Psychiatric Issues in Pediatric Oncology: Diagnosis and Management

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The presentation of intense distress of patients, parents, and others on the pediatric cancer unit remains all too common. From uncertainty and worry to suffering, grief, and loss, the emotional reality of the life-threatening and life-limiting nature of the disease is ever present. An essential skill of the psycho-oncologist (and any oncologist) is "normalization" of negative emotions and behaviors, in other words, reassuring an individual that their sadness, anxiety, fear, sense of helplessness, and possibly guilt are normal responses to a profoundly challenging experience. It can therefore be a subtle matter to determine the presence of psychopathology in people presenting in distressing situations. How much sadness or distress is "normal," when does it cross into a disorder, what behaviors are "understandable," when is mental illness present, and how do we explain it to someone who is in such a situation? This chapter addresses these questions and specific treatment recommendations when a psychiatric disorder is suspected in the pediatric oncology patient, with support from available literature and clinical experience.

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The Consultation-Liaison Child and Adolescent Psychiatrist in Pediatric Oncology

The pediatric consultation-liaison (C/L) psychiatrist, also referred to as pediatric psychosomatic specialist in some hospitals, is a child and adolescent psychiatrist with an expertise through specific experience and/or training in the psychiatric care of children and adolescents with medical illness (such as in triple board and/or psychosomatic medicine fellowship training programs). Many models of C/L psychiatry exist, but recent focus is on the development of integrated behavioral health programs embedded physically in pediatric centers, with a focus on collaborative multidisciplinary care and provider continuity (Talmi and Fazio 2012; AAP. National Center for Medical Home Implementation 2015). At a minimum, pediatric oncology programs should develop relationships with C/L child psychiatry services within their center to provide access to

A.N. Abrams et al. (eds.), *Pediatric Psychosocial Oncology: Textbook for Multidisciplinary Care*,
DOI 10.1007/978-3-319-21374-3_8

psychiatric consultation when needed. Close collaboration and mutual support between C/L child psychiatrists and pediatric oncologists, nurses, social workers, psychologists, child life, and other psychosocial clinicians is the essence of this work, from introduction of the psychiatric consultant to biopsychosocial evaluation, workup, and treatment planning.

Diagnostic Considerations

For accurate treatment formulation and clear communication with patients, families, and medical teams, it is important to be able to diagnose primary and secondary psychiatric syndromes, often in the context of complicated physical and emotional symptom burden. Psychiatric disorders may be present prior to a diagnosis of cancer (e.g., ADHD, separation anxiety disorder), precipitated by the stress of disease or treatment (e.g., reactive depression or disease related anxiety in a vulnerable patient with a family history of anxiety and mood disorders), directly caused by the disease or treatment (steroid-related psychosis or postsurgical posterior fossa syndrome), or completely coincidental to cancer (development of bipolar disorder or schizophrenia). Evaluation starts by collecting a comprehensive history of present illness from multiple sources (patient, caregiver, and hospital staff familiar with the patient). It is critical to get baseline information of the patient's development and prior psychological, emotional, and academic functioning. Discussion of family history is key for recognition of genetic predisposition for hereditary mental illnesses, mood disorders and anxiety. The child psychiatrist consultant should be familiar with cancer treatments and supportive medications, their expected courses, side effects, and treatment road maps to help with diagnosis, treatment planning, and anticipatory guidance with families. Regular examination of medication regimens and laboratory trends is essential.

Many psychiatric diagnoses are the same in children with or without cancer and must remain on the mind of the clinician: e.g., ADHD, oppositional defiant disorder (ODD), panic attacks, separation anxiety, and selective mutism. Some diagnoses, however, have particular presentations in the psycho-oncology setting and those will be discussed specifically here.

Family Functioning and Mental Illness

The impact of parent functioning on child adjustment, coping, and functioning should not be underestimated in the general pediatric psychosocial assessment and specifically in pediatric psycho-oncology (Rosenberg et al. 2014; Pai et al. 2007) (see Chap. 9, Family Interventions). The consultant should take this opportunity to screen parents for mental illness, an important part of a holistic assessment, as parent distress and impairment is common and may affect a child's coping with cancer. Parent assessment is important for understanding a child's presentation. Evidence suggests that identification and treatment of parent psychopathology, or other systemic interventions (e.g., provision of alternate caregivers for respite, etc.) to buffer the effects of parents' symptoms on children, may result in more rapid and complete resolution of psychiatric symptoms of children, with less potential for side effects of psychopharmacologic intervention (Waters et al. 2009)

Psychopharmacology for Medically Ill Children

Psychotropic medication can be safe and effective even in the medically complex pediatric oncology population. Estimates show that psychotropic medications are used in 6 % of the general pediatric population and at likely double that rate in the pediatric cancer population (Zito et al. 2003; Pao et al. 2006) The process of Federal Drug Administration approval for use of drugs in children is based on limited available evidence from specific pediatric psychopharmacologic studies (Kearns and Hawley 2014). While child psychiatrists prefer to use psychotropic medications "on-label" for their pediatric patients; it is

not uncommon that certain medications are used "off-label" when no other treatment is available or when the usual treatments are contraindicated. This practice is guided by evidence for the use of these medications in adults but not yet approved in pediatrics or FDA approval for use in pediatrics but for different disorders or symptoms than the labeling indicates.

The threshold to consider medication treatment of psychiatric symptoms is reached when symptoms interrupt or disrupt necessary medical treatment (e.g., through nonadherence, inability to communicate with or assess the patient), present safety concerns (e.g., agitation while connected to intravenous infusions or with severe thrombocytopenia), or cause the patient significant suffering. The choice of which medication to recommend follows the framework of *applied clinical therapeutics*, which is the consideration of all evidence and experience about the patient, the disease, and the medication, integrated and applied to clinical decision making. Considerations within this framework may include:

- Pharmacokinetics: *the study of the biological fate of external substances or medication administered from the moment of administration to complete elimination from the body*.
  - Routes of administration may be limited by developmental stage, nausea, gastrointestinal (GI) disease, or toxicity (e.g., impaired oral absorption in patients with severe diarrhea and transdermal formulations contraindicated with severe skin rashes).
  - Distribution can be affected by height, weight, nutritional state, and fluid balance.
  - Hepatic cytochrome p450 interactions of multiple drug regimens can profoundly affect metabolism.
  - Excretion affected by liver, GI, and renal function.
- Pharmacodynamics: *the study of a drug's biochemical and physiological effects on the body including mechanisms of action and the dose–response relationship.*
  - Drug–disease-state interactions (e.g., hypotensive effects of drugs in patients with low blood pressure; possible suppressive effects on bone marrow in patients with hematologic illness)
  - Consideration of potential serotonin syndrome and neuroleptic malignant syndrome in differential diagnosis of vital sign abnormalities
- Pharmacogenomics (or pharmacogenetics): the study of the role of genetic variations in drug response by correlating gene expression or single-nucleotide polymorphisms with drug absorption, distribution, metabolism, and elimination, as well as drug receptor target effects. *Pharmacogenetics* focuses on single drug–gene interactions, while *pharmacogenomics* encompasses a more genome-wide association approach, incorporating genomics and proteomics to consider the effects of multiple genes on drug response.
  - Patients with particular *p450 polymorphisms* are prone to nonresponse, overresponse, or increased toxicity due to individual metabolism. Genetic testing can predict this in some cases and dosing can be adjusted (Drug-Gene Alerts — Mayo Clinic Center for Individualized Medicine, 2014).
  - *Family history* of response to drugs may imply similar inherited pharmacogenomics, even if testing is not available to show this empirically.

