Putting Evidence Into Practice: Evidence-Based Interventions for Oral Agents for Cancer

Sandra L. Spoelstra, PhD, RN, and Holly Sansoucie, DNP, RN, AOCN®, CBCN®

Background: The limited evidence available suggests that adherence to oral agents for cancer is a significant clinical problem and may have a substantial impact on treatment success or failure. Adherence is a difficult issue among patients who are very sick with a life-threatening disease who often must adhere to complex treatment protocols independently at home.

Objectives: This article aims to identify effective interventions for the promotion, treatment, and management of adherence to oral agents for cancer and to synthesize the literature for use in clinical practice.

Methods: As part of the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) initiative, a comprehensive examination of the current literature was conducted to identify effective interventions for patients prescribed oral agents for cancer. The ONS PEP weight-of-evidence classification schema levels of evidence were used to categorize interventions to assist nurses in identifying strategies that are effective at improving adherence.

Findings: The majority of evidence found was conducted in conditions other than cancer; therefore, research is needed to identify whether these interventions are effective at promoting adherence in patients with cancer.

Key words: interventions; adherence; oral agents for cancer; PEP; Putting Evidence Into Practice

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Medication adherence is a complex and multifactorial problem that can influence the outcome of treatment in many conditions. The therapeutic outcome of cancer treatment for patients taking oral agents for cancer (OACs) depends heavily on adherence to the regimen (Bestvina et al., 2014; Soria et al., 2011). Reviews of OAC studies show that adherence rates are less than 80% (Puts et al., 2013; Spoelstra & Given, 2011), which may be inadequate for treating the cancer. It has been shown that 10% of patients with cancer taking OACs are not refilling their prescriptions (Streeter, Schwartzberg, Husain, & Johnsrud, 2011). The limited evidence available suggests that adherence to OACs is a significant clinical problem that may have a substantial impact on OAC treatment outcomes (Bozic et al., 2013; Gebbia, Bellavia, Ferraü, & Valerio, 2012). Therefore, as part of the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) initiative, this article synthesizes the current literature to identify effective interventions for the promotion, treatment, and management of adherence to oral medications. Because of the very limited evidence for interventions in patients with cancer, evidence for interventions aimed at improving adherence includes research done in patients with multiple chronic diseases. The weight of evidence is determined across all types of evidence, and, where possible, specific findings for patients with cancer taking OACs are discussed.

State of the Science

The International Society for Pharmacoeconomics and Out- come Research defined medication adherence as the degree or the extent of conformity to recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency for the duration of time from the initiation of the medication (Ruddy, Mayer, & Partridge, 2009). Clinicians commonly describe medication adherence in terms of a rate,
often reported in a percentage (e.g., 80%), which is the amount of medication taken divided by prescribed amount. In the current review, adherence was defined as the rate of conformity to prescribed treatment.

The National Cancer Institute, the American Society of Clinical Oncology, and ONS have each made OAC adherence a priority. Nurses in oncology settings are in a position to promote OAC adherence. Therefore, access to the latest evidence regarding how to address this challenging clinical problem is imperative. The specific aims of the current article are (a) to synthesize evidence regarding the promotion, treatment, and management of adherence to OACs in patients with cancer and (b) to discuss the process and development of the ONS PEP evidence-based interventions for OAC adherence.

Methods

Members of the OAC adherence PEP project team consisted of oncology nurses serving in a variety of roles, including a PhD- and DNP-prepared nurse, nine master’s-prepared advanced practice nurses, and four ONS staff members. Team participants were invited if they had experience working with OACs and were interested in improving patient care. Conference calls among team members were conducted to facilitate organization, establish and review guidelines, and coordinate project deliverables.

Search Strategy

An extensive review of the literature regarding medication adherence was conducted by ONS staff using PubMed and CINAHL® (see Figure 1). The search was conducted using the consolidated patient or problem, intervention, comparison, and outcome (PICO) terms shown in Figure 2 (Melnyk & Fineout-Overholt, 2010). Because of the limited number of articles regarding OAC adherence, the search included evidence in patients with cancer and other populations. Studies reviewed included meta-analyses, systematic reviews, clinical research studies, and practice guidelines published within the past 10 years. Studies selected for the review were limited to empirical research in English that examined interventions to improve medication adherence in adult patients. Because of the specificity of treatment issues in children, articles with pediatric patients (aged younger than 18 years) were excluded. Those addressing psychiatric issues and substance abuse were also excluded. The final literature search was performed in September 2014.

