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# MEASURES AND METHODS FOR SYMPTOM AND SYMPTOM CLUSTER ASSESSMENT IN ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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**OBJECTIVES:** *To provide an overview of resources for measuring symptoms and symptom clusters in adolescents and young adults (AYAs) with cancer and to examine methodological strategies for evaluating symptom clusters.*

**DATA SOURCES:** *Published research articles and clinical experience.*

**CONCLUSION:** *Limited research has addressed symptoms and symptom clusters in AYAs with cancer. Reliable, valid, and developmentally appropriate measures are needed to advance this area of research.*

**IMPLICATIONS FOR NURSING PRACTICE:** *Use of mobile technology and mixed qualitative and quantitative methods to understand AYAs' experience of symptoms and symptom clusters could enhance symptom awareness and the evidence base for practice.*

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Adolescents and young adults (AYAs) with cancer experience multiple co-occurring, interrelated symptoms as a result of their disease and treatment.<sup>1</sup> Accurate symptom assessment is vital to provide high-quality supportive care and evaluate therapies. Research that addresses symptoms among individuals with cancer has increased over the past 20 years; however, symptom research among AYAs as a distinct population is limited.

Diversity among the AYA age group with regard to growth, development, and life experiences in general creates challenges in designing studies as well as identifying appropriate symptom assessment measures. AYAs who are  $\leq 18$  years of age are most commonly treated at pediatric centers and are more likely to be included in study samples with younger children. AYAs older than 18 years are more likely to be included in studies with adults, including older adults. This division of AYAs in research has hindered advancement of symptom science that addresses this distinct group, including attention to developmentally meaningful approaches to symptom measurement.

Validated instruments for measuring symptoms across the full AYA age range (ages 15 to 39) are sparse. Additionally, researchers have used a variety of methodological strategies to evaluate symptoms and symptom clusters, making comparisons and conclusions difficult. This article presents an overview of approaches and resources for measuring symptoms and symptom clusters in AYAs with cancer, and compares and contrasts methodological strategies to evaluate symptoms and symptom clusters. The article also proposes directions to support developmentally meaningful research addressing symptoms and symptom clusters in the AYA population.

### **DEFINING AND EXPLORING SYMPTOM CLUSTERS**

AYAs with cancer, like younger children and older adults, generally do not experience single symptoms in isolation, but rather experience multiple co-occurring, interrelated symptoms.<sup>1,2</sup> Groups of two or more symptoms that occur together and are more strongly related to each other than to other symptoms are referred to as

*symptom clusters*.<sup>3</sup> The relationships among symptoms comprising a cluster may potentiate the severity of the individual symptoms and have a synergistic negative impact on distress, functional status, and quality of life.<sup>4,5</sup> Cluster-focused interventions may thus be more potent than single symptom-focused interventions by ameliorating multiple symptoms that potentially share a common biologic mechanism or by influencing a key symptom that additively or interactively exacerbates others.<sup>6,7</sup>

Studies addressing symptom clusters have predominantly focused on either younger children or older adults. These studies emphasize the clinical significance of clusters, with the presence of symptom clusters associated with poorer functional status and quality-of-life outcomes.<sup>8,9</sup> A recent review found that little was known about symptoms and even less about clusters in adolescents with cancer.<sup>1</sup> No studies have focused on symptom clusters in young adults (YAs) with cancer.

### **RESOURCES FOR MEASURING SYMPTOMS AND SYMPTOM CLUSTERS**

#### ***Quantitative Self-Report Instruments***

To date, no instruments have been developed to measure multiple cancer-related symptoms in AYAs across the age range of 15 to 39 years. Only one instrument exists to measure a single cancer-related symptom in AYAs: body image. A few have been developed and validated to measure symptoms in adolescents with cancer.

**Multiple Symptoms.** The Memorial Symptom Assessment Scale (MSAS 10-18) adapted from an adult version,<sup>10</sup> is the only instrument that has been developed to measure multiple symptoms in the targeted age group of 10- to 18-year-olds with cancer.<sup>11</sup> This tool has been used in a number of studies with adolescents, where it has demonstrated adequate reliability and validity to measure multiple dimensions (frequency, severity, and distress) of 30 common cancer-related symptoms experienced during the previous week.<sup>12-14</sup>

The symptoms included in the MSAS 10-18 were used in one study with 72 AYAs (ages 13 to 29). Though no psychometric data are available, at least one participant commented that an item related to sexual performance was needed. This item is included on the adult version but not on the 10-18 version.<sup>15</sup>