Psychiatric Treatment Planning in the Medical Setting

The final recommendation for treatment with a psychotropic medication should take into consideration practical issues such as the availability of the medication, cost, route of administration and dosage forms, dosage range, flexibility of dosing, interactions with other medications, and other special characteristics of the medication. Consultants should collaborate by problem-solving with medical teams, families, and patients for devising and implementing successful drug treatment regimens.

Informed consent for psychotropic medication should include discussion of treatment options and alternatives, risks, and benefits of the treatment, known adverse effects, dosing scheme ("How much?"), duration and timing of treatment ("How long?"), and legal and ethical considerations including off-label use and black box warnings.

Inherent to successful psychiatric treatment in the pediatric medical setting is the establishment of a four-way relationship of collaboration and open communication between the patient, parent, medical team, and psychiatric consultant. The medical team may need support and education about the consultant's formulation of the patient and their symptoms and the medical provider's own countertransference. This is traditionally considered the "liaison" aspect of the C/L work. Ideally, psychoeducation in the context of collaborative relationships will help manage all parties' expectations of the treatment effects: what symptoms will and won't respond to medications, what is an expected timeline for response to medication, and what is the role of adjunctive therapies in addition to medications. The team can then reinforce the psychiatric treatment plan as part of the patient's overall care, and the patient and parent are able to feel supported with consistent, psychologically informed care.

Psychiatric Disorders and Symptoms in Pediatric Psycho-oncology

Complex Symptom Management: Distinguishing Psychological from Medical Symptoms

Few patients with cancer present with psychosomatic syndromes that meet full diagnostic criteria, such as functional neurological symptom disorder (formerly known as conversion disorder in DSM-IV). Much more common, however, is the request to determine whether a patient has a psychological cause of unexplained or difficult to manage physical symptoms (e.g., pain, nausea/vomiting, headache, fatigue, etc.) that seem out of proportion to known pathophysiology. The interaction between psychological stressors and physical symptoms of disease is thought to account for the increased rates of anxiety disorders in young patients with medical illness (Pao and Bosk 2011). Patients with poor coping, lack of psychosocial supports, or lack of age appropriate explanations for their symptoms may be particularly at risk for this type of presentation. School-age children (or older children with behavioral and emotional regression) may present with developmentally typical somatic symptoms (such as headaches and stomachaches) as a manifestation of anxiety. A full psychiatric evaluation and review of the medical record, patterns and triggers of the physical symptoms, workup for alternate causes of the symptoms, and success of treatments attempted is warranted. Evaluation of the child's explanation of the symptoms and understanding of their own illness can uncover fears and misconceptions that may feed anxiety around a particular symptom. An understanding of the parent (or caregiver)–child relationship is helpful in determining whether parents can distinguish pain from anxiety, behavioral distress, or manipulation, in their child. For an accurate assessment, the consultant may need to confront the defensiveness that can result from a patient thinking a psychiatrist has been called because the medical team believes the symptoms (pain, nausea, etc.) are "all in my head," exaggerated, or manufactured. An up-front explanation of the mind–body connection, anxiety components of pain or nausea, and reassurance that the mental health evaluation is not an attempt to discredit the patient but to help them improve the teams' understanding and ability to treat their symptoms can help form an alliance with the patient and their family.

If anxiety or depression is present, treatment is warranted regardless of whether the psychological symptoms "cause," worsen, or are a reaction to the physical symptoms, and it is not necessary to insist the patient believes or admits to the diagnostic formulation to proceed with an evidence-based therapy. Even without realizing the full impact of their emotional distress on their physical well-being, many patients and families benefit from medical play, cognitive behavioral techniques, and motivational interviewing to reduce fear of the physical symptoms, improve

communication with medical staff, clarify medical assessment, and improve patient functioning. Family psychoeducation and support can modify family response to symptoms and reduce the unwitting reinforcement of the child's symptom with undue anxiety and attention.

Depression

Case Vignette

Nick, a 9-year-old boy, with a strong family history of mood disorders in mother, presented 3 months post-diagnosis of high-risk acute lymphocytic leukemia (HR-ALL) with severe anorexia, lethargy, and marked anhedonia persisting through a recovery period in his chemotherapy schedule, where he had not received treatment for over 2 weeks. Medical complications were ruled out and psychiatric consultation was sought. He had demonstrated irritable mood and loss of energy during steroid courses in induction and consolidation, but post-steroids the irritable mood had given way to a flat affect, helpless behaviors, and periods of crying. A G-tube was placed for nutritional repletion and support. This had stabilized his weight loss but he did not gain weight and his appetite and energy did not improve. On interview with the child psychiatrist, he reported feeling guilty for the trouble he was causing his mother since he got sick and only having interest in doing things he could no longer do like riding his bike. He asked if he would die from his cancer and shared that he thought he would, but denied wanting to die. Over the following 10 days, he and his mom were seen three times for assessment and initiation of therapy. However, he did not engage in the therapy and did not show any improvement. ***Diagnosis***: major depressive episode. ***Recommendations***: He was started on sertraline 12.5 mg daily and titrated to 50 mg daily over the course of the following month (an off-label use of a commonly used SSRI that is only FDA approved in children ages 6–17 for OCD). ***Outcome***: He had an excellent response to the medication and nutritional repletion and was able to participate in multiple integrative medicine and psychosocial supportive therapies at the center. His appetite, mood, energy, and interest improved to baseline level and he again demonstrated a mischievous wit and fascination with war-themed video games and films. He was maintained on sertraline for 2 years until 6 months post-leukemia therapy when he tolerated a slow taper off the medication.

While studies have shown that it is common for pediatric cancer patients and their families to experience intense transient distress around the diagnosis of cancer, and at other vulnerable points in the treatment trajectory, most demonstrate resilience in the face of this distress and do not meet criteria for psychopathology (Stuber 2012). A recent Children's Oncology Group (COG) prospective study of a homogeneous group of 159 children with standard risk acute lymphoblastic leukemia (SR-ALL) showed that children in this population do have a higher than expected risk for anxiety (25 %) and depression (21 %) at 1 month post-diagnosis and the risk of depression persists up to 1 year post-diagnosis, particularly in children who are Hispanic and whose families are poorly functioning (Myers et al. 2014). Similar studies are needed to investigate the risks for other oncology patient populations, who may have additional disease and treatment-related risk factors such as poorer prognosis, higher symptom burden, and cranial radiation or other CNS-related effects.

Recognition of depression is an important clinical issue. At the time of cancer diagnosis, initial adjustment difficulties with depressed or anxious mood may commonly appear due to the idea of having cancer and the rapid drastic life changes that follow. However, the acceptance (by inexperienced or nonpsychiatric staff or families) "that everyone who has cancer is depressed" or that depression is "appropriate" or normal can be misleading and allow impairing anxiety and

depression to be underdiagnosed and undertreated in this population (Ruland et al. 2009; Kersun et al. 2009). Depression may develop as a patient's vulnerability (due to a strong positive family history of psychiatric disorder or the child's own previous psychiatric history) (Rosenstein et al. 2014) becomes exacerbated by the biological and psychological stresses of cancer and treatment. As cancer treatment duration continues, patients who become clinically depressed may have difficulty coping and be less adherent with their cancer treatment which can then create a downward spiral and lead to worsening depressive symptoms (Patenaude and Kupst 2005). In survivorship, children who have significant and severe late side effects also tend to have poorer self-esteem and be more depressed (Institute of Medicine (US) and National Research Council (US) and National Cancer Policy Board 2003).

Even for experienced clinicians, it can be challenging to determine if a child with cancer has major depression given the number of overlapping somatic symptoms such as changes in sleep, appetite, level of energy or fatigue, and concentration. These concomitant neurovegetative symptoms and the mental symptoms of lassitude and apathy mimic symptoms of depression when a patient is neutropenic in the same way some animal models demonstrate cytokine-induced "sickness behaviors" (Cleeland et al. 2003). There are suggestions that a subtype of depression may be related to inflammatory pathways which could prove particularly relevant in cancer patients (Raison and Miller 2011). Clinicians working with children with cancer may need to focus on the more cognitive aspects of depression such as anhedonia, guilt, poor self-esteem, or feeling like a burden on others to distinguish more syndromic major depression. It is important to diagnose depression as it can affect quality of life and treatment adherence in patients with childhood cancer (Kersun et al. 2009).