Critical Review of the Evidence

The PEP team used a systematic approach to review, critique, and assign levels of evidence to the literature in a manner similar to prior ONS PEP teams (Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011). Critique and summary of each manuscript included sample characteristics and size, setting, study design, measures, results, conclusions, and limitations. Data extraction occurred using a tool provided by ONS staff. In total, 325 articles were reviewed, summarized, and appraised by a primary and secondary reviewer. ONS staff summarized the data in tables by type of intervention and posted to an ONS online repository for PEP team review. All findings were reviewed by the PEP team, and the ONS weight-of-evidence classification schema was applied to assign a level of evidence (Mitchell & Friese, 2015) (see Table 1).

Results

A total of 131 studies met the inclusion criteria and were included in the review. Using the level of evidence from ONS established criteria, two interventions were “recommended for practice,” three were “likely to be effective,” and several were categorized as “effectiveness not found.” No interventions were found that were “effectiveness unlikely,” “benefits balanced with harms,” or “not recommended for practice.”

Recommended for Practice

Patient monitoring and feedback: Patient monitoring and feedback to promote medication adherence includes monitoring medication taking and provision of feedback on adherence. Synthesis of the interventions in these studies was challenged by differences in how adherence was measured, method of feedback, and in some instances, lack of explanation of...
intervention components. Studies were conducted in multiple diseases. Given the level of evidence, large samples, and significant results, interventions that monitor medication adherence and provide feedback on adherence rates to patients are recommended for practice.

Three randomized, controlled trials (RCTs) that examined monitoring and feedback found higher rates of adherence. Two small-scale studies (Sabin et al., 2010; Wu, Corley, Lennie, & Moser, 2012) provided microelectromechanical systems data feedback in patients with HIV. A larger, single-site RCT in patients with hypertension found higher rates of self-reported adherence (Johnson et al., 2006).

Demonceau et al. (2013) found higher rates of adherence in 48 trials through meta-analysis when using monitoring and feedback across multiple diseases. Gwadry-Sridhar et al. (2013) conducted a systematic review of 97 studies in patients with hypertension and found improved adherence with interventions using monitoring and feedback. The systematic review on the use of OACs in patients with cancer found that 20 of 37 studies had higher rates of adherence when patient

FIGURE 2. Medication Adherence Search Terms for Computerized Databases Using PICO Schema
monitoring and feedback were provided (Revere & Dunbar, 2001).

Multicomponent interventions: Multicomponent interventions to promote adherence include the combination of patient education and counseling along with other interventions, such as reminder devices, packaging, and physician or patient feedback. Synthesis of all of the research evidence for this type of intervention is complicated by the fact that these approaches varied in terms of the specific components included in tested programs; however, the evidence in total across multiple types of patients shows significant positive effects on OAC adherence. Studies were done in patients with HIV, seizure disorders, congestive heart failure, hypertension, renal disease, chronic obstructive pulmonary disease, cancer, and other chronic conditions.

Ten RCTs examined multicomponent interventions. In seven of these studies, a significant positive effect of the intervention was found (Belzer et al., 2014; Chisolm-Burns et al., 2013; Johnson et al., 2006; Konkle-Parker et al., 2013; Lee, Grace, & Taylor, 2006; Li et al., 2013; Murray et al., 2007; Ogedegbe et al., 2012). Methods and timing of adherence measurement varied across studies, and duration of follow-up ranged from 9–18 months. Interventions were provided in person or via telephone. In two RCTs, no differences were found between intervention and control groups (Konkle-Parker et al., 2013; Stewart, McNamara, & George, 2013), and in one small study, control patients had greater adherence throughout the study (Odegard, Goo, Hummel, Williams, & Gray, 2005).

