

## Evidence for Symptom Management in the Child With Cancer

Elena J. Ladas, MS, RD,\* Janice Post-White, RN, PhD, FAAN,† Ria Hawks, RN, MS, PNP,‡  
and Kathy Taromina, MS, LAc\*

**Summary:** The use of complementary/alternative medicine (CAM) has been well documented among children with cancer. This report summarizes the research evidence on the role of CAM therapies for prevention and treatment of the most commonly reported cancer-related symptoms and late effects among children with cancer. Small clinical trials document evidence of effectiveness for select therapies, such as acupuncture or ginger for nausea and vomiting, TRAUMEEL S for mucositis, and hypnosis and imagery for pain and anxiety. Several relatively small clinical trials of varying quality have been conducted on these CAM therapies in children with cancer. Some herbs have demonstrated efficacy in adults, but few studies of herbs have been conducted in children. Larger randomized clinical trials are warranted for each of these promising therapies. Until the evidence is more conclusive, the providers' role is to assess and document the child's use of CAM, critically evaluate the evidence or lack of evidence, balance the potential risks with possible benefits, and assist the family in their choices and decisions regarding use of CAM for their child with cancer.

**Key Words:** symptom management, child, cancer

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Children with cancer experience a range of symptoms resulting from the cancer and its treatment. Surveys have found that 31% to 84% of children with cancer use complementary/alternative medicine (CAM) to cope with the side effects of cancer therapy.<sup>1,2</sup> Many children with cancer are using CAM in combination with conventional therapies, without their physician's knowledge and while registered on a clinical research protocol.<sup>1,2</sup> Parents have

reported that the feeling of "leaving no stone unturned" has driven them to use CAM. The widespread use of CAM necessitates responsible investigation of these therapies to determine the safety and efficacy in children receiving treatment for cancer.

Acute and long-term toxicities are part of cancer therapy. Nausea and vomiting, pain, anxiety, fatigue, loss of appetite, and constipation/diarrhea are symptoms that fluctuate over time and span the course of the disease, from diagnosis to end-of-life care. Survivors of childhood cancer face unique late effects such as obesity, infertility, osteopenia, reduced cardiac function, chronic fatigue, and a higher risk of second malignancies.<sup>3</sup> There are no conventional treatments that reduce the risk of developing most of the late effects. This drives many parents and patients to use CAM despite the paucity of data supporting their efficacy among survivors of child and adolescent cancer.

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH) identifies 5 domains of CAM therapies that encompass mind-body medicine, manipulative body-based practices, energy therapy, and biologic therapies, in addition to whole medical systems that are explanatory systems of theory and practice. ([www.nccam.nih.gov](http://www.nccam.nih.gov)). Of these domains, surveys have found that children with cancer frequently use biologic therapies.<sup>1,2</sup>

The use of biological-based CAM therapies lends itself to the most scrutiny as it poses the highest risk of interacting with conventional therapy. Despite this risk, there are rare reports of adverse interactions between biologic therapies and conventional medications.<sup>4-8</sup> In most circumstances, adverse events have been attributed to contamination of herbs.<sup>4-8</sup> Herbal therapies, from the Far East have been described as having lead levels that exceed those limits set by the environmental protection agency. For example, The New York City Health Department warned against the use of herbal medicines manufactured in India due to contamination with lead or mercury.<sup>9</sup> Herbs from China are also associated with microbial contamination.<sup>10</sup> Supplementation with contaminated products may have an even more pronounced effect in children who are immunocompromised.

Integrative medicine, or the use of CAM in conjunction with standard medical treatment, seeks to improve the supportive care available to patients and to

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From the \*Division of Pediatric Oncology, Integrative Therapies Program for Children with Cancer, Columbia University, 161 Ft. Washington, New York, NY 10032; †University of Minnesota, University of Minnesota School of Nursing, 707 Kenwood Parkway, Minneapolis, MN 55403; and ‡Division of Bone Marrow Transplantation, Columbia University, 161 Ft. Washington, New York, NY 10032.

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Reprints: Elena J. Ladas, MS, RD, Division of Pediatric Oncology, Integrative Therapies Program for Children with Cancer, Columbia University, 161 Ft. Washington, New York, NY 10032 (e-mail: [ejd14@columbia.edu](mailto:ejd14@columbia.edu)).

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**TABLE 1.** CAM Therapies With Evidence for Effectiveness in Managing Symptoms Associated With Cancer Therapy

