Systematic review of illness uncertainty management interventions for cancer patients and their family caregivers

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Abstract

Purpose Illness uncertainty pervades individuals’ experiences of cancer across the illness trajectory and is associated with poor psychological adjustment. This review systematically examined the characteristics and outcomes of interventions promoting illness uncertainty management among cancer patients and/or their family caregivers.

Methods PubMed, Scopus, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and Cochrane Database of Systematic Reviews were systematically searched for relevant literature. We included randomized controlled trials (RCTs) and quasi-experimental studies focusing on interventions for uncertainty management in cancer patients and/or their family caregivers.

Results Our database searches yielded 26 studies. Twenty interventions were only offered to cancer patients, who were mostly elder, female, and White. All interventions included informational support. Other intervention components included emotional support, appraisal support, and instrumental support. Most interventions were delivered in person and via telephone (n = 8) or exclusively in person (n = 7). Overall, 18 studies identified positive intervention effects on illness uncertainty outcomes.

Conclusion This systematic review foregrounds the promising potential of several interventions—and especially multi-component interventions—to promote uncertainty management among cancer patients and their family caregivers. To further improve these interventions’ effectiveness and expand their potential impact, future uncertainty management interventions should be tested among more diverse populations using rigorous methodologies.

Keywords Cancer · Illness uncertainty · Intervention · Family caregiver · Systematic review · Social support

Introduction

Illness uncertainty is defined as “the inability of a person to determine the meaning of illness-related events” [1]. It can persist across the cancer trajectory from the time of diagnosis, through treatment, to long-term survivorship [2] and can be exacerbated by disease progression [3]. Illness uncertainty is widely recognized as a common and significant source of psychosocial stress among cancer patients [4], and studies have shown that increased uncertainty adversely affects cancer patients’ psychological adjustment [5, 6], health behaviors [7], and quality of life [8, 9]. This uncertainty can also extend to cancer patients’ family caregivers. In fact, patients’ partners have often reported higher levels of uncertainty compared to patients [3]. Research has also shown that increases in family caregivers’ illness uncertainty are associated with poorer psychological adjustment to the diagnoses and progression of cancer in patients [10, 11]. For example, uncertainty about the unknown outcomes of childhood cancers (e.g., late effects of cancer treatment, relapse) can increase parents’ distress and dysfunctional behaviors [10].

To address the negative impacts of illness uncertainty on the health outcomes (e.g., quality of life) [12], researchers and practitioners have developed and implemented various interventions to help cancer patients and their family caregivers manage illness uncertainty. Three previous literature reviews have synthesized research developments related to uncertainty management interventions. In their review of interventions for managing uncertainty and fear of recurrence in female breast cancer survivors [13], Dawson and colleagues reported that the main intervention components included mindfulness, more effective...
patient–provider communication, and stress management through counseling [13]. In their integrative literature review of uncertainty among children with chronic illnesses and their families, Gunter and Duke concluded that the education and psychosocial support is important in reducing uncertainty [14]. In their recent meta-analysis of psychosocial uncertainty management interventions among adult patients with various diagnoses (e.g., cancer, HIV, heart disease) and their family caregivers [15], Zhang et al. reported that psychosocial interventions are effective in reducing short- and long-term uncertainty both among patients and their family caregivers [15].

The existing reviews have focused on patients with various types of chronic illnesses who may face different challenges from patients with cancer [16] or patients with a gender-specific type of cancer (e.g., breast cancer). It therefore remains unclear whether the findings of these reviews are generalizable to patients with other types of cancer. Additionally, although research has shown that children and adolescents with cancer are affected by illness uncertainty [17, 18], no systematic review has examined their experiences of uncertainty management interventions. Researchers and practitioners stand to benefit from a comprehensive review of the literature about illness uncertainty interventions for patients with different types of cancer across age groups and their family caregivers. To this end, our study (a) systematically reviews and synthesizes results of uncertainty management interventions for cancer patients and their family caregivers, (b) identifies the strengths and gaps in this line of research, and (c) suggests directions for future research. Specifically, our systematic review examines the characteristics of participants in studies of illness uncertainty management interventions as well as the characteristics and outcomes of those interventions.

Methods

We adapted a comprehensive systematic review protocol based on the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. This protocol was registered with PROSPERO, an international prospective register of systematic reviews, prior to the beginning of the study (registration number CRD42019128004).

Eligibility criteria

We used the population, interventions, comparator, outcomes, and study (PICO) design(s) to guide our inclusion criteria [20]. Studies eligible for inclusion are as follows: (a) targeted cancer patients and/or their family caregivers; (b) included uncertainty management in their research aims and/or as a part of the intervention’s contents; (c) reported intervention effects on illness uncertainty; (d) used randomized controlled trials (RCTs) or quasi-experimental designs; and (e) were published in English between January 1, 2000 and December 31, 2019. The search was not limited to studies using a control or comparison group.

Search methods

A university health sciences librarian helped to develop the search terms and identify relevant search databases. We conducted electronic literature searches using six databases: PubMed, Scopus, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and Cochrane Database of Systematic Reviews. The database searches used Boolean terms “OR” and “AND” with combinations of the following search terms: (uncertainty) AND (cancer OR neoplasm* OR tumor OR myeloma OR oncolog*) AND (intervention OR program OR effect OR effectiveness OR treatment OR therapy) AND (patient OR patients OR caregiv* OR family OR families) AND (psych* OR mental* OR emotion*).