Suicidal Ideation

If the oncologic disease progresses with relapses and treatment failures, it can sometimes be difficult to understand what a child means if they articulate "feeling tired of fighting." These passive thoughts about dying or "giving up" may be realistic and not a sign of intention for self-harm, but are frightening to the patient, family, and staff. Clinicians need to gently probe for active suicidal ideation in the setting of depression, but often clinicians are afraid to ask for fear of upsetting the child or "putting ideas in their head." The myth of iatrogenic suicidal ideation by asking children about suicide during an assessment has been refuted in a randomized controlled clinical trial (RCT) (Gould et al. 2005).

In adult patients at end of life, the "desire for hastened death" has been associated with demoralization syndrome and is more prevalent in patients with poorly controlled physical symptoms, inadequately treated depression and anxiety, and reduced social functioning and support (Robinson et al. 2014). While this has not been studied in children or adolescents, it is essential that pediatric clinicians obtain a comfort level and skill in discussing death and dying with parents and then with pediatric patients themselves. Prudent management of suicidality in pediatric cancer patients is to aggressively address all modifiable symptoms while ensuring the patient's safety (see Chap. 14 on palliative care). As dual-diagnosis medical–psychiatric inpatient units are rare, the inpatient pediatric oncology ward with 1:1 companion for suicide precautions may sometimes be the safest location, medically and psychiatrically, for treatment of a suicidal pediatric oncology patient.

Finally, adult survivors of childhood cancers are at increased risk for suicidal ideation related to cancer diagnosis as well as posttreatment mental and physical health problems, even many years after completion of therapy and therefore should be monitored in outpatient settings into adulthood (Recklitis et al. 2010).

Anxiety

Case Vignette

Leah, a 7-year-old girl with stage IV neuroblastoma, presents for evaluation and

treatment of anxiety in the context of antibody therapy. She has no evidence of active disease after five cycles of high-dose chemotherapy, surgical resection of primary abdominal tumor, and radiation to two small sites of bony metastases. She has undergone two prior cycles of the anti-GD2 antibody therapy, which she found very difficult to tolerate as it caused abdominal and back pain during infusion. She understands the disease and the purpose of the antibody very well and she and her parents benefited from working with child life and dance therapy to learn coping and relaxation techniques to use during treatment. On the way to the medical center for another week long course of antibody therapy, she develops stomach pain and nausea, which she says comes from "thinking about the medicine." On arrival to clinic, she is retching and unable to take her oral premedications. Parents report she is a mildly anxious child at baseline, with no history of psychiatric treatment, but report she had self-limited separation anxiety at the start of school and nightmares for 1 month after the death of grandfather last year. However, they report that over the past month, between the cycles of antibody, she has been playful, social, and interactive at home, with improving physical status after her intensive therapies. She says she is looking forward to going to school again when they return home after this cycle of antibody. ***Diagnosis***: Adjustment disorder with anxiety. ***Recommendations***: Child psychiatry recommends a trial of lorazepam 0.5 mg orally on the mornings prior to her clinic visits for the rest of this cycle and the next cycle. ***Outcome***: The next morning, after the first dose, she tolerates antibody therapy much better with minimal opiate medication for pain. By the fifth cycle, 2 months later, she only needs a single dose of lorazepam on the way to clinic the first day of treatment and copes well with treatment the rest of the week.

Anxiety symptoms are common in medically ill children, often manifesting as irritability, anticipatory anxiety for procedures, sleep disturbance, behavioral regression, and unexplained physical symptoms (Pao and Bosk 2011). Prevalence of anxiety disorders in medically ill children and adolescent age ranges from 7 to 40 % in studies, compared to approximately 13 % in the general population of children and adolescents (Lavigne and Faier-Routman 1992). In the COG study discussed above, children with SR-ALL had a higher rate of anxiety disorders at 1 month post-diagnosis but this normalized at 6 months and 12 months (Myers et al. 2014). Diagnosis of an anxiety disorder in a child or adolescent with cancer must take into account a patient's understanding of and adjustment to the illness and treatment, possible contribution of cancer and directed therapies producing anxiety symptoms (e.g., corticosteroids, thyroid abnormalities), and family coping and adjustment. Adjustment to illness is related more to psychosocial than medical factors, such as parental adjustment, socioeconomic status, social support, and intelligence, and psychotherapeutic interventions can be targeted at these factors. Psychoeducation and psychotherapeutic techniques (primarily cognitive behavioral therapy) have been developed around pediatric medical traumatic stress and coping and resiliency frameworks and form the mainstay of evidence-based universal and targeted psychosocial supports and preventive services which pediatric cancer centers should provide as standard of care (see Chap. 6 Psychotherapeutic Modalities) (Kazak et al. 2012; Pao and Wiener 2011).

When anxiety symptoms have not responded to usual psychotherapeutic interventions or disrupt a child's medical treatment (e.g., nonadherence with treatment or assessment), normal routines (e.g., prolonged sleep disruption or inability to separate from parent), or family functioning (e.g., child requires so much attention from parents that siblings are starting to manifest adverse symptoms as well), medication management of anxiety may be appropriate. Medication selection is guided by applied clinical therapeutics and one or more drugs may be appropriate, depending on the evidence base for specific

disorders, FDA approval for children, need for short- or long-term management, and comorbid medical symptoms and treatments. Family history of childhood anxiety may be relevant to the decision to medicate a child for anxiety (e.g., initiation of selective serotonin reuptake inhibitor (SSRI)) as it may indicate underlying vulnerability to anxiety across many situations and triggers and beyond a particular period of acute stress. SSRIs, selective norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, and antipsychotics are included in detailed clinical cases, the Medication section discussion, and tables in this chapter. Buspirone has not been found efficacious in the management of pediatric anxiety disorders (Strawn et al. 2012).

Posttraumatic Disorders and Symptoms

The diagnosis of pediatric medical traumatic stress (posttraumatic effects of a medical illness or related event) may be appropriate if a child or adolescent identifies cancer or aspects of their cancer treatment to be extremely traumatic. The previously held thought that PTSD occurs with high prevalence (20–30 %) in patients and family members (Stuber 2012; Bruce 2006) has been refuted recently with a matched-peer controlled study by Phipps et al., who found no higher rates of PTSD than the general population, at around 0.4 % (current, lifetime prevalence was 2.8 %.) (Phipps et al. 2014). This difference has been attributed to research methodologies used, in particular use of screening instruments (vs. diagnostic interview), focusing effects of mentioning cancer as a traumatic event prior to assessment of symptoms, and lack of the use of normal controls. It will be important that this single center study be reproduced. Diagnosis of medical PTSD should follow DSM-5 criteria, and consideration of prior traumas (not just assuming cancer is the "Criterion A event") is important. If PTSD is diagnosed, pharmacologic support for control of symptoms (anxiety, insomnia, hyperactivity/hypervigilance) and comorbid psychiatric disorders is the appropriate approach. Due to the theory that patients with PTSD have overactive adrenergic systems, anti-adrenergic medications (guanfacine, clonidine) have theoretical value and have shown some benefits in subsets of patients, but more research is needed (Strawn et al. 2010; Dowben et al. 2011). In adults, prazosin, another alpha-adrenergic blocker, has shown promise in reducing nightmares in trials with civilians and combat veterans with PTSD (Green 2014). Atypical antipsychotics and mood stabilizers also have limited benefits depending on symptoms presented and functional impairment.