**Single Symptoms.** The one instrument developed specifically for AYAs that assesses a single cancer-related symptom is the Body Image Instrument (BII). The 28-item BII demonstrated initial reliability and validity among 67 AYAs (ages 12 to 28) who had completed cancer treatment.<sup>16</sup> The BII was also used in a study of an intervention to augment psychosexual development in 21 AYAs ages 15 to 25 with cancer.<sup>17</sup>

Two instruments have been developed to measure cancer-related fatigue in adolescents. One is the Fatigue Scale for Adolescents (FS-A),<sup>18,19</sup> which was derived from qualitative work by Hinds and colleagues<sup>20</sup> and has been validated in studies with adolescents with cancer.<sup>21,22</sup> The FS-A includes 13 items that assess fatigue intensity during the past week and 11 items that address perceived causes of fatigue. A 24-hour version of the FS-A is also available.<sup>23</sup> The FS-A measures changes in fatigue over time and distinguishes between adolescents with higher and lower levels of fatigue.<sup>18,19</sup>

The PedsQL™ Multidimensional Fatigue Scale<sup>24</sup> is an 18-item self-report measure of fatigue designed for use across acutely ill, chronically ill, and healthy populations. Versions of the scale assess fatigue over the past week or month. Separate measures are available for adolescents (ages 13 to 18), young adults (18 to 25), and adults (>age 26).<sup>25</sup> Respective versions of the PedsQL™ Multidimensional Fatigue Scale have been used and validated for adolescents with cancer<sup>26</sup> and healthy young adults.<sup>27</sup>

For other common cancer-related symptoms, such as pain, nausea, depression, anxiety, and sleep-wake disturbances, researchers have used measures developed for younger children, adults, or healthy adolescents. Chemotherapy-induced nausea in adolescents has been measured using the Pediatric Nausea Assessment Tool (PeNAT), a tool with a 4-point facial expressions item, developed for ages 4 to 18.<sup>28</sup> Walker et al<sup>29</sup> measured sleep-wake disturbances in adolescents with cancer (ages 10 to 19) using the Adolescent Sleep-Wake Scale, developed for healthy adolescents.<sup>30</sup> Dyson et al<sup>31</sup> assessed depressive symp-

toms and anxiety in AYAs (ages 16 to 30) using the Beck Depression Inventory 2<sup>nd</sup> edition Fast Screen (BDI-FS)<sup>32</sup> and the State Trait Anxiety Inventory-State form (STAI-S). Visual analog scales or numerical rating scales have also been used to measure various dimensions of individual symptoms, particularly pain, in adolescents with cancer.<sup>33</sup>

As part of the Patient-Reported Outcomes Measurement Information System (PROMIS) sponsored by the National Institutes of Health Roadmap for Medical Research Initiative, adult and pediatric item banks of reliable and valid standardized self-report items for a number of symptoms have been developed.<sup>34</sup> PROMIS pediatric measures for fatigue, pain interference, depressive symptoms, and anxiety are feasible and acceptable for use with adolescents in active cancer treatment and survivorship.<sup>35</sup> Adult PROMIS measures for fatigue, sleep disturbance, wake disturbance, and depression are acceptable and feasible for use with YAs receiving chemotherapy.<sup>36</sup> Because the pediatric item banks are specified for respondents ages 8 to 18 and the adult item banks for those over 18, PROMIS does not provide single instruments for use across the specific age range for AYAs.

### Symptom Diaries

Symptom diaries support in-depth understanding of the symptom experience and the opportunity to explore the trajectories of symptoms over time. Because many cancer-related symptoms have variable trajectories, using diaries to track daily assessments of symptoms may lead to a better understanding of the individual's experience, which would not be possible with less frequent assessment. Diaries also support the inclusion of free text responses for qualitative analysis, along with more traditional scaled items. A diary-based approach to data collection may also support recruitment of a study sample extending across the AYA age continuum. Potential disadvantages of symptom diaries are participant burden and the risk of missing data.

Ream and colleagues<sup>37</sup> used diaries to explore fatigue and quality of life among 22 AYAs (ages 13 to 20). Diary items were derived from previously developed tools, and participants completed the diaries daily over a period of 1 week. Erickson and colleagues<sup>38</sup> used diaries in a sample of 20 adolescents (ages 12 to 19) to explore patterns of fatigue over a 1-month period. These diaries

included both quantitative measures and qualitative free text responses. Both studies demonstrated the feasibility of diaries for data collection.

