Anxiety in Medically Ill Children/Adolescents

Maryland Pao[1] and **Abigail Bosk**[1]

[1] Office of the Clinical Director, National Institutes of Mental Health, National Institutes of Health, Bethesda, MD

Abstract

Anxiety disorders are thought to be one of the most common psychiatric diagnoses in children/adolescents. Chronic medical illness is a significant risk factor for the development of an anxiety disorder and the prevalence rate of anxiety disorders among youths with chronic medical illnesses is higher compared to their healthy counterparts. Anxiety disorders may develop secondary to predisposing biological mechanisms related to a child's specific medical illness, as a response to being ill or in the hospital, a threatening environment, as a result of other genetic and psychological factors, or as a combination of all these factors. Additionally, exposure to physical pain early in one's life and or frequent painful medical procedures are correlated with fear and anxiety during subsequent procedures and treatments and may lead to medical nonadherence and other comorbidities. Anxiety disorders can have serious consequences in children/adolescents with chronic and or life limiting medical illnesses. Therefore, proper identification and treatment of anxiety disorders is necessary and may improve not only psychiatric symptoms but also physical symptoms. Behavioral and cognitive methods as well as psychotropic medications are used to treat anxiety disorders in pediatric patients. We will review current treatments for anxiety in children/adolescents with medical illnesses and propose future research directions.

Keywords

Chronic Illness; Pain; Posttraumatic Stress Disorder; Psychopharmacology; Cognitive; Behavior Therapy

Introduction

Anxiety is a normal reaction to life stressors and uncertainties. However, anxiety is thought to be problematic when its intensity and duration begin to impact one's functioning and quality of life.[1] General symptoms of anxiety encompass psychological as well as physical domains and symptoms may be intermittent or persist daily. Psychological symptoms of anxiety include: feeling tense, worried, fearful, crying spells and the inability to "turn off" one's thoughts, often without being able to identify a source leading to these intrusive and upsetting symptoms. Physical symptoms can include: tachycardia, tachypnea, nausea, insomnia, anorexia, diaphoresis and tremor. [1] These symptoms can be difficult to sort out

Corresponding Author: Maryland Pao, MD, Clinical Director, National Institute of Mental Health, Clinical Research Center, 6-5340, Bethesda, MD 20892, Phone: 301-435-5770, Fax 301-402-2588, paom@mail.nih.gov. Abigail Bosk, Clinical Research Center, 6-5340, Bethesda, MD 20892, Phone: 301-443-7150, Fax 301-402-2588, boska@mail.nih.gov.

in children/adolescents with medical conditions who, in addition to everyday worries about school, peers and family, have to face uncertainty about their health status. This leads patients, families, and clinicians to ask, "How much anxiety is too much? When is intervention needed?"

Anxiety disorders are thought to be one of the most common psychiatric diagnoses in children/adolescents. [2] Lifetime prevalence in the general population in the United States of any anxiety disorder is 28.8%. In terms of prevalence, approximately 13 out of 100 children/adolescents experience an anxiety disorder with the median age of onset at 11 years. [1] The most common anxiety disorders in children/adolescents are separation anxiety (2.8–8%), specific phobias (10%) and social phobias (7%). [2] These anxiety disorders tend to have an early age of onset with a median onset of 7 years for separation anxiety and phobia disorders and 13 years for social phobias. [3]

Chronic medical illness is a significant risk factor for the development of psychiatric disorders including anxiety disorders. [4] Anxiety disorders may develop secondary to predisposing biologic mechanisms related to the child's specific medical illness, as a response to being ill or in the hospital, a threatening environment, as a result of other genetic and psychosocial factors, or as a combination of all these factors. The prevalence rate as well as the adjusted lifetime prevalence of anxiety disorders is higher among children/adolescents with chronic medical illnesses compared to their healthy counterpart.[5,6] The rates of anxiety symptoms in children/adolescents with chronic illnesses range from 7 to 40%. [7–9]

The neurobiology of anxiety is discussed elsewhere in this journal, therefore this paper will focus on anxiety in children/adolescents with medical illnesses using epilepsy, pain and burns as examples. Epilepsy provides an example of how a medical illness may cause and or exacerbate anxiety, while untreated pain provides an example of how repeated exposure to aversive medical procedures can lead to anxiety, and burns provide an example of the bidirectional relationship between a medical condition and symptoms of anxiety. We will review current treatments for anxiety in children/adolescents with medical illnesses, discuss the effects of parental anxiety on children and adolescents and propose future research directions.