Delirium

Case Vignette

Psychiatry team is called to see Matthew, a 14-year-old boy with aplastic anemia, in remission 4 months post-stem cell transplant admitted with Epstein–Barr Virus (EBV) related lymphoma of multiple sites including chest and neck, to assess "anxiety." He has a history of recent airway obstruction which caused significant anxiety and is aware of his guarded prognosis and reliance on experimental anti-EBV T-cell therapy. Over the course of his 2-week admission, he has received liberal doses of hydromorphone and lorazepam to treat pain, nausea, and anxiety. Medication review reveals he is also receiving corticosteroids, multiple antifungals, and antibiotics. He had fevers a day prior to consult, but is afebrile when seen. On exam, patient is a pleasant, knowledgeable, anxious adolescent who is unable to fully participate in conversations as he nods, off in the middle of sentences due to sedation. When he awakens he asks to be reoriented "Where was I?" He apologizes for his inability to focus. He reports there have been some "misunderstandings" about his medication use with staff, and he feels persecuted as a "drug seeker." He worries that people in the hallway are talking about him. He complains of very poor sleep at night but inability to

Table 8.1 Delirium in children with cancer

DSM-5	
Acute-onset, fluctuating, usually reversible, change in mental status Disturbance in attention and awareness Change in at least one domain of cognition (e.g., memory, orientation, language, perceptual disturbances)	
Symptoms in infants and children (*hypoactive*, *hyperactive*, *or both*)	
Disoriented (both) Inattentive (both) Disorganized sleep (both) Sparse or delayed responses (hypoactive) Oversleepy (hypoactive)	Refractory agitation (hyperactive) Requiring escalating doses of sedation (hyperactive) Pulling lines and tubes (hyperactive) Withdrawal, flat affect (hypoactive)
Screening tools	*Ages for use*
Pediatric Anesthesia Emergence Delirium (PAED) (Sikich and Lerman 2004) Pediatric Confusion Assessment Method (pCAM) (Smith et al. 2011) Preschool Confusion Assessment Method (ps-CAM) Cornell Assessment of Pediatric Delirium (CAPD) (Traube et al. 2014)	Over 18 months old Over 5 years old 2–5 years old (pending publication) From newborn and up (0–21 year)
Etiologies	
Common Anesthetics (except dexmedetomidine) Antihistamines Benzodiazepines (intoxication or withdrawal) CNS disease Infection (systemic or localized) Metabolic/electrolyte derangements Opiates (intoxication or withdrawal) Scopolamine/anticholinergics Seizure Steroids (intoxication or withdrawal)	*Less common* Biological therapy (antibody or cell therapies) Catatonia CNS vascular event (hemorrhagic or embolic) Ifosfamide/other chemotherapy toxicities NMDA receptor encephalitis Other paraneoplastic encephalitis Opsoclonus-myoclonus Posterior reversible encephalopathy syndrome (PRES) (Kushner et al. 2013) Severe vitamin deficiencies (or rapid repletion in refeeding)
Behavioral/environmental interventions	
Use familiar toys, music, and caregivers Primary nursing care Frequent reorientation Nonconfrontation of delusions/hallucinations Encourage oral hydration Reduction in stimulation	Diurnal cycle preservation Encourage awake in day, sleep in night Cluster nursing care to reduce unnecessary awakenings Timing of sedating medications Early mobilization/encouragement of physical therapy

stay awake during the day. ***Diagnosis***: Delirium – multifactorial, secondary to recent fever, polypharmacy, exacerbated by poor sleep. ***Recommendations***: Child psychiatry recommended that team decrease the use of lorazepam and add olanzapine 2.5 mg at night to help manage his delirium as well as improve his sleep and alleviate nausea and anxiety. It was also recommended that he be reoriented frequently, cluster night nursing care to preserve sleep, and encourage oral intake, mobility, and physical therapy during the day. ***Outcome***: Patient showed significant improvement over the course of the ensuing 24 hours. Olanzapine greatly improved sleep and nausea and was continued in lieu of lorazepam for several weeks. Parents demonstrated improved insight and early recognition of future episodes of subthreshhold delirium which were quickly reversed. Patient engaged in ongoing psychotherapy for anxiety related to his illness.

Delirium is an acute brain dysfunction related to systemic illness, affecting 10–30 % of critically ill children in pediatric intensive care units (PICU). It carries significant risk for prolonged hospital and PICU stays and is associated in adults with increased mortality and prolonged neurocognitive sequelae. Diagnosis in children, like adults, follows DSM-5 criteria (Table 8.1) and may present as hyperactive, hypoactive, or mixed type. Research on pediatric delirium has increased in recent years with new screening and diagnostic tools and treatment algorithms (Smith et al. 2009; Creten et al. 2011; Silver et al. 2014). Pediatric clinicians must consider the differential presentation of delirium through a developmental lens. Consensus is emerging that with careful consideration of a child's baseline development and functioning in each symptom domain of delirium, it is possible to diagnose delirium from infancy and even in the context of developmental delay (Table 8.1) (Turkel et al. 2013; Silver et al. 2014). Coordination of care with family caregivers and inpatient nurses is critical to understand fluctuating mental status in delirious children.

The differential diagnosis of delirium may include undertreatment of pain or other physical symptoms, emotional distress (depression vs. hypoactive delirium), tantrums, and traumatic symptoms (Creten et al. 2011; Turkel et al. 2006). Once identified, clinicians should first seek to reverse delirium by treating underlying medical etiologies and/or removing offending "deliriogenic" medications (Table 8.1). Medical workup of the newly identified delirious patient should include blood and urine cultures, physical exam, and routine laboratories. Other workup will depend on the specific symptoms and history of each patient. In immunocompromised patients, a high index of suspicion for infection should be present.

In pediatric oncology, the most common causes of delirium include: opiates (intoxication and withdrawal), anesthesia, benzodiazepines, antihistamines, steroids, and infection. In the case of opiates, changing to another opiate ("rotation") may relieve symptoms as patients may be more sensitive to side effects of a particular drug and more tolerant of another. While most general anesthetics may be a risk factor, there is evidence that use of dexmedetomidine, during surgical procedures or for sedation in the PICU, may be protective against delirium (Dahmani et al. 2014).

Interventions for Delirium

The consulting psychiatrist can recommend a change in sedatives or anesthesia, after which dosing and management would be at the discretion of the intensivist or anesthesiologist. In addition to addressing underlying medical etiologies, staff can implement environmental changes that assist with comforting, reorienting, and promoting normal sleep for delirious patients. While environmental or sensory disruptions alone will not cause delirium, a calm and nonthreatening environment helps reduce distress and agitation in the disoriented patient and should be a goal for all hospitalized patients. When possible, clustering of nursing care (to reduce interruptions at night and preserve sleep), frequent reorientation of the patient, preservation of day/night cues (e.g., lights on in the day, off at night), early mobilization even in the PICU, and encouraging oral hydration can all improve sleep quality and reduce disorientation and agitation in delirious and at-risk patients (Silver et al. 2014).

While addressing these factors, if symptom management is required for reasons of safety or distress (e.g., the child is pulling lines and tubes, hallucinating, or frightened), the off-label use of low-dose atypical antipsychotics is the recommended intervention in adults and children (Turkel and Hanft 2014). Use of atypical antipsychotics has been found to be safe in low doses and often allows for reduced use of other sedatives, which may be causing delirium and normalization of sleep/wake cycle. As sleep disruption is now understood to be a critical mechanism and core symptom of delirium, it is not surprising that studies are investigating use of melatonin to reset (or prevent disruption of) circadian rhythm in patients at risk or already experiencing delirium. Melatonin and melatonin agonist studies in adults, which have been small, have found they are well tolerated with modest benefit in prevention but not resolution of delirium. As melatonin is known to be safe and help-

ful in multiple types of pediatric sleep disorders, it is reasonable to consider its use in targeted cases of sleep disruption (Turkel and Hanft 2014; Chakraborti et al. 2014; Özcan and Dönmez 2014).