Each of these studies offered participants the option of using paper-based diaries or completing the diaries electronically on a computer.<sup>37,38</sup> In each study, most participants elected to use the paper version, although reasons for selecting this version were not identified. Of note, these studies were conducted before the introduction and widespread adoption of more user-friendly portable devices such as tablet computers and smartphones. Electronic diaries using currently available devices may be more appealing.

### Interviews

Interviews also support in-depth exploration of the symptom experience and the meaning attached to it. Like diaries, interview-based approaches to data collection may support accrual of a wider age range within the AYA continuum. Depending on the duration, interviews also may be a source of participant burden, in particular, for an AYA experiencing multiple severe symptoms. Another limitation of the interview may be the participant's hesitation to give completely honest answers, that is, social desirability bias.

Gibson and colleagues<sup>39</sup> used semistructured interviews to explore how fatigue affected the lives of eight 16- to 19-year-olds with cancer. Hilton et al<sup>40</sup> used interviews to investigate the experience of hair loss in 19 AYAs (ages 18 to 38) with cancer. Both studies demonstrated the feasibility of using interviews to gain detailed, developmental perspectives of AYAs' symptom experiences and the effects of symptoms on their lives.

## TECHNOLOGY AS A RESOURCE FOR SYMPTOM AND SYMPTOM CLUSTER MEASUREMENT

Expanding technology, including computers and mobile devices such as Smartphones and tablet computers, provides novel mechanisms to collect data on symptoms and symptom clusters as well as to explore the trajectories of symptoms over time. AYAs are "digital natives," having grown up using technology. By mid-2014, nearly 85% of individuals 18 to 34 years in the United States owned a Smartphone.<sup>41</sup> The iPad, Apple's tablet-based computer that was introduced in 2010, is regarded as the most rapidly adopted technology.<sup>42</sup>

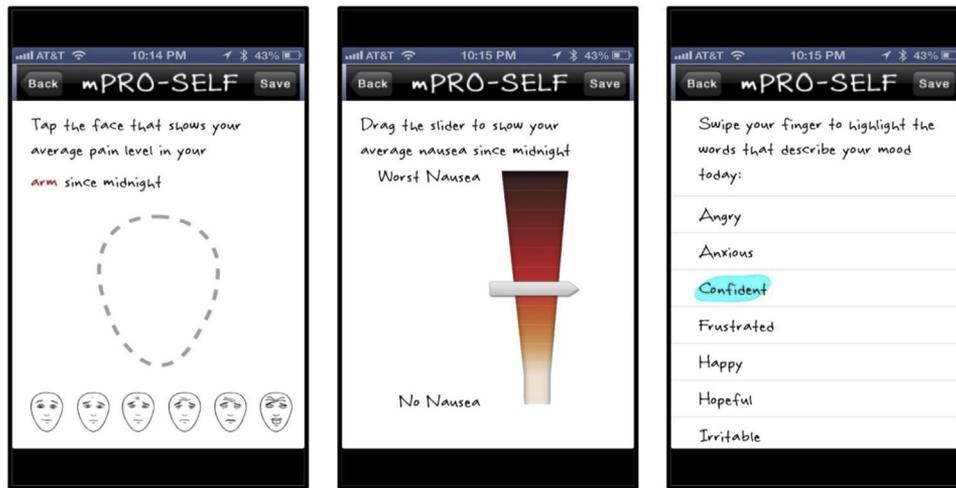
Symptom diaries are an example of a symptom assessment resource that can be adapted and refined for delivery via a computer or mobile device. The portability of mobile devices, coupled with the availability of audible prompts, may promote adherence to data entry, leading to improved understanding of symptoms with variable trajectories. Mobile phone diaries have been used by adults and children with cancer,<sup>43-46</sup> and adherence to entries has been high.<sup>43</sup> Although individuals may acknowledge personal benefit in the process of symptom tracking and review,<sup>43-46</sup> they may also report burden and invasions of privacy with frequent reminders. Real-time symptom reporting on mobile devices allows researchers to collect detailed data on symptom trajectories that were previously impractical to assess. Improved understanding of patients' symptom trajectories may lead to important discoveries regarding the etiology and treatment of these untoward effects.

### Mobile Technology Apps for Symptom Assessment in AYAs

The rapid expansion of mobile technology has also prompted a growing interest in the development of software applications (apps) for symptom assessment. The availability of resources to support app development, the formation of partnerships with software developers, and AYAs' familiarity with apps create rich opportunities for investigator-designed apps to use with AYAs.

