

Patients' attitudes toward side effects of antidepressants: an Internet survey

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Abstract Patients' attitudes toward side effects of antidepressants are likely to differ according to gender, which has not yet been fully addressed in the literature. From the 228,310 registrants, 1,305 participants who had received antidepressant drugs within the past year were identified with the Yahoo Japan research monitor through four-step screening procedures. Participants were asked as to which side effect(s) they had experienced, whether they had reported those side effects to their physicians, and whether they had taken any action to counteract them. The questionnaire was completed by 1,187 participants. Side effects were reported in 73.4% of the participants; the prevalence of self-reported side effects was significantly higher in men than women (80.4% vs. 68.3%, $P < 0.05$). The percentage of participants who reported side effects to their physicians widely differed depending on the nature of their experience, ranging from 45.7% to 89.9%; the lowest was for sexual dysfunction. The percentage of participants who had taken any action to relieve side effects varied among side effects from 26.3% for sexual dysfunction to 89.5% for dry mouth. Moreover, a lower percentage of women had reported sexual dysfunction to physicians (36.6% vs.

60.7%, $P < 0.05$) and had taken any action to counteract the problem (19.8% vs. 36.9%, $P < 0.05$). Given that patients experienced with antidepressants are likely to be reluctant to report sexual side effects, physicians should be cognizant of the potential presence of sexual dysfunction in patients who are taking antidepressants, especially for women.

Keywords Antidepressant · Side effect · Internet survey · Sexual dysfunction · Gender

Introduction

Antidepressants have played an important role in the treatment of depression for more than 50 years [3, 20]. Good adherence to medications is a prerequisite to benefit from therapeutic effects in both acute and maintenance treatments [9, 13]. Despite this fact, the available evidence generally points to inadequate adherence rates to antidepressant treatment [4, 22, 25, 30]. In fact, it has been reported to be as low as 25% in patients with a major depressive disorder [4, 22, 25], which is a serious clinical concern.

Poor adherence to the antidepressant treatment is expected to be caused by multiple reasons, including the presence of side effects caused by these medications [2, 10] and insufficient liaison between patients and their physicians [7, 29]. Indeed, side effects of antidepressant drugs have frequently been reported to discourage patients from continuing medications [19]. Moreover, it is suggested that people who have sufficiently consulted with their physicians about the side effects are more likely to continue the treatment than those who have not [6]. Since antidepressants cause various side effects, patients' response to each

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side effect should differ, depending on the nature of the problem. Further, the burden and implication of side effects may differ according to gender, which has not been investigated. Thoroughly evaluating those differences would be expected to enhance our understanding of patients' behaviors toward side effects, which in turn will help us devise more sophisticated treatment strategies with a special regard to gender differences [15]. However, while incidences of several side effects have been reported to differ between men and women [5, 11], few reports have investigated gender differences of patients' response to these side effects in the literature.

On the other hand, side effects of antidepressants do not always discourage patients from continuing their treatment in all cases since they are often manageable and tolerable [10]. Previous reports regarding the management of antidepressant side effects have been confined to physicians' perspective [2]. However, this may not entirely represent the real-world clinical practice. Patients are likely to take their own actions to ameliorate those side effects, while their physicians are not aware of their attempts. To our knowledge, there is not any report that examines patients' actions to attempt to counteract the side effects of antidepressants.

To thoroughly evaluate such patients' behaviors toward antidepressant side effects, including less frequently reported ones, a sufficient number of samples are desirable. Surveys, using the Internet, have successfully been conducted for this purpose [26]. Furthermore, since anonymous participation is guaranteed and participants are unlikely to feel any pressure from physicians or research staff under this system, we could extract more practical information that may more precisely mirror the everyday life of patients. To address this gap in the literature, we therefore conducted a large-scale Internet survey to evaluate attitudes and actions that patients took to deal with the various antidepressant side effects, with a focus on gender difference in patients who experienced with antidepressants in Japan.