To identify studies potentially overlooked by our electronic searches, our research team conducted forward and backward citation chaining and hand searched Web of Science, Google Scholar, and prominent journals in the field to identify relevant articles for inclusion. Two coauthors independently reviewed the titles and abstracts and then—if an article merited further consideration—its full text using Covidence. Covidence is a web-based software platform designed to support the efficient production of systematic reviews [21]. We resolved any discrepancies in the two coauthors’ respective decisions regarding articles’ inclusion via group discussion among all team members.

Assessment of risk of bias in the included studies

We used the Cochrane Collaboration’s Risk of Bias Tool [22] to assess various sources of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other possible sources of bias (Appendix). Each domain was endorsed with a rating of “low risk,” “high risk,” or “unclear risk” following guideline’s criteria. Two coauthors independently conducted all risk of bias assessments, and we resolved any differences in their assessments through team discussion.

Data extraction and synthesis

Two of the coauthors independently extracted relevant data from the studies that met our inclusion criteria. We compared these extracted results and resolved any discrepancies through team discussion before merging the data. Because the included studies displayed different participant characteristics, intervention components, outcomes, and follow-up periods, we could not conduct a meta-analysis of their findings. We summarized the narratives and themes of each study and its results. Guided by House’s conceptualization of social support [23], we classified each intervention’s...
components into four categories: informational support, emotional support, appraisal support, and instrumental support.

**Results**

As shown in Fig. 1, our initial search of electronic databases and records and our hand searches of other sources yielded 1156 records. After removing duplicates, we identified 681 articles for title and abstract review, of which 49 were retained for a full-text review. After removing the studies that did not meet the inclusion criteria, we included 26 articles in this review.

**Characteristics of studies**

The majority of studies were conducted in the USA (n = 16). Others were conducted in Canada, China, Japan, United Kingdom (UK), and Vietnam. Eighteen studies were RCTs; one study used a RCT crossover design [24]. Eight studies were quasi-experimental studies (i.e., five “1-group pretest-posttest” studies, two “2-group pretest-posttest” studies, and one “2-group posttest” study) (Table 1). Among the 20 studies that included a control group, 12 studies used usual care, and eight included an active control group (e.g., a self-help group [25]; groups receiving recorded and written messages [26], telephone calls [27], and delayed interventions [28]). Sample sizes of included studies ranged from 9 [29] to 968 participants [30]. Among all studies, only seven studies were guided by theoretical frameworks such as the stress and coping theory (n = 5) [30–34], the uncertainty in illness theory (n = 1) [29], the double ABCX model (n = 1) [34], and the resilience model (n = 1) [35].

