during the study (mean HAM-D

Figure 3. Mirtazapine Substitution: Hamilton Rating Scale for Depression (HAM-D) Score



[a]Timepoint of significant gender difference in HAM-D score (F = 5.38, df = 7,17; p = .03).

after 6 weeks of mirtazapine = 6 ± 3) (see Table 2 and Figure 3). The only significant gender difference found in any of the analyses was in HAM-D score at 4 weeks of mirtazapine treatment (F = 5.375, df = 7,17; p = .033), at which time women scored higher (mean ± SD = 9 ± 5) than men (mean ± SD = 5 ± 3) (see Table 2 and Figure 3).

Through retrospective analysis of patient charts, 12 patients initially reported one or more side effects during the first 2 to 3 weeks on mirtazapine treatment (indicated by moderate/severe rating on a symptom checklist[8]); the most common were sedation (N = 3), irritability (N = 6), and muscle soreness (N = 3). At week 6, 12 patients reported side effects: sedation (N = 3), irritability (N = 6), and muscle soreness/stiffness (N = 3). Two women and 1 man gained 10 to 20 lb (4.5–9 kg) in body weight (determined through progress notes and patient self-report).

DISCUSSION

This open pilot project found that for patients who have a satisfactory antidepressant response to SSRIs but experience troublesome sexual side effects, discontinuing the SSRI and initiating treatment with mirtazapine often can provide continuing remission of depression and a return of satisfactory sexual functioning. For some patients, the side effects of mirtazapine are limiting, although conceivably a more aggressive dosing schedule might have attenuated sedation. For female patients in particular, issues related to relationships and weight gain could have a serious impact on sexual functioning.

In this study, as in our previous work,[6] women had higher ASEX scores (i.e., reported more sexual dysfunction than men). This has been observed in healthy control subjects, as well as in psychiatric patients taking antidepressants or medication-free patients.

Novel antidepressants with different mechanisms of action provide a broader range of options for clinicians and patients. Because mirtazapine is still relatively new, its proper role in our therapeutic armamentarium remains to be better defined. These preliminary results suggest that mirtazapine has a low incidence of sexual dysfunction and might serve as an alternative for patients for whom this side effect compromises their quality of life. On the other hand, mirtazapine has its own profile of adverse effects.

Appendix 1 appears on page 360.

Drug names: fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft), yohimbine (Yocon and others).

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Appendix 1. Arizona Sexual Experiences Scale (ASEX)[a]

ASEX-MALE

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. Can you easily get and keep an erection?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

ASEX-FEMALE

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

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