Methods

This Internet-based survey was conducted from February 7 to 11, 2008 in Tokyo, Japan. A total of 1,305 participants were selected through the following four steps.

First, people who had already registered with the Internet Web site monitor system (the Yahoo! Japan research monitor, <http://research.yahoo.co.jp>), had agreed to participate in health-related surveys upon registration, and had been categorized as panel registrants who had suffered medical/psychiatric disease(s) were identified. Second, of the 228,310 registrants, people who met the

following criteria were extracted: residents in Japan, 20 years of age or older, having taken any prescription drug within the past two years or currently taking it, and having been diagnosed with "depressive state" or "depression" by a physician. Third, 8,100 people were randomly selected from the 11,279 extracted participants to reduce the cost for further analyses, and they were invited to participate in this survey by e-mail. In this e-mail, the details of this survey were first described; if participants agreed to participate in this survey and provided informed consent by clicking a corresponding button, a screening survey started. In this screening, the following information was collected: name(s) of disease(s) they had suffered within the past two years and whether and where they had received any antidepressant prescription(s). The number of people who successfully completed this screening was 5,559 (response rate: 68.6%). Fourth, 1,972 people who met the following criteria were identified: having taken any antidepressant drug within the past two years or currently taking it, having attended within the last two years or currently attending a psychiatric clinic, psychiatric hospital, or psychiatric department in a general or university hospital, having been diagnosed with a major depressive disorder by a physician within the past year, and having not been diagnosed with either bipolar disorder or schizophrenia. From the 1,972 people who met the inclusion criteria, a total of 1,305 participants were randomly chosen to reduce the cost for further analyses.

These screened 1,305 people were asked to complete the more detailed questionnaire. First, the information on age, gender, diagnosis, and treatment setting was collected. Next, they were shown a list of all available antidepressants in Japan at the time of this survey and asked to choose all name(s) of antidepressant(s) that they had taken within the past year. The list included the following antidepressants: milnacipran, fluvoxamine, paroxetine, sertlarine, amitriptyline, amoxapine, clomipramine, dosulepin, imipramine, nortriptyline, trimipramine, lithium carbonate, maprotiline, mianserin, setipiline, sulpiride, and trazodone.

Participants were then asked as to whether they had experienced any side effect from the antidepressants. If they had experienced antidepressant side effects, they were further asked to choose all side effects they had experienced from a list of 16 common antidepressant side effects that were a priori selected, based on the results from recent clinical antidepressant trials: headache, nausea, somnolence, vertigo/dizziness, dry mouth, constipation, diarrhea, appetite loss, insomnia, tremor, sweating, anxiety, common cold, fatigue, sexual dysfunction, weight gain, and others [8]. Participants were also asked which side effect(s) they had reported to their physician. Participants were subsequently asked as to whether they had taken any action to counteract those side effects.

Statistical analyses were performed, using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL). Differences between groups were tested, using a Mann–Whitney U test for nonparametric data or chi-square test for categorical variables. A P value of <0.05 was considered statistically significant (two-tailed), and the Bonferroni's corrections were used to correct for multiple comparisons, when applicable, where an original P value was multiplied by the number of items (e.g., original P values were multiplied by 16 in the analyses shown in Table 2).

This study was approved by the Institutional Review Board of the Zama Mental Clinic, and all subjects provided informed consent online after a complete description of the study. And this study complied with the Code of Ethics of the World Medical Association, Declaration of Helsinki.

Results

Study sample

A total of 1,187 participants completed the questionnaire (response rate: 91.0%). Demographic and clinical characteristics are summarized in Table 1. Approximately three fourths of the participants received psychiatric treatment at the time of survey; the rate was higher in women when compared to men (79.3% vs. 70.4%, $P < 0.01$). The mean total duration of treatment was four years, suggesting a majority of participants suffered chronic depression.