Anxiety Disorders in Children/Adolescents with Medical Illnesses

Children/adolescents with medical illnesses can be diagnosed with the entire spectrum of anxiety of disorders including: acute stress disorder, post-traumatic stress disorder, generalized anxiety disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, anxiety disorder not otherwise specified, panic disorder, specific and social phobias, and obsessive compulsive disorder. [10]

Anxiety disorders in children and adolescents with a medical illness often have comorbid psychiatric and physical conditions where it is difficult to separate the physiological and psychological components of anxiety. Richardson et al (2006) looked at the relationship between asthma and anxiety. During the two week study period, youth ages 11–17 years with anxiety and/or depressive disorders had significantly more asthma symptom days and higher levels of both asthma symptoms and other physical symptoms such as headaches compared to youths without diagnoses of anxiety and/or depression, even when controlling for asthma severity. Chronic worry and stress/anxiety may decrease immune function, making an individual more susceptible to infections, increasing the severity of the pre-existing physical illness. [11,12] Of note, adjustment to most chronic illnesses is not always predicted by the severity of the specific chronic illness but by other psychosocial factors such as parental adjustment, social support, intelligence etc. [13] Somatic symptoms related

to an actual physical illness may also lead to more frequent triggers for panic attacks and anxiety disorders.[14] Also, illnesses, such as asthma, diabetes, or epilepsy, that may need close medical monitoring and can result in a medical crisis may also make a child more anxious about being away from home and their caregivers and contribute to increased rates of separation anxiety in children with medical illnesses.[12,14] Interactions among disease-related and psychosocial factors are believed to account for the increased rates of anxiety disorders in children/adolescents with medical illnesses.

Additionally, many medical conditions and medications may directly result in anxiety symptoms. [15] For example, various neurological, endocrine, cardiac, pulmonary and metabolic disorders can result in organic symptoms that resemble anxiety symptoms.[15,16] When anxiety symptoms such as shortness of breath, tachycardia, or tremor present suddenly for the first time or are severe, medical etiologies for the anxiety symptoms should be evaluated. An astute clinician attempts, when possible, to differentiate anxiety secondary to a medical condition from comorbid anxiety or anxiety that is a reaction to an underlying medical illness. In order to determine which aspect of the etiology of anxiety in medically ill youth should be the treatment focus, a clinician must be familiar with the pathophysiology of anxiety as outlined earlier, as well as the pathophysiology of the specific medical illness, and the psychosocial context. A careful detailed history of the actual time course and context over which the anxiety symptoms develop and persist is important. For example, isolated symptoms of obsessive hand-washing may develop in response to being told to avoid germs. On the other hand, social phobia may exist unrelated to medical problems but be blamed on frequent school absences.

There are no tools specifically for measuring anxiety symptoms and disorders in medically ill children so it is difficult to accurately assess the prevalence rate in this population. Incidence rates vary according to type of medical illness, age range of patients, screening tool used, and whether state or trait anxiety is measured, thus making it impossible to compare the rates of symptoms and disorders in these populations.