Since antihistamines and benzodiazepines are routinely used in daily pediatric oncology care, it is common to see children who have "paradoxical" reactions and become agitated, enraged, hyperactive, disinhibited or present with the full syndrome of delirium. In general, antihistamines and benzodiazepines should be avoided for children with a history of paradoxical reactions; however, sometimes these medications are unavoidable (e.g., blood transfusions requiring premedication with antihistamines) and concomitant use of a low-dose atypical antipsychotic may be needed to offset these adverse effects. Antipsychotics and other dopaminergic drugs like metoclopramide can induce extrapyramidal symptoms (EPS) (e.g., oculogyric crisis, torticollis) or akathisia (a type of psychomotor agitation, often described as "ants in pants" or a "restless leg" type of feeling all over the body). A careful history about the timing of medications and the development of symptoms can help differentiate these types of symptoms in a patient who may have an evolving delirium in the context of polypharmacy, which is very common. Further discussion of doses and scheduling follows in the Medications section.

Withdrawal Syndromes

Some patients with cancer experience chronic symptoms such as pain, nausea, and anxiety, which may necessitate long-term administration of habit-forming medications such as opiates or benzodiazepines. This can occur in an inpatient setting (e.g., during a prolonged critical illness or stem cell transplant) or with chronic comorbidities (e.g., avascular necrosis of joints related to corticosteroids, phantom limb pain, persistent nausea) of cancer therapy as an outpatient. Acute or subacute changes in a patient's clinical status (for better or worse) may result in the rapid reduction of these medications and cause opiate or benzodiazepine withdrawal symptoms if a patient had developed physiological dependence to the drug. It is common for these sorts of dose changes, made 2–3 days prior to presentation of withdrawal symptoms, to be overlooked when a patient's medical problems are complex, acute, and fluctuating. Therefore, careful review of the medications dispensed over the course of the symptoms is important.

While the classic syndrome of opiate withdrawal includes hypertension, tachycardia, vomiting, diarrhea, and diaphoresis, milder symptoms experienced by patients still on some dose of opiate often appear psychiatric in nature, including dysphoria, anxiety, emotional lability, tremulousness, fatigue, myalgias, and nausea. With the recognition of withdrawal, these symptoms can be easily treated and reversed. For patients on a short course of opiate therapy (less than 14 days), the World Health Organization (WHO) guidelines recommend discontinuation by a taper which decreases the original dose by 10–20 % every 8 hours, gradually increasing the time interval. However, for patients on opiates for longer periods, dose reduction should not exceed *10*–20 *% per week* and management should include a measurement of withdrawal symptoms using a standard scoring system (World Health Organization 2012). The treatment of cancer-related and treatment-related pain in children is covered in Chap. 3 and in the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses.

Benzodiazepine withdrawal can present similarly, with symptoms of nausea, agitation, anxiety, tremulousness, myalgia, tachycardia, and hypertension. Benzodiazepine withdrawal, like alcohol withdrawal, can cause dangerous hypertension and seizures and should be considered in any new onset seizure in a medically complex patient who has recent exposure to benzodiazepines. As with opiates, tapers in chronic users should be slow and based on prevention of objective signs of withdrawal (like the Withdrawal Assessment Tool (WAT-1) or the Sophia Observation Withdrawal Scale). Research in the area of monitoring and guidelines for tapering of sedation and other uses of opiates and benzodiazepines in pediatrics is urgently needed (Poh et al. 2014; Galinkin et al. 2014; Ista et al. 2013).

Other Iatrogenic Symptoms

Case Vignette
Lucy, a 3-year-old girl with acute myelogenous leukemia (AML), who receives steroids for 1 week each month, has been exhibiting worsening irritability over the 7-day course of steroids each cycle. Her pediatric oncologist requests child psychiatry consultation to assess her mood and behavior. Parents report escalating outbursts to rageful tantrums in which she is inconsolable, irrational, screaming, and throwing herself on the floor for up to 90 minutes regardless of any intervention by parents. Parents note that despite offering her whatever she wants she doesn't stop until she "cries herself to sleep." She also has started threatening to pull out her central line when agitated. Her sleep is erratic, waking during the night crying and hungry. The symptoms escalate over the week and finally dissipate 2–3 days after steroids are stopped. ***Diagnosis***: Substance (corticosteroid)-induced mood disorder. ***Recommendation***: Start risperidone at 0.25 mg at bedtime and titrate up to 0.25 mg in AM and 0.5 mg at bedtime during steroid courses only. ***Outcome***: The patient responded well with better sleep at night and fewer, self-limited tantrums lasting less than 5 minutes with consolable irritability. Mother reports patient still has personality changes the week on steroids, but they are much more manageable. The patient's appetite is ravenous during the day due to the additive effects of steroids and risperidone, but with safety concerns and sleep both greatly improved, her mother feels this is acceptable.

Many cancer treatments cause iatrogenic psychiatric symptoms. Administration of corticosteroids, which is commonly used for the treatment of ALL and lymphoma, causes varying degrees of irritability, mood lability, impulsivity, lethargy and/or insomnia (Ularntinon et al. 2010). These changes can be intense but are usually limited to the duration of the treatment. Psychoeducation may be sufficient in supporting a patient and family through their course of corticosteoids, but if significant impairment is present, a short-acting agent like risperidone can be extremely helpful in reducing impairment and distress. If chronic steroid use is needed for graft versus host disease (GVHD) or other illnesses, frank clinical depression or anxiety disorders may develop which warrant other targeted therapies.

Another medication that warrants close monitoring of psychiatric symptoms is isotretinoin (Accutane), most commonly used for severe cystic acne, but due to its effect on inhibition of tumorigenesis, it has also been used in regimens treating neuroblastoma, medulloblastoma, and other skin and brain cancers. Prescription of isotretinoin in the United States can only occur if patient is registered and monitored on an FDA-administered website due to its side effects of severe teratogenicity, blood dyscrasias, and psychiatric effects, which include depression and mood lability and, rarely, suicidal ideation or completed suicide. It is often well tolerated. If needed, atypical antipsychotics can be useful for offsetting any mild to moderate psychiatric effects, but the presentation of severe psychiatric symptoms warrants reevaluating the risks and benefits of the treatment.

Interferon alpha (IFN-alpha), an immunotherapy used for treatment of metastatic melanoma, hepatitis B and C, giant cell tumors, and rarely other disorders, carries significant side effects including flu-like symptoms, fatigue, anorexia, and neuropsychiatric symptoms like depression, mania, and psychosis. It is generally better tolerated in children than adults but symptoms, if present, often respond well to targeted therapy with antidepressant, antimanic, or antipsychotic medication.

Neurocognitive Impairment

The evaluation and management of neurocognitive adverse effects of cancer illness and therapy in children and adolescents are discussed in

Chap. 10. As part of a differential diagnosis during psychiatric evaluation, neurocognitive symptoms may include impairment of any domain of cognition, in particular, memory, attention, processing speeds, and visual motor integration (Castellino et al. 2014). A patient with acquired neurocognitive impairment may present to psychiatric evaluation with secondary anxiety or frustration with daily tasks (e.g., due to reduced ability to attend or process information), amotivation, or underachievement in academics. For the assessment of inattention and other cognitive symptoms after cancer treatments, an ADHD framework is insufficient, as many at-risk patients will not meet diagnostic criteria (Kahalley et al. 2011). Of note, depression, anxiety, and PTSD can also have cognitive symptoms like attention impairment and should be ruled out. Neuropsychological testing is an essential part of evaluation and treatment planning for patients with these types of symptoms. Some patients with attentional issues due to ADHD or acquired cognitive deficits may benefit from stimulant therapy to improve performance on focused tasks (Pao et al. 2006). In pediatric cancer survivors who received CNS directed therapy (ALL with cranial radiation and brain tumors), response to methylphenidate (MPH) is less robust (45 %) than in the ADHD population (75 %) . A history of preexisting inattention/ADHD is the best predictor of response. Given that the safety and tolerability are favorable, and similar to the ADHD population, and nearly half will have a response, Conklin et al. recommend a trial of methylphenidate with a slow titration and close monitoring of treatment response and side effects (Conklin et al. 2014). See Table 8.5, Stimulants, for specific medication information.