**mOST.** An example of a mobile phone diary is the Mobile Oncology Symptom Tracker (mOST) app (Fig. 1).<sup>43</sup> The mOST app includes severity ratings for 5 commonly occurring symptoms: pain, nausea, vomiting, fatigue, and sleep quality, and it guides users to identify the occurrence of seven other symptoms, as well as provides a rating of their mood. Ten AYAs (ages 13 to 21) participated in a 3-week trial of the mOST. Overall adherence to daily entries was 91%, providing support for the mOST's feasibility.<sup>43</sup>

**C-SCAT.** The Computerized Symptom Capture Tool (C-SCAT) is another example of an investigator-developed symptom assessment app.<sup>15</sup> The C-SCAT features the 30 symptoms included in the MSAS 10-18 and uses an inductive, symptom heuristics approach to explore the AYAs' interpretation and perceptions of the meaning of their symptom and symptom cluster experience. The app guides AYAs through a series



**FIGURE 1.** Screen shots of the Mobile Oncology Symptom Tracker (mOST) used for data collection in the mPRO-SELF study. Depicted left to right are queries for assessment of pain, nausea, and mood.

of screens that ask them to identify symptoms experienced in the past 24 hours and to identify alleviating/exacerbating factors, attempted self-management strategies, and the effects of the symptom on their daily activities. AYAs identify temporal and causal relationships among symptoms they believe to be related, and they identify groups of symptoms that occur together. Finally, they give names to their identified symptom clusters and identify priority symptoms in each cluster. The app generates a final image that can be downloaded (Fig. 2). The C-SCAT demonstrated feasibility and acceptability in a sample of 72 AYAs (ages 13 to 29).<sup>15</sup> AYAs endorsed the C-SCAT's ease of use and expressed a preference for using the iPad-based app rather than a paper-based version.<sup>15</sup>

## METHODOLOGICAL STRATEGIES TO EVALUATE SYMPTOMS AND SYMPTOM CLUSTERS

### *Quantitative Methods*

Symptom cluster research with AYAs is limited to five quantitative studies in which both children and adolescents were enrolled.<sup>14,21,47-49</sup> These studies included children as young as 10 years<sup>14,47,48</sup> or 7 years of age.<sup>21,49</sup> Furthermore, these five symptom cluster studies included relatively small sample sizes that were heterogeneous with respect to types of treatment, phase within the treatment trajectory, assessment tools used, and types of statistical analyses. There is no evidence about symptom clusters in young adults.

Numerous approaches to statistical analysis of symptom clusters may be used.<sup>50</sup> These include assessment of simple or partial correlations, graphical modeling, structural equation modeling, hierarchical cluster analysis, exploratory factor analysis, confirmatory factor analysis, K-means analysis and others. No consensus has been reached on the optimal statistical approach for identifying symptom clusters.<sup>51-54</sup> Though a moderate degree of consistency has been noted when varying statistical analyses have been used on the same data set,<sup>48,51</sup> inconsistencies remain.<sup>49</sup>

The selection of statistical methods depends on factors such as whether potential clusters have been identified a priori or previously validated, the timing of symptom assessment (cross-sectional vs longitudinal), and the level of measurement (categorical vs continuous). Conceptual decisions regarding the selection of a symptom assessment tool (brief vs comprehensive), patient population (homogeneous vs heterogeneous with regard to cancer type and treatment), and recall period may also greatly impact the constellation of symptom clusters.

Assessment tool(s) should include all symptoms likely to be experienced by the sample. Homogeneous samples are preferred so that true symptom patterns may be identified, although these samples may be difficult to obtain in the AYA population. For example, patients on maintenance therapy may experience minimal symptoms and would not be appropriate as participants in conjunction with patients receiving intensive treatment. Brief and consistent recall