In general, moderate to severe anxiety is believed to affect symptom management, treatment adherence, medical outcome, and the ability of the child/adolescent to cope with illness. Proper identification and treatment of anxiety disorders can decrease not only psychiatric symptoms but also physical symptoms. [11,17–18]

Epilepsy

Epilepsy provides an example of how interactions between medical (neurological dysfunction) and psychosocial factors related to one's illness can result in anxiety symptoms and disorders in children/adolescents. [19] The physiological and neurological mechanisms of the disease are related to the presence of anxiety symptoms. It is believed that the recurrent epileptic stimulation of the amygdala may predispose patients to interictal anxiety. [20] Among youth with epilepsy, increased rates of anxiety are correlated with polytherapy of anti-epileptic medications and increased seizure frequency.[21] Psychologically, the fear of having a seizure may be associated with anxiety about separation from one's parents.[20] Children/adolescents also fear the embarrassment of having a seizure in public. This can lead to avoidance behaviors resulting in isolation of the child from age appropriate social activities which can result in both anxiety symptoms and disorders and delayed social/emotional development. [20] When assessing and treating youth with comorbid medical illness and anxiety disorders clinicians need to be mindful of not only the anxiety symptoms, but also the ways in which the physical illness may contribute (or cause) the anxiety symptoms.

Pain

Physical pain associated with medical illness, injury or treatment is associated with anxiety symptoms and disorders. Unlike epilepsy, the careful management of pain during the course of a child/adolescent's illness or injury can lessen and or prevent the development of anxiety symptoms. Painful procedures performed during the neonatal and infant period can change an individual's neural pathways for pain processing which affects the way one reacts to painful procedures later in life. [22,23] For instance, children who had painful procedures as infants experience more pain and psychological distress when receiving childhood immunizations. [23] For youth who must undergo frequent painful procedures such as bone marrow aspirations and lumbar punctures for the treatment of cancer or other serious immune deficiencies, the memory of a painful procedure early in the course of treatment can affect the pain and psychological distress associated with future procedures.[24] Furthermore, memories of painful procedures can cause youth to 1) have anticipatory fear and anxiety before subsequent procedures, and 2) develop anxiety disorders such as specific fear of blood or needle phobia, making it difficult to get through the necessary medical procedure. This suggests that the prevention of pain could play and important role in preventing the development of anxiety symptoms. Clinicians should anticipate and actively treat procedural pain in their child/adolescent patients in the hopes of ameliorating the negative physical and psychological effects of untreated pain. Age-appropriate non-pharmacologic, [25,26] and pharmacologic treatments [27–29] for procedural pain are available. [30]

Burns

Pediatric burn patients have provided researchers and clinicians an opportunity to study further the association between pain and anxiety in children. The relationship between physical pain and anxiety is bidirectional; high levels of physical pain are correlated with greater anxiety symptoms [31] and premorbid anxiety is associated with greater pain intensity. [22,32] Ratcliff et al (2006) conducted a retrospective review on pain and anxiety management in pediatric burn patients (n= 286) ages less than 3 to 19 years. This study found that the size of the burn was positively correlated with being treated with anxiolytic medications for the management of anxiety symptoms. When the burn was less than or equal to 10% of the total body surface area (TBSA), only 29% of the patients received an anxiolytic medication; when the burn was greater than 10% TBSA, use of anxiolytic medication increased to 62%; for 20–39% TBSA, 90% of the patients received anxiolytic medication. [31] The patient was more likely to receive a benzodiazepine for anxiety if he/she was also receiving continuous morphine for background pain (constant pain). When treating children/adolescents with medical illnesses, it is important to assess and treat pain because controlling pain may result in decreased anxiety symptoms and improve cooperation with future medical encounters.

Medical Illness and PTSD

Pediatric medical traumatic stress is a set of psychological and physiological responses of children and their families to pain, injury, serious illness, medical procedures and invasive or frightening treatment experiences.[1] Traumatic stress responses are more related to one's subjective experience of the medical event than its objective severity.[1] For a child/adolescent to be diagnosed with PTSD they must display one or more symptoms from each of the following three clusters: avoidance of reminders of the stressor, re-experiencing of the event (flashbacks), and hyper-arousal (e.g. hyper-vigilance, persistent heightened level of anxiety). These symptoms must occur for at least 1 month after the traumatic event and

cause functional impairment or disability. Additionally, to be diagnosed with PTSD, the symptoms listed above must be in response to a specific precipitating event or trauma. [10]

