Brief Report

Sex Differences in Response to Lithium Treatment

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Objective: Although sex differences occur with some psychotropic drug treatments, they are not well defined for mood-stabilizing agents, including lithium. The authors' goal was to investigate whether there are differences between the sexes in response to lithium.

Method: Studies identified in a literature search were analyzed for reports of sex differences in clinical response to lithium in major affective syndromes.

Results: Data from 17 studies published in 1967–1998, involving 1,548 adults treated with lithium for a mean of 38.6 months (SD=30.5), yielded similar weighted response rates to lithium in 1,043 women (65.6% [N=684]) and 505 men (61.0% [N=308]).

Conclusions: The results indicate little difference between the sexes in clinical response to lithium treatment of bipolar and related affective disorders.

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Differences between men and women in clinical as well as pharmacokinetic responses to several psychotropic medicines, including antidepressants and antipsychotic agents, have been reported (1–3). In contrast, very little is known about possible sex-based differences in the effectiveness of mood-stabilizing agents in bipolar disorder (2–4), despite the obvious importance of optimizing the effectiveness and safety of mood-stabilizing therapy in women of childbearing age. Given the uncertainty about sex differences in treatment response in bipolar disorder and the very limited amount of relevant information on newer treatments, we undertook a systematic review of available published reports of clinical response in patients treated with lithium.

Method

We carried out computerized literature searches for reports of clinical trials of lithium in patients with major affective disorders, using the MEDLINE and Current Contents databases as well as references cited in the reports so identified. We included reports that 1) used lithium as the primary treatment or permitted separate analysis of lithium-treated subjects, 2) specified or permitted determination of response rates for men and women separately, 3) involved single-sex samples not otherwise selected, and 4) involved any duration of treatment and any number of subjects.

Response to treatment was defined in each study (Table 1). We tabulated the proportions of male and female responders to all male and female subjects and computed an overall proportion (weighted average) for the entire data set for comparison with a contingency table (chi-square at the stated degrees of freedom), setting two-tailed significance at 0.05.

Results

The search process yielded 16 published studies with the required information (5–20). We added data from a 1998 study of 317 adult patients with bipolar I and bipolar II disorder from our program who had not previously been divided by sex (21), for a total of 17 studies. All reports included data for both men and women, except for one study of 88 women with major affective disorders (5), whose response rate was within the range of rates for women in other studies. Data were obtained for 1,043 women and 505 men (N=1,548 subjects), with an average of 91 subjects/study (SD=93). Five studies involved mixed samples of patients with major affective disorders that included recurrent major depression as well as bipolar disorder (5, 6, 10, 12, 18), and one involved acutely manic patients (14). All but three short-term studies reporting on men and women (11, 14, 16) involved treatment that continued for at least 6 months.

Among the 16 studies with data for both sexes, eight suggested superior results in women, and eight suggested superior results in men, although results were closely similar in three of these overall, indicating no consistent sex preference (Table 1). Moreover, response rates for women compared with men in brief studies (less than 6 months; 58.0% versus 60.0%; χ^2=0.06, df=1, n.s.) and long-term studies (65.0% versus 61.1%; χ^2=3.52, df=1, n.s.) were similar, as they were in studies of bipolar disorder (64.1% versus 61.5%; χ^2=0.88, df=1, n.s.) and major affective disorder (63.5% versus 59.9%; χ^2=2.00, df=1, n.s.). As might be expected, double-blind studies yielded significantly lower overall response rates than open trials (54.7% versus 64.8%; χ^2=4.84, df=1, p=0.03), although rates for men versus women in blind (52.8% versus 56.3%; χ^2=0.03, df=1, n.s.) and open (61.9% versus 64.9%; χ^2=2.26, df=1, n.s.) trials did not differ significantly.