Side effects of antidepressants

Side effects were reported in 73.4% of the participants ($N = 871$); men more frequently reported side effects than women (80.4% vs. 68.3%, $P < 0.01$) (Table 1). Somnolence (65.8%), dry mouth (52.7%), fatigue (46.8%), constipation (39.8%), and sexual dysfunction (37.1%) were the five most frequently cited side effects (Table 2). Men had

more frequently experienced headache, nausea, somnolence, fatigue, constipation, appetite loss, and vertigo. Prevalence rates were numerically higher only on diarrhea and sexual dysfunction in women although these differences did not reach any statistical significance.

Participants' response to side effects

The percentage of participants who had reported side effects to their physicians widely differed among side effects, ranging from 45.7% to 89.9%, and the lowest was seen in sexual dysfunction. Sexual dysfunction was further less frequently reported to physicians in women when compared to men (36.6% vs. 60.7%, $P < 0.01$) (Table 2). In contrast to the prevalence rates, women reported 9 of the 16 symptoms at the higher percentages to physicians, although this was not statistically significant.

The rate of participants who had taken any action to relieve a side effect varied among side effects from 26.3% for sexual dysfunction to 89.5% for dry mouth (Table 2). Again, a lower percentage of women tried to cope with sexual dysfunction, compared to men (19.8% vs. 36.9%, $P < 0.01$). These gender differences survived after Bonferroni's correction (Table 2). To exclude a possibility of effects of age and current treatment status, mean ages were compared between participants who had taken one of the following actions and those who had not in each gender: (1) having reported side effects to physicians (35.2 years vs. 35.3 years, respectively, in men, n.s.; 40.1 years vs. 38.3 years, respectively, in women, n.s.) and (2) having taken any action to cope with side effects (34.8 years vs. 35.5 years, respectively, in men, n.s.; 41.7 years vs. 38.3 years in women, n.s.)—no significant age difference was found. We then compared the rate of participants who were currently treated between those who had taken one of the following actions and those who had not: (1) having reported side effects to physicians (76.1% vs. 79.2% in men, 84.9% vs. 85.9% in women, respectively, n.s.) and (2)

Table 1 Demographic characteristics of participants

	Total	Men	Women	Men vs. women P value	BC- P^c
Participants, N (%)	1,187	500 (42.1)	687 (57.9)	–	–
Age, mean, years(SD)	37.2 (8.0)	34.7 (7.7)	39 (7.7)	$<0.01^a$	$<0.01^*$
Duration of therapy, mean, mo (SD)	41.7 (42.6)	41.5 (41.2)	41.9 (44.6)	0.232 ^a	–
Having experienced 1 or more s/e, N (% of participants)	871 (73.4)	402 (80.4)	469 (68.3)	$<0.01^b$	$<0.01^*$
Currently treated, N (% of participants)	897 (75.6)	352 (70.4)	545 (79.3)	$<0.01^b$	$<0.01^*$

s/e side effects

* P values were statistically significant also after Bonferroni's correction

^a By Mann–Whitney U test

^b By chi-square test

^c Bonferroni-corrected P value

Table 2 Prevalence rates of antidepressant side effects and participants' behaviors toward side effects