Many life saving medical treatments and surgical procedures are viewed as traumatic by children and adolescents. Children/adolescents with medically related post traumatic stress symptoms report procedures ranging from blood draws, to transplantation and chemotherapy as traumatic. Children/adolescents can view doctors, nurses and health care providers as inflictors of the trauma and even develop "white coat syndrome" (fear of health care professionals), can develop severe blood/needle phobia, and/or claustrophobia (making it difficult for the patient to tolerate radiographic scans). Pediatric studies on children with cancer, burns, heart disease, diabetes, human immunodeficiency virus and organ transplantation have provided evidence that post-traumatic stress reactions are seen in medically ill children and their families during active treatment and during the months and years that follow the illness/treatment. [33] As a result of these findings, the DSM-IV included medical illness as a potential precipitating traumatic event for PTSD. [10]

Numerous studies have found an increased prevalence of medically related PTSD among children/adolescent patients. Pelcovitz et al (1998) examined 23 adolescent cancer survivors, 27 physically abused adolescents and 23 healthy, nonabused adolescents; 35% of the cancer patients compared to 7% of the abused adolescents met lifetime criteria for PTSD. [34] Studies have noted that 30% of pediatric patients who receive solid organ transplant exhibit symptoms of PTSD. [35,36] Another study compared 35 youth/parent dyads who were hospitalized in the ICU compared to 33 youth/parent dyads who were hospitalized on non-ICU floors; 21% of youths on the ICU compared with none of the youths on the non-ICU floors developed PTSD. [37] Overall, these studies provide further evidence that medically related PTSD occurs in a substantial number of pediatric patients and therefore needs to be assessed and treated when present.

Stuber et al (1997) investigated risk factors associated with developing PTSD. In a study of 186 cancer survivors ages (8–20) who had completed treatment at least 1 year prior to the study, the following were positive risk factors for PTSD : 1) Life threat of illness at time of treatment (retrospective appraisal by the patient of how threatening the disease is rather than the clinician's determination of the severity of the disease and degree to which the patient experience the treatment as "hard" or "scary"; 2) Parental level of trait anxiety; 3) Family and social support with decreased social support linked to higher levels of PTSD; 4) History of other stressful experiences; 4) Time since treatment (negative correlation) and 5) Female gender.[38]

Consequences of PTSD

Medically related PTSD is linked to significant medical and psychiatric comorbidity. [39] Many studies have looked at the different domains of one's life that medical PTSD affects. In one study, 40 adolescent and young adult survivors of pediatric cancer were assessed for symptoms of somatization, PTSD and personality traits. Those who met diagnostic threshold for PTSD reported more somatic symptoms, greater psychological distress and received a lower rating of general functioning. [40,41] In a study of 78 young adult survivors of childhood cancer ages 18–37 years, one fifth of the participants met diagnostic criteria for PTSD. The participants with PTSD had a general level of heightened distress and an increased level of perception of disease threat with no objective assessment of disease severity.[38] Another study of 51 childhood cancer survivors (ages 18–37) looked at the effect of PTSD on quality of life (QoL). 22% of the participants met criteria for PTSD. None of the participants with PTSD were married and those with PTSD reported poorer QoL across all domains with social functioning, emotional well being and role limitations as the

most impaired areas. Participants without PTSD had QoL scores similar to those in the general population. [42] Medical nonadherence is also a concern in patients with PTSD. In a study of 19 child and adolescent survivors of liver transplant who were followed for at least 1 year posttransplant, those patients who displayed above threshold PTSD symptoms were significantly more likely to display medication nonadherence.[36] The children/adolescents with PTSD had significant fluctuations in their blood levels of immunosuppressive drugs. The children/adolescents who had been nonadherent to their medication became adherent when they were successfully treated for PTSD, using cognitive-behavioral therapy (CBT). [33]

Evidence-Based Treatments of Anxiety Disorders in Medically Ill Children/Adolescents

