# Electroconvulsive Therapy and Cardiovascular Complications in Patients Taking Trazodone for Insomnia

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***Background:*** Trazodone has been used widely to treat insomnia in depressed patients. When used in combination with electroconvulsive therapy (ECT), trazodone has been suspected to cause cardiovascular side effects.

***Method:*** A retrospective study was done of 100 patients who received ECT with concurrent trazodone. One patient was excluded because permission to review the patient's records had not been given. The remaining 99 patients were matched with control ECT patients.

***Results:*** No statistically significant between-group differences were identified in cardiovascular side effects, although a trend toward more orthostatic hypotension was observed in patients taking trazodone.

***Conclusion:*** Administering low-dose trazodone for insomnia in conjunction with ECT does not appear to increase cardiovascular complications. The true incidence of adverse cardiac events was not higher than 3.66% at a 95% confidence level.

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Insomnia is a common symptom for patients with major depression, and it is often treated with a hypnotic or sedating antidepressant. When patients receive electroconvulsive therapy (ECT) for depression, the treatment of coexisting insomnia is more difficult because of concern that diphenhydramine may exacerbate confusion[1] and a benzodiazepine may compromise the efficacy of ECT by increasing the seizure threshold.[2,3] A recent case series[4] described the use of flumazenil, a short-acting benzodiazepine-competitive antagonist, in doses of 0.4 to 1.0 mg to reverse transiently the effect of benzodiazepines, in order to facilitate ECT. Adding flumazenil may permit more usage of benzodiazepines for insomnia in depressed ECT patients in the future, although concerns remain about benzodiazepines being linked with falls, cognitive impairment, and drug dependence. At present, no data exist regarding the safety or efficacy of the newer nonbenzodiazepine benzodiazepine-receptor agonists zolpidem or zaleplon in ECT patients.

Although relatively low-dose trazodone has been used widely in conjunction with antidepressant medications as a hypnotic, it has not been recommended for use with concurrent ECT because of possible cardiovascular complications.[5,6] A 1984 article[7] reviewed the existing 4 reports of cardiac side effects of trazodone in depressed patients at high risk because of preexisting cardiac dysfunction. They concluded that trazodone did lower heart rate, but did not produce supraventricular arrhythmias. Compared with the tricyclic antidepressants, less orthostatic hypotension was observed with trazodone. Overall, trazodone had little effect on cardiac conduction or ventricular irritability.[7] Several subsequent cases of trazodone causing exercise-induced nonsustained ventricular tachycardia and orthostatic hypotension have been published.[8,9]

One published case report[10] addresses the issue of combining trazodone with ECT. A 52-year-old female patient with no known history of cardiac disease was treated with trazodone, 400 mg daily, for depression, which was discontinued 4 days prior to starting an acute series of ECT. After an uneventful acute course, she was restarted on trazodone, 200 mg daily, as prophylaxis and maintained with continuation ECT. The trazodone dose was skipped the evening prior to her first continuation ECT treatment. During the first continuation ECT, she had occasional isolated premature ventricular contractions followed by a brief episode of complete sinoatrial block. The authors suspected that trazodone or a drug-drug interaction between trazodone and the medications used for ECT caused the conduction delay. They cautioned physicians about providing ECT to patients receiving trazodone, given the severity of the conduction problem.[10]

## METHOD

A case-controlled retrospective study approved by the Mayo Foundation Institutional Review Board of 100 consecutive adult patients undergoing an acute series of ECT and receiving concurrent trazodone was conducted. Con-

trol ECT patients without trazodone (matched for age and gender) were selected from our patient database. Cardiac complications of ECT were defined as cardiac changes requiring medical intervention. Tachycardia and hypertension that occurred solely intraictally were not considered complications.