**Characteristics of participants**

Twenty interventions were only offered to cancer patients. Two studies targeted family caregivers (i.e., the parents of children with
| Lead author, year, and country | Study characteristics | Participant characteristics | Uncertainty measures | Results |
|-------------------------------|----------------------|-----------------------------|---------------------|---------|
| Chow, 2014, China             | N/A 2-arm RCT        | Patients newly diagnosed with gynecological cancer | MUIS                | More reduction in the Inconsistency subscale at the end of intervention in the intervention group ($p=0.026$). No significant group difference at 8 weeks. |
| Christman, 2004, USA          | N/A 3-arm RCT        | Patients with mixed cancer receiving radiation therapy | MUIS-symptom subscale | Less uncertainty in the concrete objective information intervention group ($p<0.05$). No result reported about the difference between relaxation instruction intervention group and control groups. |
| Dharmarajan, 2019, USA        | N/A 1-arm quasi-experimental | Patients with advanced mixed cancer | DCS-U               | Significant decrease over time ($p=0.02$). |
| El-Jawahri, 2010, USA         | N/A 2-arm RCT        | Patients with brain tumor with a poor prognosis | DCS-U               | More reduction in uncertainty in the intervention group ($p=0.002$). Greater decrease in uncertainty in the intervention group. |
| Germino, 2013, USA            | N/A 2-arm RCT        | Breast cancer survivors     | MUIS-S              | |
| Lead author, year, and country | Study characteristics | Participant characteristics | Uncertainty measures | Results |
|--------------------------------|----------------------|-----------------------------|--------------------|---------|
| **Theoretical basis** | **Design** | **Sample size (I and C)** | **Cancer type and stage of survivorship** | **Mean age (years)** | **Gender** | **Race** | **Measurement** | **Assessment time point** | **Results** |
| Ha, 2019, Vietnam | 2-arm quasi--experimental | 115 (57, 58) | Patients with breast cancer receiving mastectomy | N/A | 100% female | N/A | MUIS-Short Form | 1 (1 week after mastectomy) | More reduction in uncertainty in the intervention group \( (p<0.05) \). |
| Hendricks-Ferguson, 2017, USA | Stress-coping theory; double ABCX model | 1-arm quasi--experimental | Parents of hospital children diagnosis with brain tumor and a poor prognosis | N/A | 85.7% female | 69.2% Caucasian | Parent Experience of Child Illness-Short Form | 4 (BL, after session 1, session 2, and session 3) | Significant decrease over time \((p=0.0432)\). |
| Kazer, 2011, USA | Uncertainty in illness theory | 1-arm quasi--experimental | Patients with prostate cancer and undergoing active surveillance | 72 | 100% male | 100% Caucasian | MUIS-C | 3 (BL, 5 and 10-week post-BL) | No difference over time. |
| Lebel, 2014, Canada | N/A 1-arm quasi--experimental | 56 | Patients with mixed cancer and after treatment | 54.8 | 100% female | 80.8% Caucasian | MUIS | 3 (pre--intervention, post--intervention, at 3-month post--intervention) | Significant decrease over time \((p<0.001)\). |
| Liu, 2006, China | N/A 2-arm quasi--experimental | 61 (31, 30) | Patients newly diagnosed with breast cancer | I: 48.1 C: 46.6 | 100% female | N/A | MUIS | 3 (BL, 1 and 3 months after surgery) | More reduction in uncertainty in the intervention at 3 months after surgery \((p<0.01)\). |
| McCaughan, 2018, UK | Stress-coping theory | 2-arm RCT | Patients with prostate cancer and post-treatment and their spouse/partner | I: patient: 67.5 Partner: 64.1 C: Patient: 63.8 Partner: 60 | Patient: 100% male Spouse: 100% female | 100% Caucasian | MUIS | 3 (BL, post--intervention, 1-month post--intervention) | No group difference. |
| McCorkle, 2009, USA | N/A 2-arm RCT | 123 (63, 60) | Patients with ovarian cancer and prognosis of at least 6 months | I: 58.4 C: 62.2 | 100% female | I: 90.5% White C: 93.3% White | MUIS-ambiguity subscale | 4 (BL, 1, 3, and 6 months post-surgery) | Greater improvement in the ambiguity subscale in the intervention group over time \((p=0.0001)\). |
| Lead author, year, and country | Study characteristics | Participant characteristics | Uncertainty measures | Results |
|--------------------------------|----------------------|-----------------------------|---------------------|---------|
| Mishel, 2002, USA              | N/A 3-arm RCT 239    | Patients with prostate cancer and after treatment | MUIS 3 (BL, 4 and 7 months post-BL) | No group difference. |
| Mishel, 2009, USA              | N/A 3-arm RCT 256 (93,89, 74) | Patients with prostate cancer and before the treatment | MUIS Problem-solving, patient–provider communication, and cancer knowledge | Greater improvement in cancer knowledge ($p = 0.0001$), problem-solving ($p = 0.05$), and patient–provider communication ($p = 0.01$) for intervention group over time. |
| Mori, 2019, Japan              | N/A Crossover RCT 105 | Patients with breast cancer recurrence | MUIS 1-item scale 4 (after each video) | Lower uncertainty in the group viewing the video with more versus less explicit disclosure ($p = 0.032$) |
| Northouse, 2005, USA           | Stress-coping theory 2-arm RCT 134 dyads- (69,65) | Patients with breast cancer and recurrent within the previous month and their spouses | MUIS 3 (BL, 3 and 6 months post-BL) | No group difference. |
| Northouse, 2007, USA           | Stress-coping theory 2-arm RCT 263 dyads (129, 134) | Patients with newly diagnosed, recurrence, and advanced prostate cancer and their spouses | MUIS 4 (BL, 4, 8, and 12 months post-BL) | Less uncertainty in the intervention patients at 4 months ($p < 0.05$) and in the intervention spouses at 4 months ($p < 0.01$) and 8 months ($p < 0.05$). |
| Lead author, year, and country | Study characteristics | Participant characteristics | Uncertainty measures | Results |
|-------------------------------|-----------------------|----------------------------|---------------------|---------|
| Northouse, 2013, USA | Stress-coping theory | 484 dyads (159, 162, 163) Patients with mixed cancer and newly diagnosed with advanced cancer and their caregiver | Patient: 60.5 Family caregiver: 56.7 | Patients: 61.4% female Family caregiver: 55.8% female | 13.5% African American 1% Hispanic 1.3% American Indian 1.3% Asian 0.3% multi-racial | 3 (BL, 3 and 6 months post-BL) | No group difference. |
| Ritz, 2000, USA | N/A | 2-arm RCT 210 (106, 104) Patients with newly diagnosed breast cancer | I: 55.7 C: 55.3 | I: 97% White, 2% Asian, 1% African American C: 97% White, 1% Asian, 1% African American, 1% American Indian | MUIS | 6 (1, 3, 6, 12, 18, and 24 months) | Less uncertainty in the intervention group at 1 month ($p=0.001$), 3 months ($p=0.026$), and 6 months ($p=0.011$). |
| Schulman-Green, 2017, USA | N/A | 1-arm quasi-experimental 105 Patients with breast cancer and had a prognosis of at least 3 months | 52.3 100% female | | | 2 (BL and post-intervention) | No difference over time. |
| Sussman, 2018, Canada | N/A | 2-arm RCT 193 (89, 104) Patients with newly diagnosed mixed cancer | I: 61 C: 60 | I: 84% female C: 76% female | | | No group difference. |
| Tomei, 2018, Canada | N/A | 2-arm RCT 25 (11, 14) Patients with mixed cancer and after treatment | 55 100% female | 95.8% Caucasian 4.2% Asian | MUIS-C | | | Greater improvements in uncertainty in the intervention group over time ($p=0.002$). |
| Victorson, 2017, USA | N/A | 2-arm RCT 43 (24, 19) Patients diagnosed with low-risk localized prostate cancer on active surveillance | I: 71.2 C: 69.4 100% male | I: 94.44% Caucasian, 5.56% African American C: 95.65% Caucasian, 4.35% African American | IUS-Short Form | 4 (BL, 8 weeks, 6 months, and 12 months of post-BL) | No group difference. |
| Wang, 2018, China | N/A | 2-arm quasi-experimental 101 (51, 50) Parents of hospital children newly diagnosed with acute | N/A | I: 67% female C: 77% female | PPUS | 2 (BL and 3 months post-BL) | Less uncertainty in the intervention group |
| Study characteristics | Uncertainty measures | Results |
|-----------------------|---------------------|---------|
| **Lead author, year, country** | **Gender Race Measurement Assessment time** | **Uncertainty measures** |
| Wells-Di Gregorio, 2019, USA | Male | 6m o n t h s, a n d 12 months of post-BL | Lower uncertainty difference. |
| Ye, 2016, China | Female | N/A | Parents’ Uncertainty Scale; IUS – Mishel Uncertainty in Illness Scale including four subscales: ambiguity, complexity, inconsistency, and unpredictability; MUIS-C – Mishel Uncertainty in Illness Scale including four subscales: ambiguity, complexity, inconsistency, and unpredictability; PPUS – Parents’ Perceptions of Uncertainty of Supportive Care; MUIS-S – Mishel Uncertainty in Illness Scale-Survivor version; MUIS-F – Mishel Uncertainty in Illness Scale-Community Form; DCS-U – Decisional Conflict Scale-uncertainty subscale |