Since anxiety disorders can have serious consequences in children/adolescents with chronic and/or life limiting medical illnesses, prompt identification and treatment of these disorders is critical. Behavioral and cognitive methods such as guided imagery and relaxation as well as psychotropic medications are used to treat anxiety disorders in pediatric patients. While minimal data exist for treating anxiety in children with medical illnesses, treatments are extrapolated from treating anxiety disorders in children without medical disorders. Similarly, the course of treatment depends on the degree of impairment, behaviors/symptoms/disorders being targeted and developmental considerations.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a highly efficacious treatment for mood disorders such as depression and anxiety disorders.[43,44] The goal of CBT is to help the child recognize the cognitively distorted thoughts, to reality test these thoughts and to teach the patient skills to challenge irrational thoughts and replace them with more rational ones.[45] In a meta-analysis (13 studies) of healthy children (498 treatment subjects and 311 controls), there was a remission of any anxiety disorder for 56% of the subjects who received CBT versus 28.8% for controls.[45]

When using behavioral techniques and CBT with a medically ill population, the following areas should be addressed: 1) initial distress reactions at diagnosis, 2) anxiety and pain during treatment, 3) disease-related and chronic pain, 4) coexisting psychosocial distress, 5) adherence of medication regimen, and 6) provision of social skills for reintroduction of school and life after (or with) the disease. While there are no randomized control trials that assess the efficacy of CBT in children with medical illnesses, there have been a number of studies that demonstrate the utility of this treatment. The following section will outline some of the CBT techniques used in pediatric patients with chronic and/or life limiting illnesses using cancer, pediatric sickle cell (PSC) disease and inflammatory bowel disease (IBD) as examples. Pediatric cancer provides an example of a disease in which CBT has been widely used since the disease itself is painful, the treatments are often invasive and long term, and polypharmacy may not be a viable alternative. PSC provides an example of the use of CBT in a disease that is characterized by extreme physical pain, and IBD provides an example of how CBT can be tailored to the needs of children/adolescents with chronic illnesses.

CBT techniques have been useful in helping children/adolescents with cancer tolerate bone marrow aspirates (BMA). Jay et al. (1995) compared the efficacy of a CBT package which include filmed modeling of breathing exercises, imagery/distractions, positive incentive, and behavioral rehearsal to general anesthesia in children (n=19) with leukemia who received BMA. Specifically, each child watched a video of another child receiving a BMA. Following the video, the patient learned a simple breathing exercise and was instructed to

think of an image that would not cause any pain (e.g. Disneyland, eating a certain food). The child visualized this image in as much detail as possible and was instructed to think of this image when undergoing a painful procedure. The pediatric patients received this CBT intervention during one BMA and general anesthesia during the other BMA in a cross-over randomized design. There were no significant differences in the two conditions with regard to self-reported pain, fear, anxiety and pulse rate. Overall, this study demonstrated that a CBT package is effective for both physical and psychological symptoms associated with procedural distress. [46]

Pediatric sickle cell (PSC) is characterized by periods of unexpected and intense pain related to sickle cell crises. Behavioral interventions are often used with this population to help manage the physical components as well as the emotional distress associated with PSC. Cozzi et al. (1987) implemented a 13 session biofeedback intervention to target disease-related pain as well as the anxiety associated with it. The intervention combined both thermal biofeedback and electromyography (EMG) biofeedback. Thermal biofeedback involves attaching a thermometer to the hand or foot to monitor changes in peripheral skin temperature. EMG biofeedback is conducted by attaching a device with electrodes that are sensitive to signals of muscle tension to specific body parts (usually arm, chest and forehead). [47] After a baseline reading using these biofeedback techniques, children were taught relaxation techniques and then practiced these techniques in conjunction with the biofeedback in order to improve self regulation of bodily response to pain and anxiety. Children in the treatment group had significant reductions in anxiety and pain symptoms and requested less medication compared to the control group. [48]