Symptom	CAM Therapy	Evidence in Pediatrics	Evidence in Adults	Nonsignificant Findings
Nausea/vomiting	Ginger herb		Pongrojpraw and Chiamchanya, 2003 <sup>56</sup> Ernst, 2002 <sup>5</sup> Tate, 1997 <sup>58</sup>	Betz et al, 2005 <sup>57</sup>
	Aromatherapy: ginger, spearmint, peppermint		MacKenzie and Gallacher, 1989 <sup>62</sup>	Anderson and Gross, 2004 <sup>63</sup>
	Acupressure/Sea Bands		Roscoe et al, 2003 <sup>49</sup> Treish et al, 2003 <sup>50</sup>	
	Acupuncture—P6, ST36	Reindl et al, 2006 <sup>44</sup>	NIH Consensus Conference, 1998 <sup>47</sup> Shen et al, 2000 <sup>169</sup> Pearl, 1999 <sup>170</sup> McMillan, 1991 <sup>171</sup> Vasterling, 1993 <sup>172</sup>	
Mucositis	Hypnosis	Zeltzer et al, 1991 <sup>65</sup>		Syrjala, 1992 <sup>173</sup>
	Massage Glutamine	Ahles et al, 1999 <sup>86</sup> Aquino, 2005 <sup>214</sup> Anderson, 1998 <sup>80</sup>		Post-White et al, 2003 <sup>87</sup>
Pain	Traumeel Acupuncture	Oberbaum et al, 2001 <sup>84</sup> Pintov et al, 1997 <sup>106</sup> Zeltzer et al, 2002 <sup>105</sup>	Filshie, 1985, 1988 <sup>174,175</sup> Alimi, 2003 <sup>176</sup>	
Procedural, acute, chronic	Healing touch		Post-White et al, 2005 <sup>88</sup>	
	Massage	Field et al, 1997 <sup>107</sup> Hernandez-Reif et al, 2001 <sup>108</sup>	Post-White et al, 2005 <sup>88</sup> Ahles et al, 1999 <sup>86</sup>	Ahles et al, 1999 <sup>86</sup>
	Music	Malone, 1996 <sup>215</sup> Fowler-Kerry, 1987 <sup>177</sup>		
	Peppermint oil (ingested)	Kline, 2001 <sup>178</sup> Weydert, 2003 <sup>179</sup>		
Fatigue	Imagery/hypnosis	Lioffi and Hatira, 2003 <sup>101</sup> Zeltzer and LeBaron, 1982 <sup>98</sup> Hilgard and LeBaron, 1982 <sup>97</sup> Hawkins et al, 1998 <sup>99</sup> Kellerman, 1983 <sup>180</sup> Katz, 1980 <sup>181</sup> Kuttner, 1988 <sup>182</sup> Wall and Womark, 1989 <sup>183</sup> Smith et al, 1996 <sup>100</sup>	Spiegel, 1983 <sup>184</sup> Syrjala, 1992 <sup>185</sup> Syrjala, 1995 <sup>186</sup> Slooman, 2005 <sup>216</sup>	Lioffi and Hatira, 1999 <sup>187</sup> Kuttner, 1988 <sup>182</sup>
	Healing touch		Post-White et al, 2005 <sup>88</sup>	
	Massage	Iwasaki, 2005 <sup>89</sup>	Cassileth and Vickers, 2003 <sup>131</sup> Vickers et al, 2004 <sup>46</sup> Escalante et al, 2001 <sup>85</sup> Cruciani et al, 2004 <sup>90</sup> Decker et al, 1992 <sup>188</sup> Wigmore et al, 1996 <sup>30</sup>	Post-White et al, 2006 <sup>88</sup>
	Acupuncture	Esteban-Cruciani, 2001 <sup>91</sup>		
Loss of appetite/cachexia	L-carnitine		Barber et al, 1999 <sup>33</sup> Wigmore et al, 2000 <sup>34</sup> Barber et al, 2000 <sup>32</sup> Barber et al, 2001 <sup>31</sup> Gianotti et al, 1999 <sup>38</sup> Burns et al, 1999 <sup>29</sup> Micke et al, 2002 <sup>40</sup>	Gogos et al, 1998 <sup>36</sup> Fearon et al, 2003 <sup>37</sup> Falconer et al, 1994 <sup>28</sup>
	Relaxation/imagery Essential fatty Acids			Bruera et al, 2005 <sup>35</sup>
Anxiety/Insomnia	Immunocal	Melnick et al, 2005 <sup>42</sup> Grey et al, 2003 <sup>39</sup> Micke et al, 2001 <sup>41</sup>		
	Valerian	Francis and Dempster, 2002 <sup>116</sup>	Leathwood, 1982 <sup>189</sup> Lindahl and Lindwall, 1989 <sup>190</sup> Herrera-Arellano, 2001 <sup>191</sup> Donath, 2000 <sup>192</sup> Poyares, 2002 <sup>193</sup> Schmitz, 1998 <sup>194</sup>	Donath, 2000 <sup>192</sup> Balderer and Borbely, 1985 <sup>198</sup> Schulz et al <sup>120</sup> Glass, 2003 <sup>199</sup>

TABLE 1. (continued)

Symptom	CAM Therapy	Evidence in Pediatrics	Evidence in Adults	Nonsignificant Findings
	Passion flower Kava Kava		Dominquez, 2000 <sup>195</sup> Dorn, 2000 <sup>196</sup> Ziegler, 2002 <sup>197</sup> Wheatley, 2001 <sup>114</sup> Akhonzadeh et al, 2001 <sup>115</sup> Gurley et al, 2005 <sup>112</sup> Wheatley, 2001 <sup>114</sup> Pittler and Ernst, 2003 <sup>200</sup> Lehmann, 1996 <sup>201</sup> Volz and Kieser, 1997 <sup>202</sup> Emser and Bartylla, 1991 <sup>203</sup> Gould, 1973 (tea), <sup>204</sup> Masago et al (aromatherapy), 2000 <sup>119</sup>	
	German Chamomile			
	Aromatherapy: Lavender		Hardy et al, 1995 <sup>117</sup> Lis-Balchin and Hart, 1999 <sup>118</sup> Schultz et al, 1997 <sup>121</sup> Masago et al, 2000 <sup>119</sup> Wilkinson et al, 1999 <sup>126</sup> Blumenthal, 1998 <sup>206</sup> Cohen et al, 2005 <sup>136</sup> Ahles et al, 1999 <sup>86</sup> Stephenson et al, 2000 <sup>128</sup> Smith et al, 2002 <sup>127</sup> Post-White et al, 2005 <sup>88</sup> Lawvere, 2002 <sup>129</sup> Moyer et al, 2004 <sup>207</sup> Wilkinson et al, 1999 <sup>126</sup> Holland et al, 1991 <sup>132</sup>	Graham et al, 2003 <sup>123</sup> Louis, 2002 <sup>205</sup>
	Acupuncture Massage			
Anxiety/Insomnia, cont'	Hypnosis/Imagery	Deng et al, 2004 <sup>137</sup>  Zeltzer and LeBaron, 1982 <sup>98</sup> Hilgard and LeBaron, 1982 <sup>97</sup> Kellerman, 1983 <sup>209</sup> Smith, 1996 <sup>210</sup> Hawkins et al, 1998 <sup>99</sup>	Petersen and Quinlivan, 2002 <sup>133</sup> Specia et al, 2000 <sup>134</sup>  Targ and Levine, 2002 <sup>135</sup> Carlson et al, 2001 <sup>130</sup> Decker et al, 1992 <sup>211</sup> Grealish et al, 2000 <sup>212</sup>	Wall and Womack, 1989 <sup>208</sup>
Diarrhea	Music Therapy Colostrum	Berrera, 2002 <sup>213</sup> Inoue et al, 1998 <sup>71</sup> Mitra et al, 1995 <sup>72</sup> Sarker et al, 1998 <sup>73</sup> Tawfeek et al, 2003 <sup>74</sup> Szajewska and Mrukowicz, 2001 <sup>75</sup> Bin-Nun et al, 2005 <sup>76</sup> Euler et al, 2005 <sup>77</sup> Salminen et al, 2004 <sup>78</sup> Palsson et al, 2004 <sup>69</sup>		
Constipation Neuropathy	Probiotics			
	Biofeedback Glutamine Vitamin E		Vahdat et al, 2001 <sup>81</sup> Argyriou et al, 2005 <sup>83</sup>	

