Psychotropic Medication Use in Pediatric Patients With Cancer

Maryland Pao, MD; Elizabeth D. Ballard; Donald L. Rosenstein, MD; Lori Wiener, PhD; Alan S. Wayne, MD

Background: Use of psychotropic medication in medically ill adults, in particular, patients with cancer, is common. While increased use of psychotropic medications in children and adolescents in the general population has been reported, little is known about the prescribing practices for these medications in medically ill children.

Objective: To examine the frequency and types of psychotropic medications used in a population of children and adolescents with cancer.

Design: Retrospective review of the National Institutes of Health Medical Information System.

Setting: Pediatric Oncology Branch of the National Cancer Institute, National Institutes of Health.

Participants: Three hundred forty-seven patients aged 1 to 21 years who were enrolled in clinical research trials at the Pediatric Oncology Branch between January 2000 and December 2003.

Main Outcome Measures: Psychotropic medication use was analyzed according to cancer diagnosis and patient age.

Results: Fourteen percent of identified patients had been prescribed at least 1 psychotropic medication at the time of National Cancer Institute clinical trial enrollment. The most commonly used medications were anticonvulsant agents (8%) and antidepressant medications (7%), in particular, selective serotonin reuptake inhibitors. Anxiolytic medications could not be accurately assessed because of their frequent use as antiemetic agents in many chemotherapy regimens. Psychostimulant use was rare.

Conclusions: This study suggests that psychotropic medications are commonly prescribed to children and adolescents with cancer. Clinical safety and efficacy trials are needed in medically ill children at high risk for mood and anxiety symptoms.

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Cancer is the second leading cause of death in children aged 5 to 14 years and is the leading cause of nonacute death in children. Nevertheless, more children are surviving into adulthood, with 5-year survival rates significantly improving from 59% in 1974-1976 to 79% in 1995-2000. The diagnosis of a life-threatening illness in a child or adolescent is frequently associated with anxiety and depression. The judicious use of psychotropic medications may improve the quality of life for some youth with cancer who have persistent distress or posttreatment psychological and physical symptoms.

Use of psychotropic medications in children and adolescents has been a controversial topic over the last few decades. The prescription rate for psychotropic drugs in the pediatric population has reached an estimated 5.9% to 6.3%, with stimulant and antidepressant agents most commonly prescribed. Even as the frequency of use of psychotropic medications in children approaches that in adults, little research data exist on the efficacy, safety, and pharmacokinetics of these medications in children.

Data on the administration of psychotropic medications in medically ill children are even more elusive. To our knowledge, no cross-sectional study has examined use of psychotropic medications in children with medical illness, specifically, cancer. A 2005 report by Kersun and Kazak found that half of pediatric oncologists at a major children’s hospital reported prescribing selective serotonin reuptake inhibitors for pediatric patients. Most oncologists who prescribed these antidepressants had prescribed more than 1 selective serotonin reuptake inhibitor, often without input from a psychologist or a psychiatrist. Beyond this study and clinical case reports on behav-
ioral effects of psychotropic medications, little psychopharmacologic research has been reported in children with cancer or other medical illnesses.

Recognition of the need to treat distress, particularly depression, in adults with cancer began in the 1970s. A study from 1979 reported that more than half of adult patients with cancer from 5 medical centers were given at least 1 psychotropic agent. By 1998, an investigation by Cullivan et al of adult patients with cancer referred to a psycho-oncology service showed that in more than half, a psychotropic medication had been started before referral; the most common agents were tranquilizers, followed by antidepressants. Despite numerous trials, treatment of depression with antidepressants in adult patients with cancer has shown encouraging trends toward effectiveness, but with no definitive conclusions.

Despite the absence of definitive clinical data, antidepressants may be useful in treating symptoms of depressed mood in patients with cancer, such as pain, gastrointestinal tract distress, wasting, fatigue, anxiety, and cognitive impairment. Symptom researchers, including Cleeleland et al, have posited that these symptoms might be biologically associated with a type of sickness behavior similar to behavior produced in animals with lipopolysaccharide-induced bacterial infections. Sickness behavior and concomitant depressed mood may be considered an expected outcome of cancer. Recent data suggest that prophylaxis with selective serotonin reuptake inhibitors might be beneficial in preventing symptoms of depression in patients with cancer receiving chemotherapy. In a recent open-label trial (n = 15), fluvoxamine was shown to improve symptoms of depression and anxiety in children and adolescents with cancer. Antidepressants and other psychotropic medications can be used as tools to improve the quality of life in patients with cancer.

Published studies of depression and anxiety in children with chronic medical problems, including cancer, are highly limited. While depression has not been shown to be more common in medically ill children compared with healthy children, symptoms of depression are commonly reported in this population. The difficulty in assessing and treating depression in medically ill children underscores the need for further investigation. This retrospective study examines the use of psychotropic medication in pediatric patients with cancer enrolled in clinical trials and suggests new directions for further research.