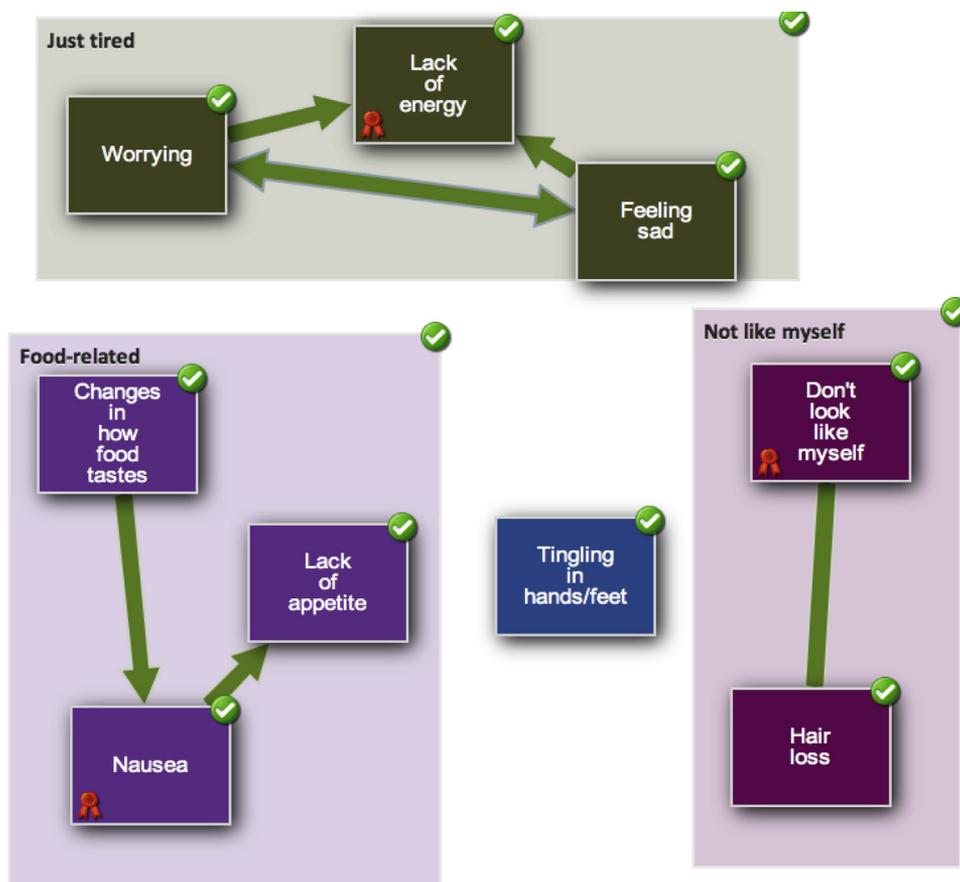


FIGURE 2. Images generated through the Computerized Symptom Capture Assessment Tool (C-SCAT).

periods should be designed. Otherwise, resulting data may suggest concurrent symptoms, when in actuality the symptoms may not be related temporally. To illustrate, nausea and constipation may be prevalent early in the week but pain and diarrhea might occur late in the week. In this situation, if a 1-week recall period is used, the symptoms may cluster erroneously. Real-time data are ideal.

#### **Qualitative Study Designs to Explore Symptoms and Symptom Clusters**

Because the experience of symptoms is unique, qualitative methods are ideal for their exploration and description. Often qualitative methods are needed as a first step to gain a thorough understanding of the symptom experience from the patient perspective. Although many qualitative methods support the exploration and understanding of the symptom experience, only a few have been used among AYAs with cancer.

**Qualitative Case Study.** The qualitative case study provides insight into a case to illuminate the complexities of a phenomenon. This methodology uses a variety of data sources to ensure that a topic is well explored and described in a variety of contexts.<sup>55</sup> One such qualitative case study involved a 16-year-old with cancer. During the first 3 months of her chemotherapy treatment she experienced multifaceted and dynamic symptom distress exacerbated by the occurrence of other symptoms (ie, pain, increased nausea, sleep alterations, and fatigue).<sup>56</sup>

**Qualitative Descriptive Design.** Qualitative descriptive design is a straightforward method that places emphasis on the participant's own words. Analysis stays very close to the data and themes are generated from the participants' own words.<sup>57</sup> Examples of qualitative descriptive design are narrative analysis, qualitative content analysis, and summative content analysis.

Narrative analysis approaches patient experiences as stories and can be particularly helpful in gaining the full picture of symptoms from the patient's own experience.<sup>58</sup> Woodgate<sup>59</sup> used narrative analysis to describe cancer and symptom courses from the perspectives of children and adolescents and their families; she reported a core narrative of "life is never the same." Qualitative content analysis provides an interpretation of meaning from the text data but consists of different coding methods. Conventional forms of analysis avoid pre-set codes and themes, whereas directed analysis utilizes predetermined codes and themes.<sup>60</sup> Summative content analysis starts by exploring word usage but then explores the meaning behind the use of the words.<sup>60</sup>

### ***Mixed Method Design***

Mixed methods may provide the ideal approach for a comprehensive assessment and evaluation of the complexity of symptoms and symptom clusters among AYAs with cancer. This method incorporates qualitative and quantitative approaches to discover information that a single approach alone may not adequately capture.