determine through scientific clinical trials which adjuvant CAM therapies are medically sound, effective, and compatible with standard chemotherapy and radiation.<sup>11</sup> Over the last decade, scientific inquiry of CAM therapies has shown that some of the agents previously considered on the “fringe” of medicine are sufficiently studied to become part of the mainstream.<sup>12</sup> Some therapies have more evidence for effectiveness (eg, hypnosis and acupuncture) than others (eg, herbal therapies and homeopathy), and clinical trials in children lag behind CAM trials in adults.

### CLINICAL APPLICATIONS—EVIDENCE FOR EFFECTIVENESS

The increased use of CAM therapies and the awareness of potential toxicities and interactions with treatment have led to the need for reliable evidence for the safety and efficacy of complementary therapies.<sup>13</sup> Complementary therapies require the same rigor in evaluating their effectiveness as that required by conventional Western medicine.<sup>14–16</sup> Rigorous research is needed to demonstrate safety, determine therapeutic dosages for children, detect interactions with other treatments, test

for effectiveness in making a difference over standard care or placebo, provide insight into the mechanism of action, and determine whether the therapy is cost-effective. Although CAM therapies often have been criticized for being used despite a lack of evidence, hundreds of systematic reviews have evaluated specific therapies.<sup>16</sup> Over 900 reports of randomized clinical trials using a CAM intervention for children were found in 4 databases, including Medline, CABHealth, and Embase.<sup>17</sup> Table 1 lists select clinical CAM studies, published to date, that provide evidence for effectiveness in managing symptoms experienced in cancer treatment and care.

In addition to scientific merit, clinical judgment, along with patient preference, cost, and convenience, determine whether a particular therapy is likely to be helpful to a particular patient.<sup>18</sup> It is important for physicians to have an open and nonjudgmental discussion about CAM with patients and their families. Surveys have found patients reluctant to disclose their use of CAM with their physician due to the fear of their physician being critical or unsupportive of the use of CAM. A risk benefit analysis can be employed regarding the safety of CAM.<sup>19</sup> Consideration should always be given toward patient characteristics and preferences, in addition to the level of evidence available in the literature. Individualizing therapies to children is especially important in determining which CAM therapies are of greatest value and of interest for the developmental age and motivation of the patient. The following section will present the reader with the clinical data supporting the most commonly reported CAM therapies for frequent side-effects encountered by children receiving anticancer therapy.

### Cachexia

Cachexia is encountered by approximately 60% of children undergoing therapy for cancer.<sup>20</sup> In children with severe cachexia the use of nasogastric or gastrostomy tubes are frequently used to deliver enteral nutrition; however, children and families are often hesitant to employ them. The use of appetite stimulants may also be prescribed for severe weight loss but these are not devoid of side-effects and may be contraindicated in patients with certain cancer diagnoses.<sup>21</sup> Patients experiencing short-term mild to moderate loss of appetite do not necessitate aggressive nutrition interventions; however, nutrition counseling on its own has not been found to be effective in improving the caloric content of diets and preventing weight loss. Temporary loss of appetite can affect a child's quality of life and can drive parents to look for CAM therapies to ameliorate the condition. Cachexia is often precipitated by nausea and vomiting which often requires management in order for cachexia to be alleviated.

Biological-based CAM therapies have been found to mediate the biochemical processes that contribute to the development of cachexia. Laboratory investigations have identified both humoral and tumor-secreting factors as primary inducers of the cachexia process.<sup>22-24</sup> Changes in levels of cytokines including tumor necrosis factor,

interleukin-6 (IL-6), interferon- $\gamma$ , leukemia inhibiting factor, and ciliary neurotrophic factor have been associated with the development of cachexia and may be impacted by some biologic CAM therapies.<sup>23,25</sup> Reductions in plasma essential fatty acids (EFAs) have been associated with the development of cachexia in adults with advanced cancer.<sup>26,27</sup> EFAs have also been found to reduce inflammatory cytokine production in patients with pancreatic cancer.<sup>28</sup> Supplementation with EFAs has been found to be well-tolerated in the adult population. A phase 1 trial in adults with cancer found the maximum tolerated dose of EFAs to be 0.3 g/kg per day. The dose-limiting toxicity was primarily gastrointestinal.<sup>29</sup>

Several clinical trials investigating the efficacy of EFAs have been conducted among adults with cancer, although no trials have been conducted among children with cancer. Five case series,<sup>30-34</sup> 2 phase 1 trials,<sup>28,29</sup> and 4 controlled, randomized trials<sup>35-38</sup> have been reported. Benefits were observed in small trials; however, in a large, randomized, placebo-controlled trial involving 200 adults with pancreatic cancer, supplementation with a nutrition supplement enriched with EFAs was not associated with the prevention of weight loss in the intervention group. However, comparisons of trials are difficult due to sample populations that included multiple malignancies, varied doses, and varied length of trials.

Other biologic CAM therapies are also undergoing investigation in the management of cachexia. Immunocal is an undenatured whey-protein derivative that provides precursors of glutathione in a form that can be used by cells. Supplementation with Immunocal in patients with HIV/AIDS and adolescents with cystic fibrosis demonstrated that Immunocal is well tolerated with no reports of adverse events.<sup>39-41</sup> Children gained weight and had improved immune function and quality of life. A small pilot study initiated by the Nutrition Committee of the Children's Oncology Group (COG) has also found improvements in clinical status including weight gain and increased levels of reduced glutathione.<sup>42</sup> Currently, a larger clinical trial of Immunocal is being planned by the Nutrition Committee of COG.

