## Clozapine Therapy During Cancer Treatment

TO THE EDITOR: Clozapine has been associated with neutropenia and agranulocytosis, leaving psychiatrists justifiably wary of its contemporaneous use with medications that induce leukopenia. However, when patients taking a stable dose of clozapine develop cancer and require chemotherapeutic agents that frequently cause myelosuppression, clinicians have little guidance as to appropriate management and potential risks. To our knowledge, five cases of clozapine patients treated successfully and receiving cancer treatment have been published (1–5). This report differs from previous reports because of persistent neutropenia in the patient even after discontinuation of chemotherapy.

**Ms. A was a 46-year-old white woman with schizophrenia who had been doing well taking clozapine since 1991 (700 mg/day, blood levels >430 ng/ml). Blood monitoring showed her total leukocyte counts to be generally above 5000/mm$^3$, with absolute neutrophil counts >3000/mm$^3$. Her other medications included perphenazine, citalopram, lorazepam, thyroxine, and oral contraceptives.**

**In September 2001, she was diagnosed with breast cancer and underwent segmental mastectomy. She began a four-cycle course of doxorubicin and cyclophosphamide and continued to take clozapine.**

**As expected, doxorubicin induced significant leukopenia (as low as 1300 leukocytes and 300 neutrophils). After the nadirs, Ms. A's counts returned to normal. However, after chemotherapy and a 6-week course of radiotherapy, her counts declined again, leveling off with leukocyte counts below 3000 and absolute neutrophil counts below 2000. Her oncologist opined that the leukopenia was not related to radiation. Ms. A's counts remained low over the next 6 months, and hematologic consultation, including a bone marrow biopsy, yielded no other cause for neutropenia besides clozapine. Ms. A remained free from cancer, infection, and psychoses after her surgery, and she remains well at this time.**

This case supports previous reports of a successful combination of clozapine and chemoradiation, although we caution that this combination should be undertaken only when the risk-to-benefit ratio for the individual patient favors continuation of clozapine and then only with close provider collaboration and monitoring. Despite expected neutropenia, no cases of agranulocytosis from clozapine-chemotherapy combinations have been reported to our knowledge, and patients appear to remain psychiatrically stable during these treatment periods.

Our patient also developed neutropenia that persisted more than 6 months after her last radiation treatment. The temporal association strongly suggests some synergistic effect on bone marrow leukocyte production that has heretofore not been reported from chemoradiation and clozapine. We caution clinicians that persistent neutropenia is a possible risk of this combination therapy. The informed and collaborative decision to continue clozapine in a subject who was psychiatrically stable for 10 years had a favorable outcome.

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## Ziprasidone-Related Tardive Dyskinesia

TO THE EDITOR: Tardive dyskinesia is a potentially irreversible serious side effect of antipsychotic medication. One of the major benefits of atypical antipsychotic drugs is their lower propensity to cause tardive dyskinesia. Quetiapine is a dibenzothiazepine that antagonizes both dopamine-2 and serotonin-2A receptors (1). Two cases of tardive dyskinesia associated with quetiapine have been reported. The first occurred in a patient with schizophrenia after many years of previous exposure to traditional neuroleptics (2), while the second was reported in a patient with type I bipolar disorder who had never been exposed to typical neuroleptics (3). Ziprasidone, a benzothiazolylpiperazine, is the only atypical antipsychotic that is an agonist at serotonin 5-HT$_{1A}$ receptor sites and an inhibitor of both norepinephrine and serotonin reuptake. We found only one report of tardive dyskinesia associated with ziprasidone, and it involved the reemergence of tardive dyskinesia in a man with type I bipolar disorder who already had a history of tardive dyskinesia with long-term treatment with typical neuroleptics (4). Here we report the case of a patient who experienced tardive dyskinesia within 2 months of treatment with ziprasidone.

**Ms. A, a 70-year-old woman with chronic hepatitis C without cirrhosis (she had had interferon therapy in 1990) and no past psychiatric history was admitted to our hospital because of a first severe major depressive episode with mood-congruent psychotic features. Her psychiatric symptoms were judged not to be the direct physiological consequence of the chronic hepatitis C. A neurological examination, analysis of CSF, and magnetic resonance imaging, including proton magnetic resonance spectroscopic studies, yielded normal results. Therapy with citalopram, 40 mg/day, and haloperidol, 6 mg/day, was begun. After 6 days, she suffered from akathisia; haloperidol was stopped and replaced by quetiapine, which was gradually increased to a maintenance dose of 400 mg/day. Concomitantly, vitamin E (α-tocopherol, 500 IU/day) was given. She received ziprasidone as an alternative to quetiapine when the latter was discontinued after 12 months of treatment because of fatigue and a mildly depressed mood. The ziprasidone dose was gradually increased to 100 mg/day, and Ms. A's depressive symptoms remitted. Repetitive involuntary jaw and toe movements were noticeable within 9 weeks of the initiation of ziprasidone treatment.**

The present case suggests that ziprasidone can be associated with tardive dyskinesia, even in someone who never had

tardive dyskinesia before and who was exposed to a traditional neuroleptic for only 6 days. Moreover, even though accumulating evidence suggests that antioxidants may be efficacious in the treatment and prevention of tardive dyskinesia (5), vitamin E was not beneficial in this patient. The incidence and prevalence of tardive dyskinesia are significantly greater in older patients (2). The age of the patient, and the parallel treatment with a serotonin reuptake inhibitor (6), together with chronic inflammatory disease, may have favored the early appearance of involuntary movements.