**Table 2** summarizes the interventions’ characteristics. Nineteen studies (73.1%) included uncertainty management as their main aim.

**Theoretical basis** Twelve studies (46%) described the theoretical frameworks used to guide different interventions. Five interventions were developed based on Mishel’s uncertainty in illness theory [27, 37-40]. Other theoretical models that guided the development of illness uncertainty management interventions also included the thematic counseling model [25], self-regulation theory [26], Leventhal’s common sense model [37], Brooten’s cost-quality model [41], self and family management framework [42], theory of self-efficacy, theory of stress and coping [31], cognitive behavioral therapy and acceptance and commitment therapy [43], and mindfulness-based stress reduction [44].

**Contents and components** All of the interventions in our sampled studies included informational support that provided knowledge and resources related to illness, treatment, procedures, and symptom management. Eleven studies included emotional and psychological support from interventionist and peer groups. Nine studies included appraisal support that provided information and skills training for self-evaluation and positive perception, such as cognitive reframe and restructuring. Five studies included instrumental support that helped improve participants’ care coordination and ability to manage resources, referrals (social services, mental health, physical therapy), and continual follow-up schedules. Sixteen studies included two or more types of intervention components.
| Lead author and year | Study aim | Intervention | Control |
|----------------------|-----------|--------------|---------|
| **Chow 2014**        | Test the feasibility of a psychoeducational intervention program\(^a\) | Thematic counseling model | Information about cancer diagnosis, treatment, side effects, communication skills, behavior therapy (e.g., deep breathing), psychological support | Nurse |
|                      |           | In-person, individual + group, 8 weeks, 4 sessions (30–60 min) | Contact after the operation and invite to join a self-help group |
| **Christman 2004**   | Examine the effects of concrete objective information and relaxation effect | Self-regulation theory and varied relaxation strategies | Information provision about symptom management, and relaxation | Audiotape + booklet, individual, N/A, 2 N/A \(^b\) |
|                      |           | Video, individual, N/A, N/A | Palliative care physician involved in video content |
| **Dharmarajan 2019** | Test the ability of a newly created video decision aid intervention effect\(^a\) | N/A | Information provision about palliative radiation therapy, process, side effects | Video, individual, N/A, N/A |
|                      |           | Video, individual, 6-min video presentation, N/A | Palliative care physician involved in video content |
| **El-Jawahri 2010**  | Determine the effect of use of goal-of-care video to improve end-of-life decision-making\(^a\) | N/A | Information about medical care | Video, individual, 6-min video presentation, N/A |
|                      |           | Video, individual, 6-min video presentation, N/A | Oncologists, critical care intensivists, palliative care physician and medical ethics experts involved in video content |
| **Germino 2013**     | Determine the effect of an uncertainty management intervention\(^a\) | Theory of Uncertainty in Illness | Information about cognitive and behavior strategies, side effects, and resources | CD, individual, 4 weeks, 4 weekly sessions (20 min) |
|                      |           | In-person, group, 6 weeks, 6 sessions (90 min) | Health care professionals with formal training in psychotherapy |
| **Ha 2019**          | Examine the effect of the uncertainty management program\(^a\) | Theory of Uncertainty in Illness | Information provision, qigong practice, emotional disclosure skills, breathing relaxing, nutrition care, ongoing communication with nurses | Nurse |
|                      |           | In-person + telephone, individual, 3 weeks, 3 in-person sessions + 2 phone follow-ups | Usual care |
| **Hendricks-Ferguson 2017** | Report feasibility, acceptability, and outcome of palliative and end-of-life communication intervention study\(^a\) | N/A | Discussion about child’s disease status, prognosis, and treatment options following diagnosis to enhance hope and nonabandonment | In-person, family, 26 weeks, 3 sessions (time varied) |
|                      |           | Neuro-oncology doctor and nurse | N/A |
| **Kazer 2011**       | Provide preliminary data on an internet intervention\(^a\) | N/A | Information about illness, cognitive reframe strategies, self-care management strategies, and life issues | Internet, individual, 5 weeks, N/A |
|                      |           | N/A | Nurse | N/A |
| **Lebel 2014**       | Develop, manualize, and pilot test the feasibility and preliminary efficacy | Leventhal’s common sense model, uncertainty in illness | Introduction about illness, cognitive restructuring and triggers, coping skills (e.g., relaxation, calming self-talk, guided imagery); emotion | In-person, group, 6 weeks, 6 sessions (90 min) |
| Lead author and year | Study aim | Intervention | Theoretical basis | Component | Mode, format, duration, dosage | Control |
|---------------------|-----------|--------------|-------------------|-----------|-----------------------------|---------|