Medications

Antidepressants (Table 8.2)

Retrospective reviews of antidepressant use in pediatric oncology patients have been conducted (Pao et al. 2006; Portteus et al. 2006; Kersun and Elia 2007; Phipps et al. 2012). In most centers, pediatric oncologists prescribe antidepressants, but fewer than 10 % of the oncologists report specifically assessing for suicidal ideation despite the institution of a black box warning on use of selective serotonin reuptake inhibitors (SSRIs) in adolescents (Phipps et al. 2012). Consultation with a child psychiatrist by the pediatric oncology medical team is encouraged for the selection and monitoring of psychotropic medications for pediatric oncology patients. There are no randomized controlled trials (RCTs) in children with cancer and depression using antidepressants including SSRIs, the current antidepressant treatment of choice in children and adolescents (Valluri et al. 2012). In the United States, only fluoxetine and escitalopram have pediatric Food and Drug Administration (FDA) indications for depression (see Table 8.2 Antidepressants). Two small open-label trials of antidepressants have been reported in children with cancer (DeJong and Fombonne 2007; Gothelf et al. 2005).

Other medications used in the treatment of depression include mirtazapine and stimulants. Mirtazapine is a noradrenergic and specific serotonin agent that is a partial 5HT-3 receptor antagonist. Its use off-label has become more popular as it is sedating, causes weight gain, has antiemetic properties, and has few significant drug interactions, but it is not FDA approved for use in children. Children and adolescents who cannot tolerate antidepressants may, assuming cardiac stability, benefit from a trial of stimulants for depression and apathy. Tricyclic antidepressants do not have demonstrated efficacy for depression in children but may be useful for headache prophylaxis or enuresis (Daly and Wilens 1998). It is important to note they can be dangerously cardiotoxic in overdose and have anticholinergic side effects (e.g., dry mouth, sedation) at therapeutic doses.

Primary considerations in antidepressant selection include drug-drug interactions and side effect profiles. Practitioners must be aware that some antibiotics commonly used in resistant infections such as linezolid, a weak monoamine oxidase inhibitor, have a small but documented risk of leading to serotonin syndrome when

Table 8.2 Preparations and dosages of antidepressant medications in children

Medication	Prescribing information (Starting dose – general range) Routes of administration	FDA indication in children	Psycho-oncology uses and specific notes
Selective serotonin reuptake inhibitors (SSRIs)			Depression Anxiety Caution with linezolid (MAOI) Note p450 interactions Black box warning
Citalopram (Celexa®) Escitalopram (Lexapro®)	5–40 mg/day, increase by 5–10 mg/day PO[a] 5–20 mg/day Increase by 5–10 mg/day PO[a]	No 12 years and older for depression	Few drug-drug interactions; EKG changes above 40 mg Few drug–drug interactions
Fluoxetine (Prozac®)	5–60 mg/day Increase by 5–10 mg/day PO[a]	8 years and older for depression; 7 years and older for OCD	Long half-life, p450 issues
Fluvoxamine (Luvox®)	25–200 mg/day, increase by 25 mg/day Max 300 mg PO	8 years and older for OCD	Sedation, dry mouth, tachycardia
Paroxetine (Paxil®)	5–20 mg/day, increase by 5 mg/day PO	No	Prohibited in Europe under 18, short half-life, increased rate of discontinuation symptoms
Sertraline (Zoloft®)	12.5–150 mg/day, Increase by 12.5–25 mg/day Max 200 mg PO[a]	Yes, 6 years and older for OCD	
Other antidepressants			
Bupropion (Wellbutrin®)	37.5–300 mg/day, increase by 37.5–50 mg/day Max 450 mg PO	No	Depression Anxiety ADHD (3rd line) Decreases seizure threshold
Duloxetine (Cymbalta®)	20–60 mg/day, increase by 10–20 mg/day Max 120 mg PO	7 years or older for generalized anxiety disorder	Depression Anxiety Pain
Mirtazapine (Remeron®)	7.5–45 mg/day, increase by 7.5–15 mg/day Max 45 mg PO[b]	No	Depression Anxiety Boosts appetite (weight gain), antiemetic, helps sleep (sedation) at lower doses
Venlafaxine (Effexor®)	18.75–300 mg/day, increase by 18.75–37.5 mg/day Max 375 mg PO	No	Depression Anxiety Pain Monitor blood pressure (hypertension) and heart rate (tachycardia)

PO per os/by mouth, *IM* intramuscular, *IV* intravenous

[a]Liquid form available

[b]Oral disintegrating tablet available http://www.micromedexsolutions.com/accessed 1/19/2015

Table 8.3 Preparations and dosages of antipsychotic medications in children

Medication	Prescribing information (Starting dose – general range) Maximum dose allowed Routes of administration	FDA indication in children	Psycho-oncology uses and specific notes
Atypical antipsychotics			*Need to monitor QT intervals*
Aripiprazole (Abilify®)	2 mg–15 mg/day, increase by 5 mg/day Max 30 mg PO[a, b], IM	6–17 years agitation in autism; 10 years or older in bipolar I; 6–18 years in Tourette's; 13–17 years in schizophrenia	Delirium (hypoactive, adults primarily); long half-life
Olanzapine (Zyprexa®, Zydis®)	2.5–10 mg/day, increase by 2.5–5 mg/day Max 20 mg PO[b], IM	13–17 years bipolar I acute, schizophrenia; depressed bipolar I with fluoxetine 10–17 years	Delirium Nausea Steroid-related mood problems
Quetiapine (Seroquel®)	12.5–50 mg/day, increase by 12.5–25 mg/day Max 600–800 mg PO	10–17 years bipolar mania; 13–17 years acute schizophrenia	Delirium Agitation Used in low doses (<200 mg/day)
Risperidone (Risperdal®, Risperdal Consta®, Risperidone M-Tab®)	0.25–3 mg/day, increase 0.25–0.5 mg/day Max 6 mg/day PO[a, b], IM	5 years or older irritability in autism; 10 year or older bipolar I; 13 years or older schizophrenia	Delirium Agitation Steroid-related mood problems
Typical antipsychotics			*Need to monitor QT intervals*
Chlorpromazine (Thorazine®)	0.25 mg/lb body weight – 50 mg (Titrate by weight) PO, IM	6 months to 12 years for nausea and vomiting; severe problem behavior; 1–12 years tetanus	Delirium Hiccups Agitation; highly sedating
Haloperidol (Haldol®)	0.25–5 mg/day PO, IM, IV	3 years or older Tourette's, hyperactive or severe behavioral problems, schizophrenia	Delirium Agitation

PO per os/by mouth, *IM* intramuscular, *IV* intravenous
[a]Liquid form available
[b]Oral disintegrating tablet available http://www.micromedexsolutions.com/accessed 1/19/2015

combined with SSRI use. Serotonin syndrome is characterized by change in mental status, autonomic instability, and neuromuscular abnormalities and can be lethal if not identified and treated by discontinuation of the SSRI and providing autonomic support. Clinicians may have to decide to discontinue either linezolid or SSRI in situations in which both medications are present. Similarly, when patients must undergo prolonged periods of no intake by mouth during transplant or postoperatively, a clinical decision as to the severity of the depression may warrant continuation of the antidepressant via liquid form or per nasogastric tube.