### METHODS

The Medical Information System of the National Institutes of Health (NIH) was reviewed retrospectively for all patients aged 1 to 21 years entering Pediatric Oncology Branch, National Cancer Institute (POB-NCI) clinical research trials between January 1, 2000, and December 31, 2003. The study was approved by the NIH Office of Human Subjects Research. Three hundred forty-seven patients were identified, and their electronic medical records were reviewed further for cancer diagnoses and psychotropic medication information. Oncologic diagnoses were grouped as sarcomas, leukemias and lymphomas, brain tumors, and other cancers. No distinction was made between recurrent and nonrecurrent cancers. While many patients (>50) participated in multiple clinical trials at the NIH, only the psychotropic medication regimen active at the time of a patient's first trial enrollment during the study period was recorded. The duration and dosage of treatment, and indications and efficacies of the prescriptions were unavailable through the Medical Information System and could not be reported. Ten additional patients who received psychotropic medication only during subsequent years were excluded from the study analysis. The psychotropic medications reviewed are listed in Table 1; the category of antidepressants includes selective serotonin reuptake inhibitors, tricyclic antidepressants, and novel antidepressants. Lorazepam, diphenhydramine, oxiapine, and zolpidem are commonly prescribed and were excluded.

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Antidepressants</th>
<th>Antipsychotics</th>
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<tbody>
<tr>
<td>Fluoxetine†</td>
<td>Mirtazapine†</td>
<td>Nefazodone</td>
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<tr>
<td>Sertraline†</td>
<td>Bupropion</td>
<td>Thorazine</td>
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<td>Paroxetine†</td>
<td>Trazodone†</td>
<td>Clozapine</td>
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<td>Amtriptyline†</td>
<td>Ziprasidone†</td>
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<td>Escitalopram†</td>
<td>Desipramine†</td>
<td>Quetiapine</td>
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<td>Nortriptyline†</td>
<td>Haloperidol†</td>
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<td>Venlafaxine†</td>
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<td>Ziprasidone</td>
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<tr>
<td>Clonidine†</td>
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<td>Olanzapine</td>
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</tbody>
</table>

*Nefazodone, thorazine, and clozapine were excluded from the search because of black box warnings or possible neuropenia. Diphenhydramine, lorazepam, oxiapine, and zolpidem are commonly prescribed and were excluded.

†Prescribed in study population.

Current and noncurrent cancers. While many patients (>50) participated in multiple clinical trials at the NIH, only the psychotropic medication regimen active at the time of a patient’s first trial enrollment during the study period was recorded. The duration and dosage of treatment, and indications and efficacies of the prescriptions were unavailable through the Medical Information System and could not be reported. Ten additional patients who received psychotropic medication only during subsequent years were excluded from the study analysis. The psychotropic medications reviewed are listed in Table 1; the category of antidepressants includes selective serotonin reuptake inhibitors, tricyclic antidepressants, and novel antidepressants. Lorazepam, diphenhydramine, oxiapine, and zolpidem are commonly prescribed and were excluded. Univariate analyses were used to describe demographic characteristics and the prevalence of psychotropic medication use.

Patient demographics are given in Table 2. Cancer diagnoses are shown in the Figure. Diagnoses are representative of the research focus of the POB-NCI and do not represent the prevalence of cancer in the general pediatric oncology population. The older age of the patients with sarcoma (mean age, 14.6 years) compared with patients with brain tumors (mean age, 9 years), leukemia or lymphomas (mean age, 10.3 years), and other cancers (mean age, 11.8 years) reflects the expected age distribution of pediatric cancers.

The rate of psychotropic medication use in children entering NCI pediatric oncology protocols was 14% over-
all, ranging from 12% to 16% by study year. Patients receiving psychotropic medications tended to be older (t = −5.76; P < .001), with only 6 patients younger than 12 years. The most commonly prescribed medications in these patients were anticonvulsants (37%), with gabapentin (n = 36) the most prescribed agent in this class. Antidepressants (35%) followed, with sertraline (n = 13) being the most commonly prescribed agent. Use of stimulant, antipsychotic, or other psychotropic medications was rare. Forty-five percent (n = 22) of the patients prescribed psychotropic medications were prescribed more than 1 class of psychotropic medication.

The NIH Clinical Center provides a unique setting for evaluation of the use of psychotropic medications in children during participation in cancer treatment trials. Our data show that this population of pediatric patients with cancer are prescribed psychotropic medications at more than twice the rate in children in the general population (5.9%-6.3%). Sarcoma was the most common cancer in our patients prescribed psychotropic medications (n = 37), which may reflect disease-specific factors. For example, patients with sarcoma often require multimodal treatment including surgery, chemotherapy, and radiation therapy. In addition, pain and altered body image are common consequences of these therapies (Patrick Mansky, MD and colleagues; unpublished data, 2006). While not included in the univariate analysis, 10 additional patients received psychotropic medications after enrolling in protocols at the NCI. Together, these findings suggest a possible relationship between psychotropic medication use and illness severity, duration, and treatment intensity. Furthermore, these statistics may underestimate rates of psychotropic medication use in the pediatric oncology population because anxiolytic drugs such as lorazepam and opiate medications were excluded.