| Liu 2006            | Examine the effects of continuing supportive care intervention study<sup>9</sup> | N/A | Information, emotional and psychological support, referral and continual follow-up | Telephone + telephone, individual, 3 months, 4 sessions (90, 30, 60, 15 min, respectively) | Nurse | Usual care |
| McCaughan 2018      | Evaluate the process and outcome of a psychosocial intervention<sup>9</sup> | Theory of self-efficacy and theory of stress and coping | Information about disease and treatments | Telephone + in-person, group + family, 9 weeks, 3 group sessions (180 min) + 2 telephone sessions | Professionals specifically trained in the intervention | Usual care |
| McCorkle 2009       | Examine the effect of a nursing intervention on quality of life<sup>9</sup> | N/A | Symptom management and monitoring, emotional support, patient education, care coordination of resources, referrals, and direct nursing care | In-person, individual, 6 months, 18 contacts (tailored to each patient's need) | Nurse | Symptom management toolkit |
| Mishel 2002         | Test the efficacy of an individualized uncertainty management intervention<sup>9</sup> | Theory of Uncertainty in Illness | Information about resources and skills to address problem; cognitive reframing | Telephone, individual + family, 8 weeks, 8 telephone calls | Nurse | Usual care |
| Mishel 2009         | Examine the effects of decision-making uncertainty management intervention<sup>9</sup> | Theory of Uncertainty in Illness | Information about prostate cancer and communication skill | DVD + telephone + booklet, Individual + family, 7–10 days, 4 telephone calls | Nurse | Usual care |
| Mori 2019           | Examine the effect of explicit prognostic disclosure on uncertainty<sup>9</sup> | N/A | Discussion about breast cancer recurrence and metastatic disease | Video, individual, N/A, 4 scripts (around 5 min) | Multiple people involved in the scripts (e.g., oncologist, palliative care physician, breast cancer survivors) | N/A |
| Northouse 2005      | Examine the effects of a family intervention on the quality of life<sup>9</sup> | N/A | Information about disease, treatments; teach dyad how to be assertive to obtain additional information; help dyad learn ways to live with uncertainty | Telephone + in-person, family, 5 months, 3 home visits (90 min) + 2 phone follow-ups (30 min) | Nurse | Usual care |
| Northouse 2007      | Examine the effects of a family intervention on appraisal variables, coping resources, symptom distress, and quality of life<sup>9</sup> | N/A | Information about disease, treatments; teach dyad how to be assertive to obtain additional information; help dyad learn ways to live with uncertainty | Telephone + in-person, family, 4 months, 5 sessions: 3 home visits (90 min) + 2 phone sessions (30 min) | Nurse | Usual care |
| Northouse 2013       | N/A | N/A | N/A | N/A | Nurse | Usual care |
| Lead author and year | Study aim | Intervention | Control |
|----------------------|-----------|--------------|---------|
| Ritz 2000            | Evaluate quality of life and cost outcomes of advanced practice nurses’ intervention | Brooten’s cost-quality model and the Oncology Nursing Society’s standards of advanced practice in oncology nursing | Nurse usual care |
| Schulman-Green 2017  | Test the feasibility and acceptability of a psycho-educational intervention | Self and family management framework | N/A |
| Sussman 2018         | Test a community-based nurse-led coordination of care intervention | N/A | Nurse usual care |
| Tomei 2018           | Test an individual cognitive-existential psychotherapy intervention | N/A | Therapists delayed intervention |
| Victorson 2017       | Examine the feasibility and preliminary efficacy of a mindfulness training program | Mindfulness-based stress reduction | Book on mindfulness titled *Full Catastrophe Living* with no specific instructions to read it |
| Wang 2018            | Evaluate the potential effectiveness of this mHealth supportive | N/A | 1 software engineer, 1 clinical nurse, and 2 nursing researchers |
**Mode of delivery, format, duration, and dosage** The studied interventions employed a variety of delivery modes. The majority of these interventions used both in-person and telephone delivery \( (n = 8) \) or in-person delivery \( (n = 7) \). The remaining eleven interventions used other delivery mechanisms including CD [27], DVDs [45, 46], telephone calls [38], informational booklets [42], internet [29], phone apps [36], or a combination of in-person delivery with DVD and CD content [43]. Most interventions were delivered to participants individually \( (n = 14) \), in a group format \( (n = 3) \) [36, 37, 44], or in family format \( (n = 4) \) [30, 32–34]. Other interventions used a combination of individual and group \( (n = 2) \) [25, 35], individual and family \( (n = 2) \) [38, 39], or group and family \( (n = 1) \) [31] delivery methods. The duration and dosage of the uncertainty management interventions varied across studies, ranging from one session [46] to 1-year period [35].

**Interventionist** In thirteen studies, nurses delivered the interventions. Five interventions were delivered by professionals who had counseling or psychosocial background and training [28, 31, 35, 43, 44]. Five interventions were designed or delivered by multidisciplinary professionals [24, 34, 36, 37, 46]. One intervention was delivered by research staff [42] and one intervention design involved physicians [47]. One study did not report on the professional background of the interventionists [26].