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## Higher Serum Triglyceride Levels in Early-Onset Schizophrenia

TO THE EDITOR: Patients with schizophrenia often have disturbances in lipid regulation (1). However, we know of no reports concerning the duration of schizophrenia and serum triglyceride levels. We report findings from a general population study of the Northern Finland 1966 Birth Cohort on the correlation between serum triglyceride levels and the age at onset of schizophrenia. The cohort is an unselected, general population birth cohort ascertained during mid-pregnancy and comprises 12,058 children in the provinces of Lapland and Oulu born alive during 1966 (2). Permission to gather data was obtained from the Ministry of Social and Health and the Ethics Committee of the University of Oulu.

In 1997, the members of the cohort currently living in Northern Finland or in the capital area were invited for a clinical examination. After complete description of the study to the subjects, written informed consent was obtained. Our study group consisted of 31 cohort members (18 men and 13 women) who were older than 16 years, appeared in the Finnish Hospital Discharge Register through the end of 1997, and had a diagnostic code of 295 (ICD-8 or ICD-9) or F20 (ICD-10). All diagnoses were scrutinized and validated for DSM-III-R criteria (3). Serum triglyceride levels were determined after an overnight fast by enzymatic methods.

We found higher triglyceride levels in the 17 patients who were ≤20 years old at the beginning of schizophrenia (mean=1.7, SD=0.7) compared with the 14 patients with later onset (mean=1.4, SD=0.9) or the 5,453 nonhospitalized comparison subjects (mean=1.2, SD=0.7). The Mann-Whitney U test showed a significant difference between the first and third groups ($p<0.01$), and Pearson's correlation coefficient showed a negative correlation between the age at onset and the level of serum triglycerides ($r=-0.35$, $p=0.05$). One explanation may be a genetic linkage since hypertriglyceridemia may be related to the more severe forms of schizophrenia. On the other hand, cognitive disorders in these patients may lead to a poor diet, and a more prolonged exposure to antipsychotics may further raise triglyceride levels. A recent study demonstrated that both novel and conventional antipsychotics may be associated with dyslipidemia but also that patients are infrequently monitored for these parameters (4). Our finding may imply that patients with early-onset schizophrenia are at special risk for the cardiovascular complications of hypertriglyceridemia, and their serum lipid levels should be monitored regularly as part of their treatment.

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## Improvement in PTSD Patients Who Care for Their Grandchildren

TO THE EDITOR: Disturbances in interpersonal relationships help define posttraumatic stress disorder (PTSD). The DSM-IV criteria for PTSD include a "feeling of detachment or estrangement from others" and "restricted range of affect (e.g., unable to have loving feelings)." Combat-related PTSD has been reported to lead to psychiatric disturbances in veterans' families (1).

Treatments for PTSD are usually not curative. Pharmacotherapy for PTSD typically does not entirely eradicate symptoms, even in trials generally reporting significant benefits, and combat PTSD may be more refractory to pharmacotherapy than noncombat PTSD (2). Improvements from psychotherapy may also be modest (3).

Given these interpersonal and treatment issues, I have been heartened to witness improvements in PTSD among Vietnam veterans who become caregivers for their grandchildren. These veterans have reported improved mood, less ruminative thinking about Vietnam experiences, and less isolation and suicidality. Of interest, a PUBMED search for articles about PTSD and grandchildren produced no articles dealing with combat veterans.

Why would caring for grandchildren be helpful to combat veterans? Child care may be an effective distraction from ru-

minative thinking because it is so demanding. One veteran, thinking of his boisterous grandson, said, "Any man who has to take care of that kid has to give up his PTSD." One veteran stated that "the laughter" of his grandchildren is helpful, while another indicated that knowing that his grandson would miss him prevents him from killing himself. This otherwise extremely isolative veteran ventures to baseball games with this grandson. Veterans also report that young children are unconditionally accepting and nonjudgmental, counteracting their sense of personal guilt and of being judged by society as "baby killers."

Although these veterans are showing improvement, it is not known how the grandchildren are faring. A study of Nazi Holocaust survivors' grandchildren suggesting an increase in behavioral disturbances among these children raises concerns (4). Are the ill effects of combat PTSD being handed down to the third generation? If so, are there interventions that might prevent this? What particular aspects of the relationship with grandchildren (e.g., distraction, altruistic mission, acceptance) yield improvements, and how should this inform our treatment of PTSD? Should assuming certain caregiving roles be encouraged by PTSD therapies? Because of the potential benefits to veterans and the uncertain effects on grandchildren, I believe that there is urgent need for careful study of the caregiver veteran-grandchild relationship.

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