Psychiatric diagnoses were determined using DSM-IV criteria by board-certified psychiatrists supervising the patients' inpatient care. None of the patients were taking benzodiazepines, diphenhydramine, or any other medication for insomnia. All patients had a physical examination and electrocardiogram (ECG) before receiving ECT. The medical conditions of the patients were identified by general internists, who completed the preanesthetic medical evaluations on all patients. The presence of any cardiac condition or use of any cardiovascular medication was defined as a positive cardiovascular history.

A Thymatron DG ECT device (Somatics, Inc.; Lake Bluff, Ill.) was used. The anesthetic medications administered to all patients included intravenous glycopyrrolate, 0.2 mg, as well as thiopental (initially, 1–2 mg/kg) and succinylcholine (initially, 1 mg/kg) titrated to each patient's needs by an anesthesiologist. The treatment team determined whether to use unilateral or bilateral stimuli on a case-by-case basis. During the first treatment session, a stimulus titration protocol was employed to determine seizure threshold, and thereafter, patients were treated at 150% and 250% of this setting for bilateral and unilateral treatment, respectively.[11] The patients were monitored with ECG, electroencephalogram (EEG), and pulse oximetry, with periodic blood pressure checks throughout the procedure and for at least 20 minutes or until the patients were hemodynamically stable in the recovery room.

Data collected included current psychiatric disorders, past history of cardiovascular disease, cardiac risk factors, trazodone dose, and other medications prescribed during the course of ECT. ECT data included stimulus settings, laterality, number of ECT treatments administered, and cardiac complications of ECT. Descriptive statistics, paired t tests for continuous variables, and appropriate paired analyses for discrete variables were employed.

## RESULTS

The medical records of 64 women and 35 men plus age- and gender-matched controls were reviewed. Both subjects and controls were treated during the same 1-year time period. In compliance with Minnesota state law, 1 patient was excluded because we lacked permission to review her records for research purposes. In this clinical sample, representative of many large ECT practices, the majority of both subjects and controls had a variety of medical disorders and were taking numerous other medications. Cardiovascular risk factors did not differ between the 2 groups, except for a trend that patients receiving trazodone were more likely to be current smokers. No significant difference was found between subjects and controls in the history of past cardiovascular disease. Premature ventricular contractions and sinus tachycardia were observed more commonly in the controls.

**Table 1. Patient Characteristics and Electroconvulsive Therapy (ECT) Data[a]**

| Variable | Trazodone (N = 99) | Control (N = 98) |
|---|---|---|
| Age, y | | |
| Range | 18–92 | 18–91 |
| Mean | 65 | 67 |
| Current psychiatric disorders, N (%) | | |
| Major depression | 72 (73) | 68 (69) |
| Bipolar mood disorder | 12 (12) | 8 (8) |
| Schizoaffective disorder | 3 (3) | 3 (3) |
| Other | 12 (12) | 19 (19) |
| Comorbid medical conditions, N (%) | 70 (71) | 66 (67) |
| Cardiovascular history, N (%) | 23 (23) | 29 (29) |
| Received β-adrenergic antagonist | 6 (6) | 7 (7) |
| Cardiovascular risk factors, N (%) | | |
| Current nicotine use | 19 (19) | 7 (7) |
| Former nicotine use | 9 (9) | 9 (9) |
| Diabetes mellitus | 4 (4) | 6 (6) |
| Hypertension | 24 (24) | 27 (27) |
| Postmenopausal without HRT | 5 (5) | 9 (9) |
| History of angina | 1 (1) | 3 (3) |
| ECT treatment data | | |
| Bilateral treatments, N (%) | 59 (58) | 57 (56) |
| Median no. of treatments in series | 7 | 7 |
| Mean energy setting, % | 40 | 40 |
| ECT cardiac complications, N (%) | | |
| Orthostatic hypotension | 2 (2) | 0 |
| PVCs | 0 | 4 (4) |
| Sinus tachycardia | 8 (8) | 11 (11) |
| Hypertension | 5 (5) | 4 (4) |
| Myocardial infarction | 0 | 0 |

[a]None of the between-group differences was statistically significant.
Abbreviations: HRT = hormone replacement therapy, PVC = premature ventricular contraction.