The treatment of cachexia may also be managed through the use of alternative medical systems. Practitioners of traditional Chinese medicine will often seek to treat cachexia through the use of herbal remedies and acupuncture. The goal of treatments with acupuncture is to return a state of balance or "chi" to the patient's system. Acupuncture has been found to be accepted and feasible within the pediatric oncology population with a low risk of adverse events.<sup>43,44</sup> The safety of acupuncture-point stimulation, by any method, has been demonstrated by several large prospective trials.<sup>45,46</sup> The incidence of an adverse event or a serious side-effect from acupuncture, when delivered by a licensed acupuncturist are 1:10,000 to 1:100,000, which is the same risk as a serious adverse event from taking penicillin.<sup>43</sup> Surveys have found a wide acceptance of acupuncture among children.<sup>43</sup> No clinical trials have investigated the efficacy of acupuncture for the treatment of cachexia in pediatric oncology.<sup>44</sup>

Practitioners of herbal medicine may also suggest digestive bitters such as ginger for use as an appetite stimulant. Digestive bitters stimulate salivary secretion; however, these teas have a strong flavor that may not be palatable to children. The use of digestive bitters in capsule or pill form may also be possible; however, it is probable that the effect would be less dramatic and likely to be ineffective. No clinical trials have investigated the efficacy of digestive bitters for the treatment of cancer-related cachexia.

### Nausea and Vomiting

CAM offers a number of primary or adjuvant options to alleviate the discomfort and consequences of the progressive triad of nausea, retching and emesis, including acupuncture, acustimulation, acupressure, aromatherapy, and the use of herbal remedies, such as ginger.

Acupuncture has a large body of data supporting its efficacy in the prevention and treatment of chemotherapy-induced nausea. The 1997 NIH Consensus conference concluded that clear evidence supports efficacy of acupuncture in the control of chemotherapy-related nausea and vomiting.<sup>47</sup> Reindl et al,<sup>44</sup> found acupuncture is feasible and accepted as a supportive therapy in pediatric oncology patients receiving emetic chemotherapy. A study initiated at the Pediatric Oncology branch of the NCI and now open COG at are investigating the efficacy of electroacupuncture treatment versus sham placebo, to reduce delayed chemotherapy-induced nausea and vomiting in pediatric and young adult patients with pediatric solid tumors.<sup>48</sup>

Several trials of acupressure wristbands have demonstrated effectiveness in decreasing the severity of acute nausea, in combination with antiemetics.<sup>49</sup> However, the trials showed no evidence for effectiveness in reducing vomiting or delayed chemotherapy-induced nausea and vomiting.<sup>45,49,50</sup> In a systematic review of 11 studies, acupressure was less effective in reducing nausea and vomiting than acupuncture, but could extend the duration of benefit of acupuncture.<sup>45</sup>

Herbs are commonly used for cancer treatment symptom management in adults. Ginger (*Zingiber officinale*) has been advocated as an antiemetic herbal preparation and has been shown to be effective for motion sickness,<sup>51</sup> nausea and vomiting associated with pregnancy,<sup>52-55</sup> and prevention of postoperative nausea and vomiting (PONV) with gynecologic surgery.<sup>56</sup> A monograph for ginger has been approved by the US pharmacopeia and is included in the National Formulary for clinical indications of nausea and vomiting. A systematic review of 24 randomized controlled trials in adults (n = 1073) found few adverse effects, but no clear evidence for efficacy of ginger for PONV.<sup>57</sup> Further research is needed to demonstrate the efficacy of ginger as an adjunctive therapy in children.

Aromatherapy is the inhaled use of essential oils for therapeutic or medical purposes. Ginger (*Z. officinale*), spearmint (*Mentha spicata*), and peppermint (*Mentha*

*piperita*) are recommended for their antiemetic and antispasmodic effects on the gastric lining and colon. Several studies show the efficacy of peppermint in reducing PONV,<sup>58</sup> chemotherapy induced-nausea,<sup>59</sup> and colonic spasms during colonoscopy<sup>60,61</sup> and after colostomy surgery.<sup>62</sup> One study however, found no greater benefit over deep breathing and placebo for PONV in 33 patients undergoing ambulatory surgery.<sup>63</sup> Aromatherapy massage was found to have a mild transient anxiolytic effect, which may be useful for the treatment of anticipatory nausea and vomiting.<sup>64</sup> A limitation of these studies is the small sample sizes and lack of testing in a pediatric population.

Hypnosis is especially effective in children. In a study of 54 children with cancer, Zeltzer and colleagues found hypnosis more effective than cognitive distraction/relaxation or placebo in reducing anticipatory and postchemotherapy nausea and vomiting.<sup>65</sup>

### Constipation

Constipation is frequently reported in children being treated with cancer and may also be accompanied by severe bowel pain. Despite the prevalence of constipation, little research has been conducted into investigating the effectiveness of CAM therapies for constipation. Constipation is a side-effect that is frequently treated through lifestyle modifications or conventional interventions; however, the efficacy of lifestyle modifications recommendations as a treatment for constipation have not been validated in randomized controlled trials.<sup>66</sup>

It is common for patients to turn to CAM therapies when conventional therapies are not able to relieve constipation, particularly when it is accompanied by pain. Patients may be looking for a natural supplement to augment the effects of conventional recommendations. Some of the most common biologic remedies used by patients are blond or black Psyllium (*Plantago ovata*), Cascara sagrada (*Rhamnus purshiana*), Olive oil (*Olea europaea*), and Castor oil (*Ricinus communis*). Psyllium increases the volume of the stool through exerting a laxative effect and acts as a stool softener by increasing stool water content.<sup>67</sup> Psyllium is a component of the dietary supplement Metamucil and has been found to be safe in children when accompanied by adequate fluid intake. The combination of blond psyllium with other natural products such as senna has been found to increase its effectiveness.<sup>68</sup>

Cascara sagrada was formerly recognized by the FDA as an effective treatment for constipation; however, this designation was removed in 2002 due to the paucity of clinical trials supporting its use.<sup>68</sup> Cascara sagrada has been found to stimulate intestinal peristalsis; whereas castor oil seems to increase fluid secretion. Each of these agents is likely to be safe in children; however, none of these remedies are indicated for long-term use. Caution should be used in prescribing natural laxatives to children under the age of 12. Administration of natural laxatives to children under 12 should only be administered under the observation of a physician. As with conventional

agents, it is prudent to monitor electrolyte status and encourage intake of fluids.