Uncontrolled studies demonstrated mixed results. One observational study of 130 patients with hypertension showed higher adherence with the use of the combination of GlowCaps® for reminder alerts, automated telephone calls for missed doses or refills, patient feedback reports, and payment to those with adherence greater than 80% (Agency for Healthcare Research and Quality [AHRQ], 2011; Stuurman-Bieze, Hiddink, van Boven, and Vegter, 2013) reported a lower rate of nonadherence among patients on lipid-lowering medication with a multicomponent intervention compared to historic controls; however, this report was limited by the lack of information regarding the actual adherence measure used. Another observational study of patients with HIV with known adherence problems showed no effect of combined interventions (Krummenacher, Cavassini, Bugnon, & Schneider, 2011). In a small quasiexperimental study, the combination of education, counseling, and reminder aids resulted in reduced missed doses and improved refill adherence (Levy et al., 2004). Tschida et al. (2012) compared the medication possession ratio of patients with cancer who participated in a specialty program of education, refill reminders, adherence screening, and counseling to that of historic controls, and participants showed improved medication possession ratio and fewer refill gaps with the specialty program. In the study, patients self-selected the type of follow-up for adherence (Tschida et al., 2012). A retrospective study of patients using OACs showed no difference in adherence with education, counseling, and monitoring reports to providers (Khandelwal, Duncan, Ahmed, Rubinstein, & Pegus, 2012). A small observational study of patients using various OACs found that most interventions that addressed adherence were related to adverse event management (Wong, Bounthavong, Nguyen, Bechtoldt, & Hernandez, 2014).

### TABLE 1. Putting Evidence Into Practice Weight-of-Evidence Classification Schema

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Recommended for practice</td>
<td>Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.</td>
<td>At least two multisite, well-conducted, RCTs with at least 100 participants Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence</td>
</tr>
<tr>
<td>Likely to be effective</td>
<td>Effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion.</td>
<td>One well-conducted RCT with fewer than 100 participants or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating</td>
</tr>
<tr>
<td>Benefits balanced with harms</td>
<td>Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.</td>
<td>RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations</td>
</tr>
<tr>
<td>Effectiveness not established</td>
<td>Data currently are insufficient or are of inadequate quality.</td>
<td>Well-conducted case-control study or poorly controlled RCT Conflicting evidence or statistically insignificant results</td>
</tr>
<tr>
<td>Effectiveness unlikely</td>
<td>Lack of effectiveness is less well established than those listed under not recommended for practice.</td>
<td>Single RCT with at least 100 participants that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies</td>
</tr>
<tr>
<td>Not recommended for practice</td>
<td>Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.</td>
<td>No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 participants Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence</td>
</tr>
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Effectiveness of multicomponent interventions was examined in seven systematic reviews. Zedler, Kakad, Colilla, Murrelle, and Shah (2011) reported that three of six studies that reported improved adherence used multicomponent interventions. A comparative effectiveness report with 33 studies concluded that case management and multicomponent interventions had moderate benefit (Viswanathan et al., 2012a). Six additional systematic reviews demonstrated benefit (Banning, 2009; Bryant et al., 2013; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; Higgins & Regan, 2004; Kavookjian & Wittayakunukorn, 2014; Parker, Mills, & Abbey, 2008). The review by Kavookjian and Wittayakunukorn (2014) included six studies in patients with hematologic cancers and reported that four of five studies using multicomponent interventions showed significant improvement. This review was limited by relatively few studies and study designs with high risk of bias. Banning (2009) reported a systematic review of various adherence interventions in 20 studies focused on older adult patients. They reported that most interventions had variable effects, but multicomponent interventions were more effective than those that had a single focus. This report noted that standardized pharmacy interventions had variable results, and in one study, the intervention by an individual without clinical experience was a barrier to adherence (Banning, 2009).

Likely to Be Effective

Text messages: Text message interventions to promote adherence included one-way messages sent to the patient and two-way messages sent to the patient with a patient response. Studies with standardized and tailored messaging were found. The evidence in total across multiple types of patients and conditions found that text message interventions were likely to be effective at improving medication adherence.