Ninety-one patients were prescribed trazodone for insomnia alone, 6 for insomnia and agitation, and 2 for unknown reasons. The dosage ranged from 25 mg to 300 mg, with 86% of patients taking 100 mg q.h.s. or less, consistent with typical trazodone usage for insomnia.[5] Table 1 shows the demographic data, psychiatric diagnoses, cardiac risk factors, ECT treatment data, and cardiovascular side effects. Trazodone was discontinued during the ECT course in 3 patients for reasons unrelated to ECT. A trend existed for 2 patients receiving trazodone to have more orthostatic hypotension. The trazodone dosage was 50 mg/day for the first patient, who was also receiving levodopa for Parkinson's disease. This patient developed orthostatic hypotension associated with tachycardia that persisted until 5 days after the trazodone was discontinued. The second patient received 100 to 150 mg of trazodone, and the orthostatic hypotension associated with tachycardia started prior to the initiation of the course of ECT.

## DISCUSSION

Trazodone use in conjunction with ECT has been avoided because of scattered case reports describing rare cardiovascular complications in patients both with and without cardiac disease. The cardiac issues observed for both groups were representative of those seen in ECT patients in tertiary referral centers.[12] This retrospective case-controlled study did not show a higher rate of trazodone-associated cardiac complications in a group of ECT patients as compared with controls.

The statistically insignificant degree of trazodone-associated orthostatic hypotension is unrelated to ECT and is consistent with trazodone's propensity to cause this condition because of its antagonism of $\alpha_1$-adrenergic receptors.[9] The other medical disorders and/or medications or controls could have contributed to the premature ventricular contractions and sinus tachycardia observed more commonly in the controls. Trazodone did not appear to affect the frequency of cardiovascular complications, and, on the basis of these data, trazodone possibly decreased sinus tachycardia and premature ventricular contractions, which is consistent with the Himmelhoch et al. report.[7]

These patients were primarily taking low-dose trazodone to target insomnia. Since relatively few patients were taking higher-dose trazodone, the rate of cardiovascular side effects for patients taking higher doses remains unknown. The cardiac side effects of trazodone are thought to be dose dependent and less common at doses less than 300 mg q.d.[7] However, at present, the most common usage of trazodone is for insomnia at doses of 100 mg or less used as adjuvant therapy with another antidepressant medication.

Although this study describes the observed side effects in a relatively large group of patients and compares them with an appropriate control group, these data do not preclude the possibility of serious complications related to trazodone in this patient population. However, based on these data, the true incidence of adverse cardiac events is not higher than 3.66% at a 95% confidence level. Trazodone-associated cardiovascular side effects appear to be rare,[7] meaning that a conclusive negative study would need to review the experience of more than 99 subjects. The cost of a large-scale study of this issue is prohibitive. Nonetheless, our observation that a reasonably large group of ECT patients tolerated trazodone without cardiovascular side effects is reassuring to the practicing psychiatrist. Because of the scarcity of clinical ECT research, often psychiatrists decide to combine a psychotropic medication (including clozapine, bupropion, and lithium, which may increase the risk of neurologic complications) with ECT without the benefit of definitive studies.[13–15] Ideally, more large-scale studies that are generalizable to a clinical ECT practice will be conducted to assist psychiatrists with the selection of coadministered psychopharmacologic agents.

## CONCLUSION

Low-dose trazodone (50–100 mg) can be used in combination with ECT without significantly increasing the risk of cardiovascular complications. The true incidence of adverse cardiac events is not higher than 3.66% at a 95% confidence level, based on this series of 99 patients. Trazodone may be a safe alternative to benzodiazepines and diphenhydramine for ECT patients experiencing insomnia.

*Drug names:* bupropion (Wellbutrin), clozapine (Clozaril and others), diphenhydramine (Benadryl and others), flumazenil (Romazicon), succinylcholine (Anectine and others), trazodone (Desyrel and others), zaleplon (Sonata), zolpidem (Ambien).

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