Mind-body interventions may also be a resource for treatment of constipation. One of the most well-researched mind-body interventions for the management of constipation is biofeedback. Biofeedback is a training technique in which people are taught to improve health and performance by learning to recognize signals within their bodies. A comprehensive review of biofeedback as a treatment for functional constipation concluded that biofeedback was effective in treating chronic constipation when compared with standard interventions.<sup>69</sup>

## Diarrhea

Diarrhea is a common side-effect of cancer therapy, yet most of the published research investigating CAM therapies for the treatment of diarrhea in children has been in newborns, malnourished children, or children with HIV/AIDS. Most of these trials have investigated the use of different biologic CAM therapies as a treatment for diarrhea. Many of the studies have been conducted in populations with compromised immune systems or in patient populations that are challenged with similar side-effects due to conventional treatment. It is plausible that these remedies may be applicable to children undergoing treatment for cancer.

Colostrum is the milk secreted by mammals within the first few days after giving birth. Colostrum is distinct from milk produced during the postpartum period in that it contains high concentrations of antibodies (IgG, IgM, and IgA), cytokines (IL-1 $\beta$ , IL-6, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ ), growth factors (insulinlike growth factor I and II, transforming growth factor- $\beta$ , epidermal growth factor), lactoperoxidase, and lactoferrin.<sup>70</sup> Colostrum as a dietary supplement is most commonly obtained from cows; however, one study in children undergoing bone marrow transplantation used colostrum obtained from humans.<sup>71</sup> Hyperimmune bovine colostrum has obtained FDA orphan status for AIDS-related diarrhea.<sup>68</sup> It is unclear whether the use of colostrum is associated with transmission of disease.

Much of the research on colostrum in children has investigated its efficacy as a treatment for infection-induced diarrhea. Few trials have been randomized; most of the studies have been case series. Among the randomized trials, one well-designed trial administered colostrum to 75 infants (age 6 to 24 mo) with rotovirus-induced diarrhea; colostrum supplementation was associated with significant reductions in the duration of diarrhea as compared to controls.<sup>72,73</sup> In another randomized study, colostrum added to infant formula decreased the incidence of diarrhea in newborns.<sup>74</sup> The duration of severe graft versus host disease in children after an allogeneic bone marrow transplant was reduced with supplementation with colostrum in one case series.<sup>71</sup> No adverse events were reported.

Probiotics are one of the most frequently used biologic CAM therapies used in children. Probiotics have been investigated in children with viral or antibiotic-

induced diarrhea. A number of studies have investigated lactobacillus gg in children with viral-induced diarrhea and have reported encouraging findings.<sup>75</sup> Probiotics have been prescribed to newborns with no reports of adverse events, although no studies have been published in children with cancer.<sup>76,77</sup> Because the use of probiotics contain live active organisms, there has been hesitation in prescribing their use among patients with compromised immune systems; however, large, randomized, clinical trials in immunocompetent patients have rarely reported any adverse events.<sup>78</sup>

## Neuropathy

Glutamine and vitamin E are 2 supplements that are associated with encouraging results for the prevention of neuropathy in adults with cancer. Glutamine is a nutrition supplement that has been used for the prevention and treatment of chemotherapy-induced mucositis in children with cancer with no reports of adverse events.<sup>79,80</sup> Its role in preventing peripheral neuropathy was investigated in patients with stage IV breast cancer receiving paclitaxel. Glutamine was associated with a reduction in the incidence of motor weakness ( $P = 0.04$ ) and abnormalities in gait ( $P = 0.016$ ).<sup>81</sup> No toxicities were reported. A trial of glutamine in children receiving vincristine is underway.<sup>82</sup>

Vitamin E was associated with a reduction in the incidence of neuropathy in the treatment group as compared with controls in a group of 31 adults with cancer.<sup>83</sup> The neuroprotective effects of vitamin E need to be further investigated in the pediatric population.

## Mucositis

Mucositis affects a large proportion of children undergoing treatment for cancer at some point in their therapy. In children undergoing bone marrow transplantation, mucositis can be debilitating and severely painful. Many times mucositis can result in extended periods of administration of total parental nutrition due to the patient's inability to swallow.

Two biologic CAM therapies have demonstrated encouraging results in children with cancer. Once considered an alternative therapy, glutamine is a nutrition supplement that is routinely used for the prevention of mucositis among children with cancer. Administration of glutamine was found to be effective in preventing the duration and severity of mucositis in children undergoing bone marrow transplantation.<sup>79,80</sup> However, the large amount of liquid required for glutamine administration can be prohibitive in children with severe mucositis and may affect compliance.

TRAUMEEL S is a homeopathic remedy that has been found to be effective in reducing the stomatitis in children undergoing bone marrow transplantation. In a randomized, placebo-controlled, double-blind clinical trial TRAUMEEL S was administered to 32 pediatric patients undergoing a bone marrow transplant.<sup>84</sup> TRAUMEEL S was associated with significant reductions in the

severity and duration of stomatitis ( $P < 0.01$ ). No adverse events were reported. These findings are being followed up in a larger clinical trial among children with cancer through COG.

## Fatigue

Fatigue is prevalent in persons with cancer at any age and is associated with malaise, lethargy, asthenia, and decreased mental attention and energy. Despite the inherent problem of fatigue in children and adults with cancer, there are few interventions known to ameliorate this debilitating symptom. Several isolated CAM studies suggest potential efficacy for acupuncture, Healing Touch, and massage.