	Prevalence rate				Rate of participants who have reported the side effect to their physicians				Rate of patients who have taken any action to relieve the side effect			
	<i>N</i>	%	<i>P</i> ^a	BC- <i>P</i> ^b	<i>N</i>	%	<i>P</i> ^a	BC- <i>P</i> ^b	<i>N</i>	%	<i>P</i> ^a	BC- <i>P</i> ^b
1 Headache												
Men	106	21.2			86	81.1			93	87.7		
Women	114	16.6	0.04		86	75.4	0.31		83	72.8	<0.01	0.09
2 Nausea												
Men	143	28.6			125	87.4			111	77.6		
Women	122	17.8	<0.01	<0.01*	99	81.1	0.16		84	68.9	0.11	
3 Somnolence												
Men	285	57.0			243	85.3			234	82.1		
Women	288	41.9	<0.01	<0.01*	252	87.5	0.43		219	76.0	0.07	
4 Fatigue												
Men	206	41.2			161	78.2			152	73.8		
Women	202	29.4	<0.01	<0.01*	168	83.2	0.20		128	63.4	0.02	0.38
5 Dry mouth												
Men	201	40.2			131	65.2			190	94.5		
Women	258	37.6	0.36		196	76.0	0.01	0.16	221	85.7	<0.01	0.03*
6 Constipation												
Men	175	35.0			143	81.7			154	88.0		
Women	172	25.0	<0.01	<0.01*	145	84.3	0.52		132	76.7	<0.01	0.10
7 Diarrhea												
Men	19	3.8			12	63.2			10	52.6		
Women	33	4.8	0.40		24	72.7	0.48		22	66.7	0.32	
8 Appetite loss												
Men	70	14.0			49	70.0			47	67.1		
Women	45	6.6	<0.01	<0.01*	35	77.8	0.36		24	53.3	0.14	
9 Insomnia												
Men	61	12.2			56	91.8			48	78.7		
Women	84	12.2	0.99		73	86.9	0.35		68	81.0	0.74	
10 Tremor												
Men	92	18.4			66	71.7			41	44.6		
Women	102	14.8	0.05		73	71.6	0.67		34	33.3	0.17	
11 Vertigo												
Men	145	29.0			115	79.3			103	71.0		
Women	116	16.9	<0.01	<0.01*	96	82.8	0.48		81	69.8	0.76	
12 Sexual dysfunction												
Men	122	24.4			74	60.7			45	36.9		
Women	202	29.4	0.06		74	36.6	<0.01	<0.01*	40	19.8	<0.01	<0.01*
13 Anxiety												
Men	44	8.8			33	75.0			36	81.8		
Women	40	5.8	0.05		32	80.0	0.59		28	70.0	0.21	
14 Flu-like symptoms												
Men	12	2.4			4	33.3			12	100.0		
Women	15	2.2	0.80		9	60.0	0.18		12	80.0	0.11	
15 Sweating												
Men	42	8.4			20	47.6			17	40.5		
Women	56	8.2	0.88		32	57.1	0.35		21	37.5	0.77	
16 Weight gain												
Men	117	23.4			76	65.0			73	62.4		
Women	139	20.2	0.19		83	59.7	0.39		88	63.3	0.95	

* *P* values were statistically significant also after Bonferroni's correction^a *P* value of gender difference estimated by chi-square test^b Bonferroni-corrected *P* value

having taken any action to cope with side effects (72.1% vs. 80.0% in men, 87.2% vs. 85.2% in women, respectively, n.s.)—no significant difference was found.

Discussion

To our knowledge, this is the first large-scale survey to evaluate patients' response to various antidepressant side effects that focuses on gender difference in patients who experienced antidepressant treatments. The results demonstrated that the rate of patients who had reported side effects to their physicians widely differed among side effects, and it was also influenced by gender. Specifically, it has been implied that men and women have different responses to sexual side effects.

The present survey revealed that approximately half the patients who experienced with antidepressants did not report sexual dysfunction, a finding in line with the previous reports. Montejo et al. [17, 18] conducted a cross-sectional study in Spain, including 308 patients with depression who were receiving selective serotonin reuptake inhibitors. In this study, only 14.2% of patients spontaneously reported sexual dysfunction to their physicians, and 55.3% reported it only when they were asked by physicians. Marwick [14] also reported that 68% of 500 adults were embarrassed to report sexual dysfunction to their physicians in their cross-sectional survey in the United States. While patients' behaviors toward sexual side effects are likely to be subject to their cultural backgrounds, it is also suggested that the rate of patients who did not report such side effects to their physicians has been reported to be high irrespective of geographic regions [14, 17, 18]. These findings, including ours, emphasize the need of screening this potentially problematic side effect when antidepressants are prescribed.