CBT has been effective in decreasing symptoms of depression in children/adolescents with inflammatory bowel disease (IBD). Szigethy et al. (2004) used the pre-existing Primary and Secondary Control Enhancement Training (PASCET), a manual-based CBT that is efficacious in treating depressed youths, [49] and added a social skills training, family educational approach and physical illness narrative. [50] These modules aim to enhance self-understanding and illness comprehension. Szigethy et al (2004) piloted this CBT manual on 11 adolescents (mean age 14.8 years) with IBD. Before CBT treatment, 9 adolescents met *DSM-IV* criteria for current major depression and two for minor depression. After the completion of treatment, 10 adolescents no longer met criteria for any depressive disorder and one subject met criteria for minor depression. Overall, the participants had significant improvements in depression, global adjustment and physical functioning. In another study using the PASCET-PI (physical illness version), Szigethy et al (2007) compared the effectiveness of the CBT treatment to treatment as usual (TAU) (i.e. no CBT) in patients 11–17 years old with IBD and mild to moderate subsyndromal depression. The participants in the PASCET-PI group compared to the TAU group showed significantly greater improvement in the Children's Depression Inventory, Children's Global Assessment Scale and Perceived Control Scale for Children.

While these two studies conducted by Szigethy et al. only looked at the effects of CBT targeted for children and adolescents with comorbid medical illness and depression, it is hypothesized that this treatment would also be beneficial for youths with an anxiety disorder(s). The PASCET-PI is thought to help adolescents accept the uncontrollable elements of having a chronic physical illness and assist them in establishing thoughts and behaviors that can help them control the aspects of their illness that they are able to. Also, the use of physical illness narratives has been shown to decrease social isolation and foster positive reactions in youths with pediatric illnesses.[51,52] Overall, using CBT in children with medical illness appears to have promise, but only one specific technique has been manualized (Szigethy et al 2007). More studies are needed that assess the effectiveness of CBT, targeted for children with medical illnesses, on the reduction of anxiety symptoms.

However, clinicians should be aware of the usefulness of CBT in helping pediatric patients deal with pain and anxiety.

Medications

Selective serotonin reuptake inhibitors (SSRIs) are safe and effective in reducing anxiety in children/adolescents.[53–56] Fluoxetine is the only FDA-approved SSRI for depression in young children (older than 6 years). Fluoxetine and sertraline are approved for obsessive-compulsive disorder in children older than 6 years; fluvoxamine is approved for those who are 8 years and older. Escitalopram is approved for depression in children 12 years and older. Citalopram or escitalopram may lead to fewer drug-drug interactions in medically ill patients. Fluoxetine, with its active metabolite norfluoxetine, and fluvoxamine are potent inhibitors of cytochrome P-450 (CYP) 3A3 and 3A4 and are contraindicated with macrolide antibiotics, azole antifungal agents, and several other medications.

Clinicians prescribe SSRI's to children/adolescents with comorbid physical illness(es) and anxiety disorder(s), but there is limited data regarding their use in this patient population. One open-label trial evaluated the safety, tolerability, and benefit of 100mg/day of fluvoxamine for the treatment of major depressive disorder (MDD) or anxiety disorders in children/adolescents with cancer (n=15). [57] In the study, fluvoxamine was well tolerated by all subjects; none had abnormal findings on liver or kidney blood tests, none had changes in medical status and none reported suicidal ideation. After 8 weeks of treatment, 64.3% of the patients with MDD and 80.0% of the patients with anxiety disorders responded to treatment as assessed by self-report measures.[57] A second open-label study investigated the response of pediatric oncology patients with MDD (n=4) to 10–20 mg/day of citalopram. [58] In all four cases, citalopram was well tolerated (all patients had normal liver function) and improved depressive symptoms within 2–4 weeks of starting treatment.[58] Lastly, there is one case report of citalopram use in a 4 year old diagnosed with leukemia and dexamethasone-induced mood disorder (Joshi 2008). The child received 2.5 mg/day of citalopram with marked improvements in mood within 2 weeks after treatment was started, and returned to baseline mood and behavior after 4 weeks of treatment.[59] These studies provide promising evidence that SSRI's are a safe and effective treatment for this patient population; however randomized controlled trials are needed.