**Intervention outcome**

**Illness uncertainty assessment** The scale most commonly used to measure an intervention’s effect on uncertainty was the Mishel Uncertainty in Illness Scale (MUIS) \( (n = 19) \). This scale has different versions including MUIS-Community version [48], MUIS-Survivor version [27], MUIS-Short version [40], and Parents’ Perception of Uncertainty [36], which is based on the MUIS and measures parents’ uncertainty. Other studies measured uncertainty using the symptom and ambiguity subscale of MUIS [26, 49], the Decisional Conflict Scale-uncertainty subscale [46, 47], Parent Experience of Child Illness-Short Form [34], and the Intolerance of Uncertainty Scale [43, 44]. One study measured uncertainty using a 1-item scale [24]. One study measured uncertainty using three proxy measures (i.e., problem-solving, patient–provider communication, and cancer knowledge) [39]. Most studies assessed illness uncertainty outcomes using a longitudinal design with two time points \( (n = 6) \); three time points \( (n = 12) \); four time points \( (n = 6) \); or six time points \( (n = 1) \) [41].

**Illness uncertainty outcomes** Overall, 65% of studies \( (n = 17) \) suggested that an illness uncertainty management intervention had a positive effect on uncertainty outcomes. Out of the eighteen RCTs, eleven studies demonstrated that the

| Lead author and year | Study aim | Intervention | Theoretical basis | Component | Mode, format, duration, dosage | Interventionist | Theoretical basis | Component | Mode, format, duration, dosage | Interventionist | Theoretical basis | Component | Mode, format, duration, dosage | Interventionist | Theoretical basis | Component | Mode, format, duration, dosage | Interventionist | Theoretical basis | Component | Mode, format, duration, dosage | Interventionist |
|----------------------|-----------|--------------|------------------|-----------|-------------------------------|----------------|------------------|-----------|-------------------------------|----------------|------------------|-----------|-------------------------------|----------------|------------------|-----------|-------------------------------|----------------|------------------|-----------|-------------------------------|----------------|------------------|
| Wells-Di Gregorio 2019 | Evaluate the intervention targeting a common symptom cluster in advanced cancer | Cognitive behavioral therapy; acceptance and commitment therapy | Information about interaction of thoughts, behaviors and physical tension, sympathetic arousal, stress, appraisal, coping, problem-solving, mindfulness practice, relaxation therapy | In-person + DVD + CD, individual, 6 weeks, 3 sessions (90 min) | Postdoctoral fellows in psychosocial oncology | Mentor who received training from psychologists | N/A | Delayed intervention | N/A | Usual care | N/A | N/A | N/A | N/A | N/A |
| Ye 2016 | Examine the efficacy of a multidisciplinary mentor-based program | Cognitive behavioral therapy | Information about interaction of thoughts, behaviors and physical tension, sympathetic arousal, stress, appraisal, coping, problem-solving, mindfulness practice, relaxation therapy | In-person, individual + group, 1 year, 11 sessions (150 min) + 1 group discussion | Mentor who has received training from psychologists | N/A | N/A | Peer education and support covered | N/A | Usual care | N/A | N/A | N/A | N/A | N/A |

*Table 2 (continued)*

*Study represents uncertainty management as its main aim*
participants in the intervention group reported significant less uncertainty than those in the control group at follow-ups. Of these studies, eight assessed outcomes at multiple time points. Five studies reported more reduction in uncertainty in the intervention group over time [27, 28, 35, 39, 49]. Among eight quasi-experimental studies, three with a control group found that participants in the intervention groups reported significantly less uncertainty compared to those in the control group [36, 40, 45]. Among five quasi-experimental studies without a control group, three showed that intervention participants reported a significant decrease in uncertainty over time [34, 37, 46].

Risk of bias assessment

We evaluated each study’s risk of bias using the Cochrane Collaboration’s Risk of Bias Tool (Table 3). The eighteen RCTs had unclear (n = 11), high (n = 2), or low (n = 5) risk of bias. Most trials were classified as having unclear risk of bias because they did not describe the method used to generate the allocation sequence or report any strategies to maintain intervention fidelity (e.g., consistent intervention use among participants). We found that six quasi-experimental studies had high risk of bias. Most quasi-experimental studies used one-group pre- and post-designs without a control group; therefore, they had high risk of bias in random sequence generation and baseline imbalance.