Antipsychotics (Table 8.3)

Off-label use of antipsychotics, particularly atypical antipsychotics, may be beneficial for symptom management for children with cancer in several clinical scenarios. As discussed above in the section on pediatric delirium, atypical antipsychotics are the recommended treatment for symptoms of agitation or distress in delirious infants and children. Their use in this setting may reduce exposure to other offending agents causing delirium, decrease time the patient is delirious, decrease traumatic disorientation and distress, and reduce length of stay in the PICU

and hospital. Quetiapine and risperidone have been most commonly cited. Dose ranges have been anecdotally reported (Turkel and Hanft 2014; Silver et al. 2010) (Table 8.3), but studies are needed to determine the safest and most efficacious dosing regimens in medically ill children. In situations where a child is unable to take oral medications, low-dose intravenous haloperidol may be used.

For children with disabling corticosteroid-related mood and behavioral changes, medication treatment may be warranted. Risperidone has been widely used for this complaint, because it is generally well tolerated and rapidly effective (in the first 1–2 days of administration) and has a safety record (and FDA approval) in children with autism down to age 5 years. In this setting, risperidone is prescribed during steroid courses only and can be discontinued between cycles of treatment (Ularntinon et al. 2010). Children with irritability, impulsivity, or mood swings due to CNS insults, like brain tumors or posterior reversible encephalopathy syndrome (PRES), can also benefit from risperidone or other low-dose antipsychotic (Pangilinan et al. 2010).

Olanzapine was found to be effective against chemotherapy-induced nausea in adults in the early 1990s. It has been found most useful for delayed nausea and works with moderate and highly emetogenic chemotherapy regimens (Wang et al. 2014). It is hypothesized that its efficacy for this symptom can be attributed to its activity at multiple types of nausea-related receptors (dopamine, serotonin, antihistamine, etc.). Similarly, it is known to stimulate appetite and cause weight gain, a side effect which may be beneficial in the medically anorexic population. A meta-analysis examining 47 studies for safety of olanzapine use in children under 13 years showed it was well tolerated with 15 % EKG changes and 9 % extrapyramidal symptoms, thus setting the stage for further trials examining its use in this population (Flank et al. 2014).

In general, the side effects of weight gain, appetite stimulation, and sedation can be secondary benefits for many pediatric oncology patients, and during the short-term symptomatic use of these drugs, metabolic side effects are not usually seen. Monitoring of EKG is important in hospitalized children on antipsychotics as illness, electrolyte abnormalities, and polypharmacy may predispose these children to prolongation of QTc interval (corrected QT interval, a measurement of the interval between Q wave and T wave on EKG tracing, representing electrical depolarization and repolarization of the ventricles, corrected for normal changes in relation to the patients current heart rate.) QTc prolongation, usually defined by QTc>500 ms, is a congenital or acquired change in electrophysiologic function of the heart and is a risk factor for a potentially fatal cardiac arrhythmia, known as torsade de pointes. Discontinuation of causative drugs may be warranted. Cardiology consultation can be valuable in situations where medications are critical for patient management. It is important that serum levels of magnesium, potassium, and calcium, which affect heart function, are repleted if deficient in this context. In general terms, atypical antipsychotics prolong QTc less than typical antipsychotics, with olanzapine and aripiprazole having the least QTc prolongation overall. Further studies are needed into the absolute and relative risks of QTc prolongation and link to risk for torsades de pointes (Hasnain et al. 2014).

Benzodiazepines (Table 8.4)

The use of benzodiazepines in oncology is ubiquitous mostly in the context of nausea and anxiety management but also for sleep, muscle relaxation in musculoskeletal pain, and sedation for procedures or long-term critical illness. Pediatric oncology clinicians are comfortable using this class of medications, particularly lorazepam and diazepam for symptom management of nausea, anxiety, and sleep and midazolam for sedation and usually follow dosing in the Harriet Lane, Micromedex, or other pediatric guides. The child and adolescent psychiatrist consultant may be involved in complex symptom management where balancing the benefits of these medications with their side effects can be delicate. Benzodiazepines may cause sedation, confusion, respiratory depression, delirium, and, particularly in young, developmentally delayed

Table 8.4 Preparations and dosages of benzodiazepine medications in children

Medication	Prescribing information (Starting dose – general range) Maximum dose Routes of administration	Approximate equivalence	Route of administration	Onset of action	Psycho-oncology uses and specific notes
Clonazepam (Klonopin®)	0.25–3 mg/day 0.01 mg/kg/24 h ÷ q8 h, increase by 0.25–0.5 mg/day	0.25 mg	PO[a]	Slow	Anxiety REM-sleep disorders
Diazepam (Valium®)	2–10 mg/day IV: 0.04–0.25 mg/kg, increase by 1–2 mg/day PO: 0.12–0.8 mg/kg/day	5 mg PO, PR 2.5 mg IV	PO, IV, IM, PR	Intermediate	Anxiety Muscle relaxation
Lorazepam (Ativan®)	0.5–6 mg/day, increase by 0.25–0.5 mg/day	0.5 mg PO, IV	PO, IV	Rapid	Nausea/vomiting Anxiety Catatonia
Midazolam (Versed®)	0.025–0.05 mg/kg IV Max 0.4 mg/kg 0.25–1 mg/kg PO Max 20 mg	2.5 mg IV	PO[b], IV, IM	Rapid	Procedural sedation

PO per os/by mouth, *IM* intramuscular, *IV* intravenous, *PR* per rectum

[a]Oral disintegrating tablet available http://www.micromedexsolutions.com/accessed 1/19/2015

[b]Liquid form available

or neurologically impaired children, "paradoxical reactions." Tolerance, dependence, and withdrawal are important to monitor and can be avoided with careful medication tapers. The primarily hepatic metabolism of lorazepam makes it a safe choice in renal impairment. It is also well tolerated in hepatic failure and can be given in a continuous drip for palliative sedation. Short-acting alprazolam, while highly effective for acute situational anxiety, has a limited role in treatment of most oncology patients whose "triggers" are often frequent and repeated. The repeated use of short-acting benzodiazepines can lead to marked, undesired swings in emotional and physiological withdrawal symptoms due to additive effects of onset/offset of action of the drug and the underlying anxiety. In patients requiring continuous coverage of symptoms with benzodiazepines, longer acting agents such as clonazepam may be desirable and (as with opiates) cross tapering of the drugs can be safely accomplished with careful attention to published benzodiazepine equivalency references (and in Table 8.4) and close supervision of the patient (Watson 2009). Weaning schedules and careful monitoring for withdrawal are discussed above. Clonazepam is also helpful for generalized anxiety and is an adjunctive management of anxiety components of pain or while waiting for antidepressant onset of action.

The effects of chronic benzodiazepine exposure, as well as other anesthetic and sedative exposure, in the developing brain are not well understood, but animal studies in mice and in vitro models have raised concern about neurotoxicity. Research is ongoing to identify cellular mechanisms of action and developmental windows of vulnerability to these toxic effects in humans (Mintz et al. 2012).