In adults with cancer, acupuncture reduced cancer-related fatigue by 31% over 6 weeks of treatment. However, comparison subjects receiving usual care in another center also had less fatigue (24% reduction).<sup>46,85</sup> One week of 20-minute upper body massage sessions was effective in reducing fatigue in 35 adults undergoing bone marrow transplantation.<sup>86</sup> In a study of 230 adults with cancer, however, 4 weeks of weekly full body massage was close to, but not quite significantly better in relieving fatigue than the control condition ( $P = 0.057$ ).<sup>87</sup> Four sessions of Healing Touch were effective in reducing fatigue.<sup>87</sup>

In children with cancer, massage had no effect on fatigue in 23 children receiving weekly massage for 4 weeks.<sup>88</sup> Mothers ( $n = 68$ ) had less fatigue and greater vigor, however, when they received massage when their children were in the hospital for cancer treatment.<sup>89</sup>

L-Carnitine is a supplement used as a cardioprotectant secondary to anthracycline therapy. In preliminary clinical studies, carnitine deficiency was found in 67% of adult cancer patients<sup>90</sup> and 60% of pediatric patients with AIDS and chronic illness presenting with fatigue.<sup>91,92</sup> Carnitine is required to carry fatty acid across the inner mitochondrial membrane where fat oxidation and adenosine triphosphate synthesis take place.<sup>93</sup> Several chemotherapy agents have been found to interfere with this network,<sup>94</sup> resulting in alterations in energy utilization and balance and resulting skeletal muscle fatigue and cardiac muscle inefficiency. In a preliminary report of a randomized phase 2 clinical trial, 1 week of carnitine supplementation reduced fatigue and improved functional status and mean free carnitine levels in adult hospice patients. Importantly, no adverse events were reported.<sup>90</sup>

In a well-designed and blinded clinical trial in the United Kingdom, individualized homeopathic treatments were found to improve general fatigue secondary to chronic fatigue syndrome, compared with a placebo. Other measures of fatigue were not significantly different, however, and the authors conclude that the evidence is equivocal, but weak.<sup>95</sup> Fatigue is a complex condition with many contributing mechanisms. Treatments effective for noncancer fatigue may not be effective for cancer-related fatigue.

## Pain

Mind-body therapies have gained acceptance for supportive care of adults with cancer, and several randomized clinical trials support the efficacy of relaxation, imagery, and hypnosis in alleviating cancer pain.<sup>19</sup> In children, most pain-related hypnosis studies address procedural-related pain. In 9 studies, conducted between 1982 and 1999, reductions in pain were present, but findings were inconsistent among studies and only 3 studies used appropriate control groups.<sup>96</sup> Four studies reported greater benefit in highly hypnotizable subjects.<sup>97-100</sup> A more recent and rigorously controlled study of 80 pediatric cancer patients undergoing lumbar puncture determined therapist-guided hypnosis effective in reducing pain and anxiety.<sup>101</sup> In a review of empirical evidence for the efficacy of CAM interventions for pain symptoms in children, Tsao and Zeltzer<sup>102</sup> concluded that self-hypnosis/guided imagery/relaxation for recurrent headache pain qualified as an empirically supported therapy, using the American Psychological Association Task Force criteria (1995). Hypnosis for procedural and postoperative pain was possibly efficacious.

In addition to mind-body techniques, acupuncture and massage are most often shown to relieve symptoms and improve physical and emotional well-being.<sup>103,104</sup> Although acupuncture is deemed effective for acute cancer-related pain,<sup>103</sup> randomized trials are needed to confirm its value for treatment of chronic cancer-related pain.<sup>19</sup>

Zeltzer and colleagues completed a phase 1 study investigating the feasibility and acceptability of acupuncture and hypnosis for 31 children with a variety of chronic pediatric pain syndromes.<sup>105</sup> Despite the lack of a control group and ability to differentiate the 2 intervention effects, the treatment was feasible and highly acceptable to children and provided preliminary evidence of pain reduction. Only one controlled acupuncture study exists in children, which demonstrates a clear reduction of migraine pain.<sup>106</sup>

Similarly, several small studies found massage effective in reducing short-term pain in adults with cancer, but long-term effects require further study.<sup>19</sup> In a more recent study of 230 adults with cancer, 4 weekly sessions of therapeutic massage effectively reduced short-term pain and use of nonsteroidal anti-inflammatory medications, in comparison to the cross-over control condition.<sup>87</sup> Two small pediatric studies demonstrate reduced pain with juvenile rheumatoid arthritis<sup>107</sup> and dressing changes for burns.<sup>108</sup> Gaps in research remain, and efficacy studies with larger samples are needed to test effectiveness for chronic pain, long-term effects, and pediatric populations.

## Anxiety-insomnia

Among persons with cancer, insomnia, fatigue, and anxiety are highly intercorrelated.<sup>109</sup> Herbal sleep aids such as valerian (*Valeriana officinalis*), passionflower, and kava (*Piper methysticum*) are some of the most commonly used herbal products. Several botanicals have

demonstrated some efficacy as “natural sedatives” based on both clinical and preclinical studies.<sup>110</sup> Although St. John’s Wort has been shown to be effective for mild-to-moderate depression, it is a potent cytochrome P450 inducer and should not be used concomitantly with chemotherapy.<sup>111</sup> Kava kava was found more effective than placebo for reducing anxiety, stress, and insomnia and may be a viable nonpharmacologic remedy.<sup>112</sup> Reports of hepatotoxicity-related deaths have been reported with kava kava.<sup>113</sup> German chamomile demonstrates anxiolytic activity in animals; however, there are few clinical trials testing efficacy and indications that chamomile may interfere with anthracycline chemotherapy.<sup>14</sup>

Block and colleagues provide a detailed review of 21 clinical studies testing Valerian for tolerability and efficacy in reducing insomnia in comparison to placebo or pharmaceutical intervention.<sup>110</sup> In all trials, Valerian was more effective than placebo, or equal to benzodiazepines, in improving most measures of sleep quality, without the residual sleepiness or reduced vigilance or reaction time. Effects were dose-dependent with single doses ineffective and daily dosing for 7-14 days improving sleep outcomes. When Kava was given with Valerian, the combined treatment reduced insomnia better than either product alone.<sup>114</sup> Passionflower (*Passiflora incarnata*) is a little studied mild sedative, often combined with valerian in preparations. Only one clinical study demonstrated efficacy similar to benzodiazepines.<sup>115</sup>

In children, a small pilot study of 5 subjects found Valerian more effective than placebo at reducing sleep latency and time awake at night, and increasing sleep time and quality of sleep.<sup>116</sup> Valerian seems to have a wide margin of safety and is not metabolized via the cytochrome enzymes, suggesting no interaction with chemotherapy agents.<sup>112</sup> Valerian can potentiate effects of sedatives, hypnotics, and anesthetics, and should be avoided before scheduled surgery.<sup>14</sup> There are no known studies determining long-term safety and efficacy and issues of tolerance and dependency.