**Table 3** Assessment of study quality based on published data using Cochrane Collaboration’s criteria

| Lead author and year | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Deferential intervention use | Baseline imbalance | Level of risk |
|----------------------|-----------------------------|------------------------|---------------------------------------|-------------------------------|------------------------|---------------------|--------------------------|-----------------|--------------|
| Chow 2014            | L                           | L                      | L                                     | L                             | L                      | H                   | L                        | H               | L            |
| Christian 2004       | U                           | L                      | L                                     | L                             | L                      | U                   | L                        | L               | U            |
| Dharmarajan 2019     | H                           | U                      | L                                     | L                             | L                      | L                   | L                        | H               | H            |
| El-Jawahri 2010      | U                           | L                      | L                                     | L                             | L                      | U                   | L                        | U               | H            |
| Germino 2013         | L                           | L                      | L                                     | L                             | L                      | L                   | L                        | L               | L            |
| Ha 2019              | H                           | L                      | L                                     | L                             | L                      | U                   | L                        | L               | H            |
| Hendricks-Ferguson 2017 | H                    | U                      | L                                     | L                             | L                      | L                   | U                        | H               | H            |
| Kazer 2011           | H                           | U                      | L                                     | L                             | H                      | L                   | U                        | H               | H            |
| Lebel 2014           | H                           | U                      | L                                     | L                             | L                      | U                   | H                        | H               | H            |
| Liu 2006             | H                           | U                      | L                                     | L                             | L                      | L                   | U                        | H               | H            |
| McCaughan 2018       | U                           | L                      | L                                     | L                             | L                      | H                   | L                        | L               | H            |
| McCorkle 2009        | U                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | U            |
| Mishel 2002          | U                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | U            |
| Mishel 2009          | U                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | U            |
| Mori 2019            | L                           | L                      | L                                     | L                             | L                      | L                   | L                        | L               | L            |
| Northouse 2005       | U                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | U            |
| Northouse 2007       | U                           | L                      | L                                     | L                             | L                      | U                   | L                        | L               | U            |
| Northouse 2013       | U                           | L                      | L                                     | L                             | L                      | U                   | L                        | U               | U            |
| Ritz 2000            | U                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | U            |
| Schulman-Green 2017  | H                           | U                      | L                                     | L                             | L                      | L                   | U                        | H               | H            |
| Sussman 2018         | L                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | L            |
| Tomei 2018           | L                           | L                      | L                                     | L                             | L                      | L                   | U                        | L               | L            |
| Victorson 2017       | L                           | L                      | L                                     | L                             | L                      | U                   | L                        | L               | U            |
| Wang 2018            | H                           | U                      | L                                     | L                             | L                      | L                   | U                        | H               | H            |
| Wells-Di Gregorio 2019 | L                       | L                      | L                                     | L                             | L                      | L                   | L                        | L               | L            |
| Ye 2016              | U                           | L                      | L                                     | L                             | L                      | L                   | L                        | U               | U            |

L, low risk; H, high risk; U, unclear
family caregivers. We found that all interventions evaluated in the included studies provided informational support. Other intervention components included emotional support, appraisal support, and instrumental support. The majority of studies used both in-person and telephone or in-person intervention delivery modes. The majority of studies suggested positive effects of illness uncertainty management–related interventions on uncertainty outcomes. With only two studies focused on parents of children and adolescents with cancer, the majority of interventions were only offered to cancer patients, who were mostly older adults, female, and White.

Overall, the majority of studies (65%) found that illness uncertainty management–related interventions had positive effects on uncertainty outcomes. Multi-component interventions, which used integrated resources to target multiple aspects of illness uncertainty such as informational support and emotional support, appear to be the most effective in managing illness uncertainty in cancer patients and their family caregivers. For example, Lebel et al. found that one intervention proved effective when employing a combination of introductory material about illness, cognitive restructuring and triggers, coping skills (e.g., relaxation, calming self-talk, guided imagery), and practice expressing emotion and confronting specific fears [37]. However, the positive effects of only a few interventions appeared to endure over time, possibly indicating that many interventions’ duration should be extended or include booster sessions as needed [38].

In general, we found that uncertainty management interventions were comprised of a variety of components including informational, emotional, appraisal, and instrumental support. Informational support is the key to helping cancer patients and their family caregivers manage uncertainty. Our findings corroborate those of two previous literature reviews of psychosocial interventions for managing uncertainty in childhood cancer patients and adult patients with different chronic illnesses [14, 15]. Findings from these reviews may also collectively indicate that individualized educational interventions provide information that empowers patients to successfully develop positive coping mechanisms. These findings are consistent with core tenets of Mishel’s uncertainty in illness theory, which posits that uncertainty occurs when patients lack the information or knowledge needed to fully interpret an illness and its treatment [1]. Informational support can enlarge patients’ information and knowledge base, enabling them to better understand an illness and thus experience less uncertainty. Moreover, when uncertainty occurs, it can be difficult for patients to form a cognitive structure [1]. Appraisal supports such as cognitive reframing can help patients reinterpret their illness and view a traumatic event as manageable [38]. Emotional and instrumental support can also provide patients with psychosocial resources to manage their uncertainty.

Most interventions were delivered using either in-person and telephone or in-person formats. This finding contrasts with Zhang et al.’s systematic review and meta-analysis of patients with chronic illnesses, which identified written educational materials as the most frequently used mode of intervention delivery [15]. Given the complexity of information provision and cancer patients’ potential for psychosocial distress, in-person meetings may be the preferred mode of intervention delivery. A format combining in-person and follow-up telephone components can both evaluate patients’ current understandings of their illness and help them reassess their emotional responses [27]. Our systematic review found limited evidence of the effectiveness of technology-based (e.g., web-based, apps) uncertainty management interventions [29, 36]. This area of research is still emerging, as indicated by the recent publication dates of studies of these technology-based interventions, their pilot and feasibility research aims, and their use of small sample sizes. Given these interventions’ potential ability to provide cost-effective psychosocial services [50] to manage uncertainty across the cancer care continuum, researchers should develop and evaluate technology-based interventions for uncertainty management using a rigorous research design (e.g., RCT) with a sufficiently powered sample.

Notably, only four interventions were offered jointly to cancer patients and their spouses or partners, and only one of these reported significant improvement in the uncertainty outcome among cancer patients and their spouses [33]. This comparatively low number perhaps reflects the challenges to conducting family-based research, such as explaining the purpose of the research to multiple participants, having an extended recruitment phase that involves contacting and obtaining consent from more people, and high refusal rates [31, 51]. The small number of interventions that included spouses or partners is striking, as family caregivers play key roles in supporting cancer patients [52] and often experience higher levels of uncertainty than patients [3]. Interventions delivered to patients’ family caregivers can improve their knowledge, coping skills, and quality of life [53], which will in turn improve cancer patients’ care and outcomes (e.g., quality of life) given the synergetic interdependent relationships between cancer patients and their family caregivers [54]. There is a pressing need for future research to inform the development of interventions designed to manage uncertainty for both cancer patients and their caregivers.

