Table. Selected Placebo-Controlled Relapse Prevention Trials of SSRI Antidepressants*

Trial	Entry Criteria	Definition of Relapse
Fluoxetine hydrochloride[2]	17-Item HDRS score ≤7	HDRS score >14 for 3 weeks or met the *DSM-IV* criteria
Sertraline hydrochloride[3]	CGI-I ≤2	CGI-S ≥4
Paroxetine hydrochloride[4]	21-Item HDRS score ≤8	At least 1 of the following: CGI-S ≥4 or increase in CGI score of at least 2 points or met the *DSM-III-R* criteria or opinion of investigator or depressive symptoms >7 days
Citalopram hydrobromide[5]	MADRS ≤12	MADRS ≥25 and clinical judgment

*HDRS indicates Hamilton Depression Rating Scale; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity of illness; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*; and MADRS, Montgomery-Asberg Depression Rating Scale.

and not a science until more studies like that of Sackeim et al are conducted.

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1. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285:1299-1307.
2. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression: a prospective assessment during long term fluoxetine treatment. *Am J Psychiatry*. 1998;155:1247-1253.
3. Doogan DP, Caillard V. Sertraline in the prevention of depression. *Br J Psychiatry*. 1992;160:217-222.
4. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. *Int Clin Psychopharmacol*. 1993;8:189-195.
5. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *Int Clin Psychopharmacol*. 1995;10(suppl 1):29-35.
6. Piccinelli M, Wilkinson G. Outcome of depression in psychiatric settings. *Br J Psychiatry*. 1994;164:297-304.

In Reply: Dr Abrams contends that in our continuation pharmacotherapy study the remission rate of 55% for open-phase treatment with ECT was low and this was due to 90% of patients receiving right unilateral ECT with an inadequate electrical dose.[1] Abrams incorrectly describes our treatment methods. While the minimal dose was 150% above seizure threshold, a higher dose often was used. In addition, of the 262 patients who started with right unilateral ECT, 50.3% were switched to bilateral ECT and received a mean (SD) of 7.1 (4.3) bilateral ECT treatments. Overall, the remission rate for patients treated only with right unilateral ECT was 68.5% compared with 43.8% for patients who were switched to bilateral ECT or who were treated with only bilateral ECT ($\chi^2_1=17.68$, $P<.001$).

Three factors should be considered in evaluating the ECT remission rate. First, our remission criteria were strict, requiring a 60% reduction in HRSD scores and a maximum score of 10 both immediately following ECT and 4 to 8 days later. Of the 176 initial patients who were remitters immediately following ECT, 9.7% had not remitted at the second assessment. In pharmacological trials of major depression, the most common definition of response is simply a 50% reduction in HRSD scores. In our study, 84.2% of patients met this weaker criterion immediately following ECT. Second, we have shown in our study[1] and other samples[2,3] that patients with established medication resistance during the index episode have an inferior response to ECT. Among patients with nonpsychotic depression, the remission rate was 69.5% among those who had not received an adequate medication trial during the episode compared with 47.1% among those exhibiting medication resistance ($\chi^2_1=8.61$, $P=.003$). Overall, 72.2% of 212 patients with nonpsychotic depression met the criteria for medication resistance. Third, only a minimum of 5 ECT treatments was required for patients to be included in the ECT efficacy analyses. This was done to avoid bias due to early withdrawal. However, 8 ECT treatments may be considered minimal for defining an adequate ECT trial.[4] Of those patients who were nonremitters, 38.5% received fewer than 8 treatments.

Abrams suggests that the continuation pharmacotherapy trial was biased in favor of high relapse rates because of the insufficent symptomatic improvement during the ECT phase. Because of the strict remission criteria, the 84 patients in the continuation trial had minimal symptoms, with a mean (SD) HRSD score of 5.5 (3.0) at trial outset and an improvement of 83.9% (9.3%) relative to pre-ECT baseline. This low level of symptoms is classified as remission by virtually all experts in the field.[5,6]

Drs Doraiswamy and Scates point out that patients with major depression are at risk of frequent relapse or recurrence, but US regulatory requirements for approval of antidepressant medications do not require demonstration of efficacy in relapse prevention. They also note that there has been little standardization in the methods used to demonstrate effective relapse prevention. These are serious concerns, because most patients with major depression require long-term treatment. Standardization in methods used to assess both acute efficacy and effectiveness in relapse prevention is needed. We hope that our study contributes to this goal.

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1. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285:1299-1307.
2. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57:425-434.

3. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry*. 1996;153:985-992.
4. Daly JJ, Prudic J, Devanand DP, et al. ECT in bipolar and unipolar depression: differences in speed of response. *Bipolar Disord*. 2001;3:95-104.
5. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom F, Kupfer D, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1081-1098.
6. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.

Relationship Between Postmenopausal Hormone Replacement Therapy and Ovarian Cancer

To the Editor: Dr Rodriguez and colleagues[1] found a direct association between the use of hormone replacement therapy (HRT) and the risk of ovarian cancer. Data from other cohort and case-control studies, however, are less consistent.[2]

To further explore this issue, we updated the analysis of a collaborative reanalysis of European case-control studies of ovarian cancer.[3] The present analysis study included 2501 women with histologically confirmed epithelial ovarian cancer and 5882 controls enrolled in 5 case-control studies: 2 were conducted in Greece, 1 in the United Kingdom, and 1 in Italy between 1979 and 1991, all previously reported,[3] plus another case-control study conducted in 4 Italian locations between 1992 and 1999.[4]

The 5 original datasets were combined in a uniform format that included comparable variables, such as age, socioeconomic level, parity, oral contraceptive use, menopausal status, type of menopause, age at menopause, as well as HRT use, duration of use, and time since last use. Odds ratios (ORs) were estimated using unconditional logistic regression models, including the above terms plus study center.

The TABLE shows the distribution of ovarian cancer cases and controls according to HRT use and the corresponding multivariable ORs. In comparison with women who had never used HRT, the OR for ever users was 1.28 (95% confidence interval [CI], 1.05-1.56). The risk was 1.11 for use less than 2 years and 1.41 for use 2 years or more. With reference to time since last HRT use, the OR was 1.37 for less than 10 years since last use, 1.13 for 10 to 14 years, and 0.95 for 15 or more years since last use. By comparison, Rodriguez et al[1] found relative risks (RRs) of 1.51 (95% CI, 1.16-1.96) for ever users and 2.20 (95% CI, 1.53-3.17) for those who used HRT for 10 or more years.

Table. Use of HRT Among Patients With Ovarian Cancer and Matched Controls*

	No. of Cases	No. of Controls	OR (95% CI)†
HRT use			
Never	2330	5385	1.00 (Referent)
Ever	171	297	1.28 (1.05-1.56)
Duration of HRT use, y‡			
Never	2030	4806	1.00 (Referent)
<2	75	156	1.11 (0.83-1.48)
≥2	46	75	1.41 (0.97-2.05)
Time since last HRT use, y‡			
Never	2030	4806	1.00 (Referent)
<10	65	108	1.37 (1.00-1.89)
10-14	20	42	1.13 (0.66-1.95)
≥15	29	72	0.95 (0.61-1.48)

*HRT indicates hormone replacement therapy; OR, odds ratio; and CI, confidence interval.
†Estimates from unconditional logistic regression models, including terms for age, study center, sociocultural level, parity, oral contraceptive use, menopausal status, type of menopause (natural or surgical), and age at menopause.
‡The sum does not add up to the total because of some missing values. Information on duration of use and time since last use was not provided by 1 Greek study[5] and 1 United Kingdom study.[6]

Our updated analysis, including the largest number of ovarian cancer cases from a European population, gives further support to the hypothesis of a moderately positive association of HRT use in menopause with ovarian cancer risk, with a pattern of risk similar to that well known for breast cancer.[7]

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1. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA*. 2001;285:1460-1465.
2. La Vecchia C, Brinton LA, McTiernan A. Menopause, hormone replacement therapy and cancer. *Maturitas*. In press.
3. Negri E, Tzonou A, Beral V, et al. Hormonal therapy for menopause and ovarian cancer in a collaborative re-analysis of European studies. *Int J Cancer*. 1999; 80:848-851.
4. Tavani A, Gallus S, La Vecchia C, et al. Physical activity and risk of ovarian cancer: an Italian case-control study. *Int J Cancer*. 2001;91:407-411.
5. Tzonou A, Day NE, Trichopoulos D, et al. The epidemiology of ovarian cancer in Greece: a case-control study. *Eur J Cancer Clin Oncol*. 1984;20:1045-1052.
6. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer*. 1989;60:592-598.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350:1047-1059.

To the Editor: Dr Rodriguez and colleagues[1] suggest that if others confirm their findings, a possible increase in risk of dying from ovarian cancer should be added to the list of possible estrogen-related adverse effects to be discussed with patients considering HRT. They based this recommendation on finding that 31 women died from ovarian cancer among women who in 1982 self-reported using HRT for 10 years or more. This is a relatively small number of events, which weak-