Certain results from this retrospective review are striking. The rare use of psychostimulants was unexpected, especially in comparison with prevalence rates in the non-medically ill pediatric population. These patients, in particular, might have had low rates of behavioral, attentional, or internalizing problems, which may account for the low frequency of antipsychotic and psychostimulant use. Also, the physicians might have had an unknown preference for antidepressant and anticonvulsant agents. An analysis by Jensen et al28 has shown stimulants to be one of the best researched classes of psychotropic medications in children for both efficacy and safety. While these agents have been suggested to have limited clinical applications in children without a psychiatric disorder,49 psychostimulants may still be useful in pediatric patients with cancer by treating fatigue, poor concentration, and opiate-induced sedation.

The frequent use of mood stabilizers and antidepressants in this population of children with cancer was not unexpected. Mood stabilizers, such as gabapentin, are used in the treatment of peripheral neuropathy, which is commonly associated with both cancer and adverse effects of therapy (eg, tumor compression, surgery, and treatment with vinca alkaloids). Gabapentin has been shown to be well tolerated in childhood epilepsy and has applications in pediatric pain relief.30 Although gabapentin is a less potent mood stabilizer, it has been associated with treatment of mood in children.31 Other mood stabilizers, such as carbamazepine and valproic acid, are thought to be less clinically useful in medically ill pediatric patients because of delayed onset of action, drug interactions, and multiple toxicities (eg, hepatic, hematologic, and metabolic abnormalities).30 Tricyclic antidepressants are also often used to treat insomnia and pain in pediatric populations.

Despite controversy about the use of antidepressants in children and adolescents, a published report suggests that these agents are prescribed by approximately half of pediatric oncologists.9 This practice suggests that physicians are responding to clinically significant symptoms. Most children with terminal cancer have been described by their parents as having fatigue, pain, dyspnea, gastrointestinal tract symptoms, and “no fun” toward the end of life.32 While end-of-life issues were not addressed in this study, all children with cancer have these issues.
symptoms at some point, and some may find relief from the use of psychotropic medications during the course of their cancer treatment. Treatment of symptom clusters such as depressed mood and fatigue in cancer has been gaining acceptance because psychopharmacologic treatment for subthreshold psychiatric disorders may improve the quality of life in pediatric patients with cancer. Multiple contributions to symptoms of mood and anxiety disorders, such as illness severity, duration of illness, school absences, parental separation, activity limitations, and adverse effects of cancer treatments, are not ameliorated by psychotropic medication. Psychopharmacologic management is not intended to replace other comprehensive and multimodal interdisciplinary support or treatment of psychological symptoms and pain but to serve as an adjunct treatment when symptoms become debilitating. Further research to determine the efficacy of each medication class is needed to close the clinical practice gap in this medically ill population.

This retrospective investigation has a number of limitations. The method used to identify patients could not account for repeat patients who were enrolled before 2000. Anxiolytic agents could not be adequately assessed because of the frequent use of lorazepam in cancer treatment. Multiple medication use, cancer onset, and treatment, and neither the onset nor duration of cancer were assessed. Medication treatment and duration and the indications for and efficacy of the medication use could not be assessed beyond the point of entry into a protocol. While patients with brain tumors are at risk for seizures, no patients with brain tumors in this study (n=42) received an anticonvulsant drug from the NIH. Since the black box warning on antidepressants in October 2004, a substantial decline in antidepressant prescription frequency has been reported, with a possible increase in atypical antipsychotic prescription in children and adolescents. It is unclear whether these changes will be found in medically ill populations as well. Medications prescribed by non-NIH providers may not have been recorded in the computer records, leading to underestimation of use.

Children and adolescents participating in NCI trials comprise a select population of families within a single institution with the motivation to participate in clinical trials. Consequently, these patients may not be representative of or directly generalizable to the general population. Many of these patients have more severe illness than seen in the general population with cancer, but yearly, on average, 13 patients with newly diagnosed sarcoma were enrolled in pediatric oncology trials at the NCI, showing that the study population is comparable with pediatric oncology clinic samples.

This study was undertaken as an initial step in investigating the psychopharmacologic treatment of mood and anxiety symptoms in children with cancer. While symptom relief is a concern in this population, we recommend a comprehensive assessment for psychiatric syndromes when treating pediatric patients with cancer. Medications are not a substitute for respectful and open communication with patients. Psychological support, with or without psychotropic medications, is always indicated in a depressed or anxious child with cancer. Brain development and medical complications such as absorption difficulties and drug-drug interactions are additional considerations when giving a child psychotropic medication. We believe that the judicious prescription of psychotropic medications is an essential component of the comprehensive care of children and adolescents with cancer. Prospective treatment and prophylaxis investigations using psychotropic medications in pediatric patients with cancer should be considered, and such data should be collected in future pediatric cancer trials.

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REFERENCES