We also found that approximately three fourths of the participants just suffered sexual dysfunction without taking any action to counteract it. This lack of coping action may be associated with their feeling of hopelessness toward this annoying side effect. Marwick reported that 71% of 500 healthy adults in the United States felt that it was hopeless to receive any help for sexual dysfunction [14]. Side effects of antidepressants are known to often discourage patients from continuing medications [19]; among them, sexual dysfunction is especially a common side effect, leading to the discontinuation of antidepressant treatment [27]. On the other hand, people who have sufficiently consulted with their physicians about the side effects of antidepressant drugs are known to more frequently continue the treatment than those patients who have not [6]. Given these facts, further investigations are warranted to effectively screen sexual dysfunction and to consider the effective management for this side effect.

Another intriguing finding in the present study is that a lower percentage of female patients reported any sexual side effects to their physicians and took any action to counteract it, compared to male patients. This contrasts to the fact that females more frequently reported other side effects. Considering that a majority of physicians are men in Japan (82.8%) [16], women may be hesitant to report and discuss their sexual problems with their male physicians. This finding may be applicable to clinical settings in other countries, including the United States where the rate of female physicians is also lower (27.8%) [1]. In fact, Rosenberg et al. [24] found that 80% of women with sexual side effects failed to discuss this issue with their mental health care providers in the U.S. These findings point to the need of physicians' awareness of the potential presence of sexual dysfunction in patients who are receiving antidepressants, especially in women.

The results of our study must be interpreted in light of limitations due to the study design. First, our study was subject to selection bias since participants in Internet surveys are limited to those who have Internet access and therefore tend to be younger [23]. Furthermore, people who were registered with the Yahoo Japan research monitor may not represent the general population. Indeed, Japanese people who are able to use the Internet is 75.3% [12], and the mean age in our sample is slightly younger than that in the present Japanese population (37.2 years vs. 43.9 years) [21]. Moreover, participants in this survey might have been subject to another selection bias; people who are willing to participate in this type of survey may be more likely to complain about side effects, suggesting that real-world clinical settings may be associated with a greater degree of the underreporting problem that we found in the present study. Second, the data included in this survey were self-reported due to the nature of an Internet-based survey. The diagnosis of participants with depressive disorders in this study was also self-reported, indicating a possibility of having included false-positive patients with depression. Third, a possibility should be acknowledged that perceived side effects are not necessarily the direct results from treatment with antidepressants [28]. Fourth, the severity of illness and side effects, which were not thoroughly evaluated in the present study, could have confounded the results. We therefore performed additional preliminary analysis to see whether the gender difference that we observed in the main analysis in terms of sexual dysfunction would be replicated in a subgroup of people who found sexual dysfunction bothersome (30 men and 76 women). This analysis shows that the gender difference was also observed in this subgroup (report rate: men 70.0% vs. women 46.1%, $P = 0.032$; coping rate: men 56.7% vs. women 31.6%, $P = 0.026$). Therefore, effects of the severity of side effects may be minimal, although this has to be confirmed in future

investigations. Fifth, the reliability of self-reported data on the presence of side effects may be associated with patients' over- or underestimation. Sixth, since scales and questionnaires used in clinical trials may not always include all relevant side effects that we observe in clinical practice, adding an open-ended questionnaire would have been ideal. Finally and most importantly, cross-sectional surveys can never address long-term treatment outcomes. These limitations may be always associated with Internet surveys and therefore have to be acknowledged.

Conclusion

Given that patients are expected to be reluctant to report sexual dysfunction, especially women, physicians should be particularly cognizant of this side effect in patients with depression. In addition to demonstrating the feasibility and relevance of Internet surveys in patients who experienced with antidepressants, the intriguing observations from this study have important implications for the treatment strategy of antidepressants. To effectively screen those patients, it may be useful to incorporate a brief self-report questionnaire on sexual function in a routine treatment program, especially for women, which in turn would be expected to improve patients' adherence to medications and therefore outcomes.

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