Integration of qualitative and quantitative approaches can occur with data collection, analysis, and/or interpretation. In mixed methods designs, data can be collected concurrently or sequentially, with the first method used informing the other.<sup>61</sup> Ream and colleagues<sup>37</sup> used a concurrent method to examine fatigue severity and its effects on daily functioning among 22 AYAs (13 to 20 years) who were receiving or had completed cancer treatment. Quantitative fatigue scores indicated high levels of fatigue among the group receiving cancer treatment that declined over time; however, semi-structured interviews discovered that some adolescents continued with significant fatigue that compromised their daily functioning post-therapy.

Similarly, data analyses with mixed methods can occur simultaneously through integration of qualitative and quantitative data or separately and then compared and contrasted.<sup>61</sup> Hedstrom and colleagues<sup>62</sup> examined distress among adolescents with cancer by analyzing anxiety and depression questionnaire scores and structured interviews separately. Anxiety and depression scores were low overall, but the interviews indicated a wide range of distressing aspects related to their disease and

treatment. Quantitative measures alone may not convey symptom experiences in a comprehensive manner.

In addition to data collection and analysis, mixed methods can be used to disseminate findings, with presentation of numerical and narrative data combined or transformed from narrative to numerical representation or from numerical data to descriptive wording.<sup>61</sup> This innovative method of research can accurately appraise and thoroughly represent symptoms and symptom clusters among AYAs with cancer.

### **IMPLICATIONS FOR NURSING PRACTICE AND RESEARCH**

The current state of the science related to symptoms and symptom clusters in AYAs as a distinct group is limited because the majority of research has related to the adolescent experience. Young adults included in study samples with adolescents have been 29 years of age or younger, leaving those between 30 and 39 particularly underrepresented in this body of research.

Strategies to advance symptom and symptom cluster research among AYAs with cancer include the formation of research collaborations across pediatric and adult institutions. Although the field of AYA symptom researchers is relatively small, effective research networks can support the accrual of study samples that represent the AYA age continuum and samples that are homogenous with regard to type of cancer and stage of treatment, factors that can influence the symptom experience.

Reliable and valid measures that are relevant and developmentally meaningful for AYAs are urgently needed. Rather than developing new instruments, validating existing instruments developed specifically for adolescents or adults in AYA samples may be more useful. When selecting instruments, the salient issue may be the concept of interest and whether the proposed instrument adequately addresses the concept based on the theoretical principles underpinning the study. For example, an investigator could use the MSAS rather than the MSAS 10-18 as a multi-symptom assessment scale or the FS-A to investigate the trajectory of fatigue. In either case, justification for the selected instrument should be articulated. To further establish reliable and valid symptom measures for AYAs, investigators should report the

psychometric properties from their studies of their chosen instrument(s) used with their AYA sample and, if possible, the feasibility and acceptability.

Approaches to data collection should likewise be developmentally meaningful to AYAs. The widespread adoption of mobile technology within the AYA population and expanding uses of technology as a platform for instrument delivery provide new approaches for understanding the AYAs' symptoms and the consequences of symptoms on their day-to-day lives. Technology also supports novel approaches for exploring the symptom experience from the AYAs' perspectives. Electronic symptom diaries can be used to detect symptoms before they become severe, provide guidance on self-care interventions, or track responses to symptom management strategies. Symptom tracking may foster self-advocacy, independence, and self-management, skills of particular importance for younger AYAs as they transition to assume responsibility for their own health care.

Both quantitative and qualitative methods offer opportunities for expanding symptom and symptom cluster assessment among AYAs. Developing symptom cluster research guidelines to promote a sound and consistent approach to the study of symptom clusters that provides attention to the homogeneity of the study sample, timing of symptom measures, and the recall period may enhance the ability to identify symptom clusters.

Although symptom and symptom cluster research among AYAs is limited, awareness of the need for valid and reliable approaches to symptom and symptom cluster assessment in this group is growing. Likewise, opportunities to expand this area of research are growing. Continued efforts to validate measures across the AYA population and the use of developmentally meaningful approaches to data collection have the potential to support a better understanding of the symptom experience in this vulnerable population. This knowledge can then be applied in research and clinical settings to develop interventions to alleviate the burden of symptoms.

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