Mood Stabilizers

The presence of a family or personal history of bipolar disorder or a manic reaction to steroids or antidepressants could necessitate the need for a mood stabilizer in patients with cancer. During cancer treatment, however, the choice of mood stabilizers is particularly limited. Most antiepileptic drugs usually used for mood stabilization

are to be avoided due to hepatic p450 enzyme interactions affecting chemotherapy metabolism and hematologic side effects. Valproate and valproic acid have been shown to have some antitumor properties, but even so are usually avoided in oncology patients because of metabolic interactions, blood dyscrasias, and hepatotoxicity. Lamotrigine has antidepressant and mood-stabilizing properties, although research is ongoing regarding its role in bipolar spectrum disorders; its practical use, which requires slow titrations for starting and discontinuing to avoid triggering Stevens–Johnson syndrome, may be difficult to maintain through some cancer treatment regimens. Levetiracetam is a commonly recommended antiepileptic for seizure prophylaxis and control in pediatric oncology because it has limited p450 interactions, but does not have strong mood-stabilizing properties and can have significant behavioral side effects (Ruggiero et al. 2010). Lithium requires close management of fluid and electrolytes to avoid nephrotoxicity and may cause leukocytosis, electrocardiographic changes, and thyroid toxicity. Atypical antipsychotics are a well-tolerated option for mood stabilization in cancer patients.

Stimulants (Table 8.5)

The use of stimulants in pediatric oncology is surprisingly low, compared to the general pediatric population, according to a review of psychotropic prescribing in pediatric oncology (Pao et al. 2006). Many families stop stimulant medication for a child previously diagnosed with ADHD when the child is not attending school and/or on treatment for pediatric cancer, but if

Table 8.5 Preparations and dosages of stimulant medications in children

Medication	Prescribing information (Starting dose – general range) Maximum dose allowed Routes of administration	FDA indication in children	Psycho-oncology uses and specific notes
Stimulants			*Monitor weight loss*, *decreased growth*, *insomnia*, *tachycardia*, *hypertension*, *headaches*, *irritability*, *tics*
Dextroamphetamine/ mixed amphetamine salts (immediate release) Dexedrine	2.5 mg orally once or twice daily (am and noon); increase by 2.5 mg/day at 1-week intervals to optimum response Max 40 mg/day PO[a]	3 to 16 years immediate release for ADHD; 6 to 16 years sustained release for ADHD, narcolepsy	Poor attention and concentration ADHD Depressed mood with fatigue
Methylphenidate Ritalin (immediate release)	2.5–5 mg orally twice daily (am and noon); dose adjustments of 2.5–5 to 10 mg at weekly intervals Max dose 60 mg/day PO[a, b] patch	6 to 17 years for ADHD	Poor attention and concentration ADHD Depressed mood with fatigue
Modafanil Provigil®	50–100 mg orally to start for at least 1–3 days, then titrate up as needed, typical dose 100–200 mg Max dose 400 mg PO	Over 16 years for narcolepsy, obstructive sleep apnea	Depression with fatigue, adjunct

ADHD attention deficit hyperactivity disorder, *PO* per os/by mouth

[a]Liquid form available

[b]Oral chewable tablet available http://www.micromedexsolutions.com/accessed 1/26/2015

they present with behavioral or emotional issues during cancer treatment, it may be warranted to restart. These medications may be useful for symptom management of opiate-related sedation, radiation-related somnolence syndrome, or adjunctive treatment of depression, although they have been largely disproven to be of benefit in cancer-related fatigue in randomized controlled trials in adults (Ruddy et al. 2014). Anorexia and insomnia may be treatment-limiting side effects of stimulants in this population.

As mentioned above, the use of stimulants in pediatric cancer survivors with inattention and other cognitive complaints is a subject of ongoing research. Studies show a trial of methylphenidate (MPH) is warranted if stimulants are not medically contraindicated, for ALL patients and brain tumor patients who are struggling with executive functioning. Gains were seen on objective measures of attention, teacher report of academic and social skills, and parent reports of academic and executive functioning (turning in assignments, planning ahead, etc.) While response rates did not approach those of the ADHD population, 45 % of children with these complaints did benefit and tolerated the medication well (Conklin, et al. 2014). Over the first year of treatment with MPH, pediatric cancer survivors do experience small but significant deceleration in body mass index (BMI) and weight but not height (Jasper et al. 2009).

Other Psychotropic Medications and Dietary Supplements

The α-2 agonists clonidine and guanfacine are used frequently for adjunctive treatment of ADHD, particularly for hyperactivity, aggression, and insomnia symptoms and comorbid tic disorders. Patients should be monitored for hypotension, bradycardia, and somnolence (Hirota et al. 2014). Clonidine has also been explored as a treatment for PTSD, thought to modulate adrenergic system dysregulation; however this is yet to be proven in randomized controlled trials (RCTs). Along with guanfacine, it may also be useful for management of steroid-induced insomnia and dysregulation as an alternative medication to children in whom benzodiazepines or antipsychotics are contraindicated or poorly tolerated (such as those with CNS insults or developmental delays.) (Pangilinan et al. 2010)

The dietary supplements omega fatty acids (n3FAs) and melatonin warrant a brief discussion because of their low side effect profile, evidence base of possible psychiatric benefits in certain subpopulations, and common use in community samples. N3FA supplementation, found deficient in most Western diets low in fish and nut intake, is postulated to reverse a potentially proinflammatory state and prevent or reverse certain cardiovascular and psychiatric disorders. Studies have focused on the n3Fas EPA and DHA, derived from fish oil, but remain mixed as to their efficacy in treatment of unipolar depression and bipolar disorder in adults. Side effects are minor GI upset, possible rapid cycling in bipolar disorder, and hypothetical risk of bleeding in combination with other thrombolytic medications (aspirin or warfarin) or illness states. Herbal supplements, including n3FAs should be avoided during chemotherapy as potential interactions are largely unstudied but have implications in treatment efficacy (Mischoulon and Freeman 2013; Omega-3 | Memorial Sloan Kettering Cancer Center 2014). Melatonin, not a medication but a natural supplement, has proven efficacy and safety in a myriad of pediatric sleep disorders; however, it has not been tested in pediatric cancer patients (Carter et al. 2014; Özcan and Dönmez 2014). Pediatric starting doses range from 1 to 3 mg but much higher doses have been reported safe. As it is a non-prescription supplement, it is unregulated by the FDA and care must be taken that patients (or hospital pharmacies) choose reputable brands to purchase (see Integrative therapies Chap. 16) .

Conclusions

The diagnosis and management of psychiatric problems can greatly enhance the care of the pediatric oncology patient, from significantly improving quality of life and reducing suffering to managing psychiatric comorbidities

that allow for life-saving or life-prolonging oncology treatment to continue. Psychotropic medications are an important treatment modality in the psycho-oncologists' "toolbox" and should be prescribed in the context of comprehensive, multimodal, multidisciplinary care. Evidence-based psychotherapies delivered by trained mental health clinicians, directed at specific psychiatric disorders, and symptoms should be sought for children with cancer and their families throughout the disease trajectory. Consultation psychiatrists may work in many practice settings, but whether functioning as a medication consultant or multidisciplinary team leader, it is the physician's responsibility to provide a comprehensive, holistic approach in assessment, diagnosis, and treatment planning for the child with cancer and their family.

Clinical Pearls

Collaboration and open communication between the patient, parent, medical team and psychiatric consultant is essential for successful psychiatric treatment in the pediatric medical setting. A proactive explanation of the mind-body connection, the contribution of anxiety to pain or nausea, and reassurance that the mental health evaluation is intended to improve the teams' understanding and ability to treat their symptoms, can help form an alliance with the patient and their family.Psychotropic medication in the medically complex pediatric oncology population can be a safe and effective tool to provide relief of psychological/psychiatric symptoms and facilitate oncologic treatment. Clinicians working with children with cancer may need to focus on the more affective aspects of depression (vs. the neurovegetative symptoms) such as anhedonia and hopelessness to diagnose major depression and distinguish it from the effects of illness and treatment. Depression in the context of cancer can affect quality of life and treatment adherence.Standardized screening tools and patient education materials for pediatric delirium should be used to engage nurses and parents in identifying delirium in children of all ages. Delirium risk factors can be minimized, and environmental and pharmacologic interventions can improve mental status.

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