Aromatherapy with inhaled lavender (*Lavendula angustifolia*) has been shown to have sedative effects (increased sleep time and greater drowsiness and relaxation) without toxicity.<sup>117-121</sup> Absorption into the blood stream is rapid via the nasal and lung mucosa and very low levels are required to produce a sedative effect.<sup>122</sup> Only small clinical studies have been conducted, with inconclusive evidence for efficacy over placebo in one study in adults with cancer.<sup>123</sup>

Progressive muscle relaxation has been extensively studied and shown to be effective for improving sleep in persons with insomnia.<sup>124</sup> A meta-analysis of 59 studies showed improved sleep induction and maintenance with psychologic interventions. An NIH consensus panel concluded that relaxation and biofeedback improve some aspects of sleep, but the improvement may not be clinically significant.<sup>125</sup>

Several studies support potential efficacy for massage in reducing anxiety. One week of upper body partial

massage reduced anxiety and distress in adults undergoing bone marrow transplantation, but had no effect on overall mood, pain, or depression.<sup>86</sup> The addition of essential oils to massage enhanced the anxiolytic effect in patients at the end of life.<sup>126</sup> In 230 adults with cancer, four weekly sessions of therapeutic massage effectively reduced anxiety and mood disturbance in comparison to the crossover control condition.<sup>87</sup> In other studies, massage enhanced mood<sup>127,128</sup> and reduced anxiety in women with ovarian cancer.<sup>129</sup>

Several randomized clinical trials demonstrate effectiveness of relaxation, imagery, hypnosis, or music therapy to reduce anxiety and distress in adults with cancer.<sup>130-135</sup> Acupuncture also effectively reduced anxiety disorders and general anxiety levels in adults with cancer, and was effective or more effective than antidepressants for patients without cancer.<sup>136</sup>

In children, hypnosis is particularly effective in reducing anxiety and distress.<sup>137</sup> Several studies by Zeltzer and colleague found hypnosis more effective than cognitive distraction/relaxation or placebo in reducing anxiety in children with cancer.<sup>98</sup> Although Healing Touch and therapeutic touch are widely used in pediatric hospitals to reduce stress and anxiety, no studies were found in pediatrics.<sup>138</sup>

## CAM AND INTEGRATED PALLIATIVE CARE

CAM therapies help to improve quality of life and demonstrate symptomatic benefit across the continuum of treatment for childhood cancer. The World Health Organization’s definition of palliative care encompasses ‘active total care’ of the child and family from the day of diagnosis, up to, and including, a time when the disease may no longer be curable. Integration of CAM modalities into palliative care is a natural extension of “holistic,” alternative care, where the goal is to provide physical, psychological, social, and spiritual support at the time of a terminal illness.<sup>139</sup> CAM interventions, which are family centered and child-focused, can be delivered on an inpatient/outpatient hospital-based setting, as well as in the home. The aim of the interventions are to minimize pain and suffering and to provide practical, emotional and physical support. This approach is consistent with goals of the Initiative for Pediatric Palliative Care, a consortium of institutions, academic centers and professional organizations, whose aim is to enhance the care delivered to children living with life-threatening illness.<sup>140</sup>

Conventional therapy alone has not eliminated pain and suffering at the end of a child’s life. Families report that the symptoms of anorexia, nausea, vomiting, constipation, and diarrhea are not adequately treated by conventional means.<sup>141</sup> By parental report, 89% of children suffered “a lot or a great deal” within the last month of life. The most common symptoms experienced by children at this time included fatigue, pain, dyspnea, anorexia, nausea and vomiting, constipation and diarrhea. Of these symptoms the most commonly treated were pain (76%) and dyspnea (65%). The successful response



rate was 27% for pain and 16% for dyspnea.<sup>141</sup> Table 1 reviews the literature for evidence of CAM effectiveness in treating these symptoms in children receiving conventional therapy. There is no literature, at this time, on the use of these CAM interventions in the pediatric palliative setting, but the efficacy for treating the individual symptoms has been well established. A small pilot study of an adult population in a palliative-care setting, published by Gadsby et al<sup>142</sup> indicated that acupuncture-like transcutaneous electrical nerve stimulation can improve fatigue and a sense of overall well being. A review of the literature on clinical trials on CAM for the management of pain, dyspnea, and nausea and vomiting near the end of life of adult patients found support for the use of CAM modalities, most specifically for pain and dyspnea.<sup>143</sup>

Palliative care should also include interventions offered to parents and siblings, as well as other caregivers, who can suffer both psychologic and physical distress during the child's end of life and consequent phase of bereavement.<sup>144</sup> These symptoms may include fatigue, depression, insomnia, and pain (headaches and musculoskeletal pain). CAM interventions can ease the burden of this suffering (Table 1 provides references for efficacy of CAM modalities in these areas for both adults and children).

To succeed in providing optimal palliative care for children with advancing cancer, an innovative interdisciplinary approach is recommended.<sup>145</sup> The interdisciplinary nature of palliative care and the developing team work among doctors, nurses, social worker, child life specialists and other healthcare professionals, of multiple disciplines, has set the stage for the integration of CAM modalities into accepted practice in the care of the child suffering with unresponsive cancer. This process provides an opportunity for each of the 2 traditions of health care to work together and learn from each other.<sup>146</sup> Anghelescu et al<sup>144</sup> recommends symptom management that uses integrated therapies and interventions that focus on the child as a whole human being and not just the one symptom at a time. The 5 domains of CAM therapy and alternative medicine systems welcome this process.

### CAM AND SURVIVORSHIP

As conventional medicine becomes increasingly effective at treating children with cancer, the challenges of survivorship have become a priority research area. Studies have estimated that 60% to 70% of children will have at least one disability as a result of cancer therapy. Survivors are challenged with issues related to energy balance, fatigue, bone density, pain syndromes, and anxiety, and are at increased risk for heart disease, osteoporosis, infertility, and second malignancies.<sup>3</sup>

Surveys in survivors of adult cancers have found that the use of CAM extends into survivorship.<sup>147,148</sup> This trend has also been observed in survivors of childhood cancer, who report they use CAM to reduce risk of

relapse, cope with late effects from cancer therapy, or reduce their risk of developing a late effect.