Since response rates also did not differ significantly between studies of subjects with bipolar disorder (63.1%) and mixed affective disorder (64.9%) (χ^2=2.82, df=1, n.s.) or between short-term (58.7%) and long-term (64.7%) studies (χ^2=2.12, df=1, n.s.), all data were pooled. This pooled analysis yielded overall response rates of 65.6% (684 of 1,043) in women and 61.0% (308 of 505) in men. The response rate for all 1,548 patients was 64.1% (N=992);

TABLE 1. Response to Lithium Treatment in Women and Men

Study	Year	Diagnosis	Design	Months	Outcome	Women			Men		
							Responded			Responded	
						N	N	%	N	N	%
Baastrup and Schou (5)	1967	Major affective disorders	Open	6.0	Clinical improvement	88	70	79.5			
Angst et al. (6)	1970	Major affective disorders	Open	32.8	Clinical improvement	196	121	61.7	48	23	47.9
Melia (7)	1970	Bipolar disorder	Blind	24.0	Nonrecurrence	6	2	33.3	1	1	100.0
Cundall et al. (8)	1972	Bipolar disorder	Blind	12.0	Nonrecurrence	10	5	50.0	6	4	66.7
Dunner and Fieve (9)	1974	Bipolar disorder	Blind	36.0	Nonrecurrence	23	13	56.5	21	13	61.9
Hoffmann et al. (10)	1974	Major affective disorders	Open	24.0	No major recurrence	85	66	77.6	35	24	68.6
Donnelly et al. (11)	1978	Bipolar disorder—depressed	Blind	1.0	Depression rating	19	12	63.2	14	9	64.3
Poole et al. (12)	1978	Major affective disorders	Open	60.0	Clinical improvement	55	32	58.2	44	23	52.3
Rybakowski et al. (13)	1980	Bipolar disorder	Open	54.0	Nonrecurrence	39	29	74.4	22	5	22.7
Taylor and Abrams (14)	1981	Bipolar disorder I—manic	Open	1.5	Clinical recovery	78	43	55.1	33	19	57.6
Abou-Saleh and Coppen (15)	1986	Bipolar disorder	Open	70.8	Clinical improvement	18	13	72.2	13	9	69.2
Rosenthal et al. (16)	1986	Bipolar disorder	Open	0.3	Clinical improvement	3	3	100.0	3	2	66.7
Lusznat et al. (17)	1988	Bipolar disorder	Blind	12.0	Scale improvement	6	4	66.7	11	1	9.1
Aagaard and Vestergaard (18)	1990	Major affective disorders	Open	24.0	Clinical improvement	48	25	52.1	30	24	80.0
Kusalic and Engelsmann (19)	1998	Bipolar disorder I	Open	24.0	Clinical improvement	23	17	73.9	6	6	100.0
Maj et al. (20)	1998	Bipolar disorder	Open	60.0	>50% clinical improvement	138	116	84.1	109	93	85.3
Tondo et al. (21)	1998	Bipolar disorder I and II	Open	54.0	Ill ≤10% of the time	208	113	54.3	109	52	47.7
Total (17 studies)						1,043	684	65.6	505	308	61.0

more women than men responded to lithium treatment (χ^2=3.11, df=1, p=0.08) (Table 1).

Discussion

These results do not support the view that there are consistent and robust differences in clinical responsiveness in women and men in short-term or long-term studies involving lithium as a primary treatment for bipolar or major affective disorders. This lack of a clear sex difference, and even a nonsignificant tendency toward slight superiority in women, may be somewhat surprising because women are more likely than men to have rapid-cycling bipolar disorders (22). However, the sex difference in rapid cycling is substantially less than had been proposed and may have little effect on overall treatment responses because only about 15% of patients with bipolar disorder ever experience rapid cycling (22). Moreover, a recent study (23) did not find major differences in response to long-term treatment with lithium in patients with rapid-cycling disorder compared with patients who had other bipolar disorders.

The present results are limited by variability in the number of subjects, duration of treatment, and diagnostic and outcome measures in the 17 studies analyzed. Nevertheless, these studies do not indicate that women and men with bipolar or related major affective disorders differ appreciably in their clinical responses to lithium treatment. The sexes may show subtle differences in eliminating lithium, however: women may clear lithium less efficiently than men or vary more in lithium clearance, perhaps in association with the menstrual cycle (2) as well as during pregnancy (24). In addition, women may be at higher risk for hypothyroid effects of long-term lithium treatment (2). On the other hand, lithium appears to have more limited teratogenic risk than commonly used antimanic anticonvulsants (24–26). Therefore, lithium maintenance treatment remains an attractive option for the treatment of bipolar disorder in women of childbearing age.

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