Our review also indicates that future research must diversify the age, gender, and racial distributions of sample
populations used to evaluate the outcomes of illness uncertainty interventions. Although previous research has shown that uncertainty is a common experience for children and adolescents with cancer [14], we identified only two interventions that assisted the parents of children with cancer to manage uncertainty [34, 36], and no intervention in our sample targeted children and adolescents with cancer. Therefore, because experiences of uncertainty can vary across different age groups or developmental stages [55], researchers should develop age-appropriate interventions that take into account the specific needs of children and adolescents with cancer. Furthermore, most of the participants in the intervention studies in this review were female, White, and older adult cancer patients. Future research regarding illness uncertainty management interventions should create strategies to increase the number of male patients and family caregivers in intervention programming. Although recruiting men for clinical trials is difficult because men are often reluctant to access services and to recognize that they need help [31], male cancer patients (e.g., prostate cancer) often experience uncertainty about their treatment decision-making and/or their management of cancer treatment-related symptoms and side effects [3, 56]. Finally, although two interventions succeed to include a sufficient number of African American cancer patients [27, 38], the majority of the study populations were White. Given that one study found that African American cancer patients reported higher levels of uncertainty than White cancer patients [3], future intervention should be tailored to help patients from minority groups and researchers should gather data about the effects of interventions using more diverse samples of cancer patients and their family caregivers.

According to the Cochrane Collaboration’s Risk of Bias Tool, most studies had “unclear” or “high risk” of bias due to their unclear reporting. Many studies have unclear reporting of the study procedures that do not meet reporting standards. Future studies should provide complete, clear, and transparent information about how to create and present a research methodology and findings in accordance with CONSORT criteria and flowchart templates.

Limitations

This review’s findings should be considered in light of several limitations. The studies we sampled differed considerably in their study participants’ demographic variables (e.g., older, female, and White cancer patients), types of interventions, outcome measures, and timing of follow-ups. We could not conduct a meta-analysis that synthesizes their discrepant findings, which would have provided more rigorous evidence of the effects of uncertainty management interventions for cancer patients and their family caregivers. Additionally, our review only focused on interventions’ effects on uncertainty outcomes. Future research should examine the effects of uncertainty management interventions on other outcomes in order to get a more comprehensive picture of the effect of interventions. We also focused only on peer-reviewed published studies and may have missed relevant studies from the gray literature. Excluding unpublished studies likely increases the potential for biased findings; however, we included studies that reported non-significant results, thus mitigating the possibility of publication selection bias.

Clinical and research implications

Our review has numerous implications for future clinical practice and research. Providing uncertainty management interventions with multiple components at different phases of the cancer trajectory may significantly reduce uncertainty and facilitate adaptation among patients and family caregivers. There is strong evidentiary support that multi-component interventions yield effective outcomes. However, more research is needed to compare the discrete effects of different intervention components, modes of delivery, and formats on uncertainty management outcomes among cancer patients and their family caregivers. This research should also include study populations with diverse backgrounds (e.g., by age, gender, and/or race), and in particular seek to engage children and adolescents with cancer, males, and African Americans—all groups for whom few if any tailored uncertainty management interventions currently exist.

Conclusion

This systematic review underlines the promising potential of uncertainty management interventions—especially interventions involving multiple components including informational, emotional, appraisal, and instrumental support—to help cancer patients and their family caregivers manage illness uncertainty. Future research needs to employ a rigorous research methodology in order to test uncertainty management interventions among a diverse population and to ensure complete and accurate reporting of the research procedures and findings.
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Code availability Not applicable

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Data availability All studies included in this review are publicly available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Table 4 Cochrane Collaboration’s criteria for assessing risk of bias

| Domain                      | Criteria                                                                 |
|-----------------------------|--------------------------------------------------------------------------|
| Sequence generation         | Allocation sequence was adequately generated.                           |
| Allocation concealment      | Allocation of group assignment could not be foreseen before randomization. |
| Blinding of participants, and personnel | Knowledge of the allocated intervention by participant and personnel was adequately prevented during the study. |
| Blinding outcome assessment | Knowledge of the allocated interventions by outcome assessors was adequately prevented during follow-up. |
| Incomplete outcome data     | Incomplete outcome data were adequately addressed.                       |
| Selective reporting         | The study was free of apparent selective outcome reporting.              |
| Deferential intervention use| Reported outcome was among participants who similarly used interventions |
| Baseline imbalance          | Reported outcome was among balanced participants’ characteristics across groups. |

Random number table
Computer random number generator
Coin tossing
Card or envelope shuffling
Throwing dice
Used central allocation including telephone or web-based randomization
Used sequentially numbered, opaque, sealed envelopes
No blinding but unlikely that the outcome was influenced. Blinding ensured for participants and key study personnel and unlikely to have been broken.
No blinding but not the outcome is not influenced. Blinding of outcome assessment ensured, and unlikely to have been broken.
No missing outcome data
Missing outcome data unlikely related to true outcome
Missing outcome data balanced across groups with similar reasons for missing data across groups
Plausible effect size among missing outcomes not enough to have impact on observed effect size
Missing data have been imputed using appropriate methods.
Study protocol available and all prespecified outcomes of interest reported
Study protocol is not available, but all expected prespecified outcomes reported.
All participants used intervention and complete all sessions.
Adjusting the statistical analysis according intervention use
Include all randomized participants
Used stratified randomization or minimization
Adjusting in the statistical analysis for baseline variables.
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