The most common domain of CAM used by survivors are biologic therapies. Although the risk of interaction with a conventional agent is less of a concern in the survivor population, biologic therapies are not devoid of possible adverse effects. The chemistry and mechanism of action of many nutrition and herbal remedies has not been well characterized. Some biologic therapies have been found to stimulate cancer growth particularly tumors that are hormone-sensitive.<sup>149–152</sup> Many biologic therapies have also been found to stimulate the immune system.<sup>153,154</sup> It is unknown whether biologic therapies that exert an effect on the immune system are safe for patients who have undergone stem cell transplantation. Immune-enhancing remedies may increase the risk of graft vs. host disease. Survivors of child and adolescent cancer are at increased risk for second malignancies, some of which are hormone sensitive.

The promotion of healthy lifestyle behaviors has been recommended to survivors of cancer to potentially modify the incidence of late effects and reduce the risk of cancer recurrence.<sup>155</sup> Although the role of CAM among survivors of cancer is largely unknown, investigators have begun to include CAM as a component of lifestyle education programs. One lifestyle education program that included yoga, breathing exercises, relaxation techniques, group support, individual counseling, and group lectures on yogic philosophy led to decreased measures of plasma glucose and lipid profiles.<sup>156</sup> Yoga has been associated with improvements in spatial and verbal memory test scores in children.<sup>155</sup> Several studies have specifically investigated the effectiveness of various meditation programs used with children. Consistent positive effects have been observed in reducing anxiety, hyperactivity and behavioral difficulties as well as increasing self esteem, academic performance, attention and concentration, communication skills and interpersonal relationships.<sup>157–162</sup> The utility of mind/body interventions among survivors of childhood cancer remains to be determined.<sup>163,164</sup>

Survivors of childhood cancer frequently report difficulty in coping with chronic fatigue and anxiety. Many of the previously described therapies for patients undergoing cancer therapy may also be applied to the survivor population (Table 1).

Maintenance of a healthy energy balance has become an emerging health issue among survivors of childhood cancer, given the rising incidence of childhood obesity. Many biological-based therapies have been promoted to increase energy expenditure, modulate carbohydrate metabolism, increase satiety, modify fat absorption or synthesis, increase water elimination, or promote weight loss through an unknown mechanism.<sup>165</sup> The safety and efficacy of most of these promoted weight loss supplements has yet to be determined, thus patients should be counseled to avoid these supplements until further evidence is available. Promoting healthy lifestyle

**TABLE 2.** Resources on Complementary/Alternative Medicine

## Centers/Institutions:

- National Center Complementary Alternative Medicine (<http://nccam.nih.gov/>)
- National Cancer Institute PDQ (<http://www.cancer.gov/cancertopics/pdq/cam>)
- Children's Oncology Group ([www.childrensoncologygroup.org](http://www.childrensoncologygroup.org))
- Integrative Therapies Program for Children with Cancer, Columbia University ([www.carolann.hs.columbia.edu](http://www.carolann.hs.columbia.edu))
- Memorial Sloan Kettering (<http://www.mskcc.org/mskcc/html/11570.cfm>)

## Databases:

- National Library of Medicine (MEDLINE) ([www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/))
- The Natural Medicines Comprehensive Database ([www.naturaldatabase.com](http://www.naturaldatabase.com))
- The Cochrane Library. (<http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME>)

## Book references:

- Physicians Desk Reference for Herbal Products. Published by Medical Economics Company, Inc, Montvale, NJ
- Physicians Desk Reference for Nutritional Supplements. Published by Medical Economics Company, Inc., Montvale, NJ

## Product Information:

- Consumer Lab ([www.consumerlab.com](http://www.consumerlab.com))

## Journals:

- Alternative Therapies in Health and Medicine (InnerDoorway Health Media, Inc)
- Integrative Cancer Therapies (Sage Publications)
- Journal Complementary/Alternative Medicine (Mary Ann Liebert, Inc, Publishers)

and increased activity should continue to be emphasized until further research is conducted.

## CONCLUSIONS

Relief of cancer-related symptoms is essential in the supportive care of children with cancer, which extends into survivorship or end of life care. Complementary therapies such as acupuncture, hypnosis/imagery, and massage therapy can help reduce symptoms when conventional treatment does not bring satisfactory relief or causes undesirable side-effects. Several relatively small clinical trials of varying quality have been conducted on these CAM therapies in pediatric oncology. Preliminary evidence has emerged for their safe and effective use. Some herbs have been shown to be effective in adults, but few studies have been conducted in children. Further investigation with larger randomized clinical trials is warranted for each of these promising therapies.

Counseling patients on the safety and efficacy of CAM is a challenge to healthcare providers, as there is a paucity of data from well-designed research trials. Guidelines for assessing the safety and efficacy of many CAM therapies have been previously published and may serve as a guide to health care providers when counseling patients on CAM.<sup>19</sup> It is important to assess and document the child's use of CAM, critically evaluate the evidence or lack of evidence, balance the potential risks with possible benefits, and assist the family in their choices and decisions regarding use of CAM for their child with cancer. Health care providers should initiate open, nonjudgmental discussions with patients and parents regarding CAM use. Unexpected toxicities or responses to treatment may be a result of an interaction between CAM remedies and will warrant close observation. Guidelines for monitoring patients combining CAM with conventional therapy have been previously published.<sup>166</sup> Table 2 provides additional resources for health care providers.

The aim of evidence-based practice is to provide the best care based on the best available research.<sup>167</sup> Additional research on CAM in children is needed to determine efficacy and outcomes, dosage, provider effectiveness, cost, and mechanism of action. CAM intervention trials have historically lacked the control and rigor of randomized controlled medical trials. Comparisons across studies are complicated by inclusion of heterogeneous populations and weaknesses in study methodology.<sup>168</sup> Clinical trials are needed to determine outcomes on consistent and standardized interventions tested in homogeneous populations over time. Until the evidence is more conclusive, the providers' role is to assess and document the child's use of CAM, critically evaluate the evidence or lack of evidence, balance the potential risks with possible benefits, and assist the family in their choices and decisions regarding use of CAM for their child with cancer.

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