Benzodiazepines, such as lorazepam, are frequently used in low doses in conjunction with nonpharmacologic distraction techniques, and may be useful for procedures that induce considerable anxiety in children. Clonazepam is a longer acting benzodiazepine that may be helpful with more pervasive and prolonged anxiety symptoms. Benzodiazepines may cause sedation, confusion, and behavioral disinhibition or paradoxical activation so their use should be carefully monitored, especially in those patients with preexisting central nervous system dysfunction. Clinicians should be wary of benzodiazepine withdrawal precipitated by abrupt discontinuation when transferring a patient from prolonged stays in intensive care settings.

Antihistamines are frequently used to sedate anxious children but should be avoided for persistent anxiety since their anticholinergic properties can precipitate or worsen delirium. Diphenhydramine, hydroxyzine, and promethazine may be helpful for occasional insomnia. Intravenous diphenhydramine may be misused, particularly by adolescents, because it can induce euphoria when given by intravenous (IV) push. [60] Very high doses of IV diphenhydramine can provoke seizures.

Tricyclic antidepressants are useful for treating insomnia, weight loss, anxiety, and some pain syndromes. Amitriptyline and desipramine are approved for depression in children who are 12 years or older; nortriptyline is approved for depression in children 6 years and older.

Child psychiatrists often prefer to use nortriptyline since it has a higher therapeutic index and blood levels are easily measured.

Antipsychotic medications are used for delirium and occasionally in low doses for anxiety. Haloperidol is approved for use in children older than 3 years. Risperidone is approved for irritability in autism in children 5 years and older. Aripiprazole is approved for use in acute mania in children 10 years and older but may be difficult to use in medically ill children because of the long drug half-life and potential for drug interactions that would be difficult to reverse. Atypical antipsychotic medications have been useful in low doses but there are no controlled trials.

It is important to ascertain all the medications a chronically ill child/adolescent is taking in order to assess for drug-drug interactions as well as to be sure other medications are not causing or exacerbating anxiety symptoms. In summary, pharmacotherapy may be a useful adjunct to behavioral and family therapies in reducing anxiety in the patient and providing patients and their families with strategies to use in coping with illness particularly when anxiety disorders are causing significant functional impairment (Pao and Kazak 2009), [1] but more targeted studies are needed.

Treatment of PTSD

Cognitive Behavioral Therapy

Due to the deleterious effects of PTSD on a child's social, emotional, educational and biological development, [61] treatments that can prevent its development are highly beneficial. CBT is believed to be an effective treatment for PTSD in children with medical illnesses even though to date there has been no studies investigating the efficacy of CBT in this population. There have been studies that yield positive outcomes using trauma-focused CBT in children who have nonmedical PTSD. A randomized, multicenter, controlled trial of 229 children, ages 8–14 used a manual to deliver imagery exposure-based CBT treatment. The trauma-focused CBT was superior to the child-centered therapy on all outcome measures including reduction of PTSD symptoms. [62]

Medications

Opiate medications, due to their inhibitory effects on the neurological system, are believed to be a potential preventative agent of PTSD in the setting of significant ongoing pain. [63] A study conducted by Saxe et al (2001) that investigated the relationship between morphine dose and the development of PTSD in pediatric patients with acute burns (n=24, ages 6–16) found that the dosage of morphine received was negatively correlated with the development of PTSD symptoms over a 6 month period. Morphine inhibits the action of the amygdala and the locus coeruleus (LC) and has been shown to greatly decrease the hyperadrenergic state by inhibiting norepinephrine production in the LC and to decrease fear conditioning by decreasing norepinephrine turnover in the amygdala. [62,64]

While morphine may also inhibit the development of PTSD by decreasing the physical pain associated with a traumatic injury such as a burn, it is not believed that pain inhibition is the route by which morphine decreases PTSD. Saxe et al (2001) found that the amount of physical pain during the time of acute assessment was unrelated to the 6-month change in PTSD symptoms and the relationship between morphine dose and change in PTSD symptoms was present even when controlling for the child's/adolescent's self reported level of pain. Randomized control trials are needed to more fully investigate morphine's protective action against PTSD development. However, the Saxe et al study (2001) shows a promising effect of morphine's ability to inhibit the development of PTSD in burn patients.

Parental Anxiety

When treating children with chronic medical illnesses, it is also important to consider parental (caregiver) anxiety. Anxiety in parents of medically ill children/adolescents is common and understandable. However, it is imperative that the level of parental anxiety is recognized and appreciated when talking about medical decisions and treatment options for the child/adolescent and when communicating with the parents throughout the course of treatment. When health information is misconstrued, overinterpreted or overemphasized by a parent, it may lead to a constellation of behaviors and parent-child interactions that are now referred to as a Vulnerable Child Syndrome (VCS), [65] though this might be more aptly described as a vulnerable parent syndrome.

Still relevant today, the cardinal features of VCS includes symptoms of: 1) *pathological separation difficulties* (e.g. poor infant sleep or abdominal pain (school phobia) in older children), 2) *infantilization* (e.g. "overprotective, overly indulgent and oversolicitous while the child is overly dependent, disobedient, irritable, argumentative, and unco-operative"), 3) *bodily overconcerns* (e.g. where the child has many physical complaints and the parent (usually the mother) has difficulty differentiating between self-limited illness and potentially serious illness) and 4) *school underachievement* (e.g. delay starting school due to separation anxiety) (Green and Solnit, 1964). Predisposing factors to VCS include a history of infertility, miscarriage, illness during pregnancy, prematurity, a life-threatening illness experience or the child having a chronic medical illness especially if there is hospitalization during the first year of life such as for hyperbilirubinemia. [65–68]

The prevalence of a community sample at risk for VCS was estimated at 10% [67] but maybe higher today with the advent of NICUs and improved survival of premature children as well as children with other chronic illnesses.[69] As expected, parental anxiety can exacerbate the child/adolescent's own anxiety. Thus, helping to manage and mitigate parental anxiety may also lead to reduced anxiety symptoms in the child/adolescent. Effective communication is the key to prevention and management of VCS. It is important to identify those at risk and offer reassurance and support early on during the course of treatment. It is helpful to tell parents clearly when time-limited medical problems such as neonatal hyperbilirubinemia are over and will not recur. It may even be therapeutic to discuss directly the possible adverse effects of excessive parental concern on a child's development and behavior and the importance of encouraging appropriate autonomy after acknowledging the parent's frightening illness experience. VCS does not necessarily persist into school age if the child stays healthy. It is important to understand the history (if any) of anxiety disorders in the family. This is helpful in understanding the child's/adolescent's genetic vulnerability for anxiety and also the extent to which anxiety is part of a family system. [1]

Parental temperament and coping skills strongly influence how their child copes since children take their cues for coping and adaptation to illness primarily from their parents. Parents who have coped successfully with their child's illness and are able to isolate their own fears and anxieties during crises are better able to enhance their child's understanding of the illness and to facilitate self-care and independence in their child.[70] Parental trait anxiety has been associated with increased child distress during procedures.[71] Children with very anxious mothers often have less distress during procedures when their mothers are not present.[72]

Brief parental behavioral interventions used for the prevention of anxiety in young children (3–4 years) at risk for developing anxiety disorders, as measured by child behavioral inhibition and parental anxiety, have shown promise.[73] This intervention took place with small groups of parents during eight sessions. These sessions included: education on the

development, maintenance and treatment of anxiety disorders in young children, techniques on parenting an anxious child with the specific aim of decreasing parental overprotection, graded exposure to the child's fears, application of cognitive restructuring for the parent's own worries, and maintenance and relapse prevention. The children whose parents completed this parental intervention had significant reduction in the severity and frequency of anxiety disorders relative to the comparison group. [73] This type of parental intervention shows promise and may be useful to adapt to medically ill populations.

Future Directions

More research is needed that looks at the relationship of medical trauma on neurobiology (circuitry and HPA-axis functioning) and the development of anxiety disorders and PTSD in medically ill children/adolescents. The effects of medical trauma need to be investigated during the neonatal period and throughout childhood into young adulthood. Clinicians treating chronically ill youth should be aware of the many ways that medical illnesses, including the diseases themselves and the treatments, can result in psychological and physiological changes that can put these children/adolescents at risk for developing an anxiety disorder that requires intervention.

Acknowledgments

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