Mbuagbaw et al. (2013) conducted a meta-analysis on three trials in patients with HIV and found that weekly text messages were more effective than daily text messages. Six systematic reviews found that 13 of 19 studies reported a positive effect of text messages on adherence (Halpern, Lopez, Grimes, Stockton, & Gallo, 2013; Horvath, Azman, Kennedy, & Rutherford, 2012; Nglazi, Bekker, Wood, Hussey, & Wysonge, 2013; Pellowski & Kalichman, 2012; Revere & Dunbar, 2001; Vervloet, Linn, et al., 2012). Nine RCTs in patients with heart disease, HIV, diabetes, and asthma found higher rates of medication adherence using text messages (Hardy et al., 2011; Huang, Li, et al., 2013; Lester et al., 2010; Mbuagbaw et al., 2012; Park, Howie-Esquivel, Chung, & Dracup, 2014; Petrie, Perry, Broadbent, & Weinman, 2012; Pop-Eleches et al., 2011; Strandbygaard, Thomsen, & Backer, 2010; Vervloet et al., 2011; Vervloet, van Dijk, et al., 2012). A quasiexperimental study in patients with diabetes who had visited the emergency department found improved adherence with text messages sent three times per week (Arora, Peters, Agy, & Menchine, 2012). Three observational studies found that the number of missed doses declined (Foreman et al., 2012; Lewis et al., 2013; Rodrigues et al., 2012).

Two small-scale RCTs in patients with HIV (da Costa et al., 2012) and in use of birth control (Hou, Hurwitz, Kavanagh, Fortin, & Goldberg, 2010) found no difference in adherence rates. Two larger RCTs in patients prescribed antibiotics after emergency department care (Suffoletto, Calabria, Ross, Callaway, & Yealy, 2012) and in patients with diabetes (Shetty, Chamukuttan, Nanditha, Raj, & Ramachandran, 2011) found no difference in adherence rates using text messages.

Automated voice response: Automated voice response (AVR) interventions ranged from daily to weekly to monthly calls to assess, prompt refill, motivate, remind, or promote medication adherence. The evidence across diseases, with three studies using patients with cancer, showed that AVRs were likely to be effective at improving medication adherence.

RCTs using AVR biweekly in patients with diabetes (Piette et al., 2000), using daily AVRs in patients with memory loss (Ownby, Hertzog, & Czaja, 2012), using AVR to promote inhaler use (Bender et al., 2010), using three AVR calls to motivate patients to take lipid-lowering medications (Stacy, Schwartz, Ershoff, & Shreve, 2009), and using AVR for prescription refill reminders (Derose et al., 2013) found improved adherence. RCTs by Spoelstra et al. (2013a; 2013b) and Decker et al. (2009) using AVRs found improved OAC adherence in patients with cancer. However, several of these studies measured adherence by self-report and had small sample sizes.

Two large-scale RCTs using AVR in African Americans with hypertension (Migneault et al., 2012) and prompting medication refill in patients with chronic obstructive pulmonary disease on steroids (Völlmer et al., 2011) found no improvement in adherence. A pilot study found no difference in adherence rates when the AVR prompted reports of previous-day adherence (Hettema, Hossieinb, & Ingersoll, 2012).

Treatment of depression: Treatment of depression demonstrated effectiveness in promoting medication adherence in a meta-analysis of 29 trials in people with HIV treated with antiretroviral therapy (Sin & DiMatteo, 2014). A variety of interventions to treat the depression were used, including individual and group cognitive-behavioral therapy and medications, with stronger effects in patients who were clinically depressed.

Effectiveness Not Established

Education: Conn et al. (2009) conducted a meta-analysis that found that educational interventions were effective. In systematic reviews in patients with hypertension, HIV, cancer, and other chronic conditions, education improved adherence rates (Banning, 2009; Gwadry-Sridhar et al., 2013; Revere & Dunbar, 2001; Williams, Manias, & Walker, 2008). In RCTs in patients with multiple chronic conditions, ulcerative colitis, osteoarthritic, and breast cancer, education had no effect on medication adherence (Bennett, Glasziou, Del Mar, & De Lootse, 2003; Elkjaer, 2012; Hadji et al., 2013; Silverman, Nasser, Natrass, & Drinkwater, 2012). Saez-Benito et al. (2013) conducted a systematic review of 15 studies and found inconclusive results. Mixed results were found, and effectiveness of educational interventions could not be established.

Psychoeducation: Numerous studies reported on the use of education and counseling to improve medication adherence. The Case Management Society of America (2010) and the British Association for Sexual Health (Poppa et al., 2004) recommend including education and counseling in approaches to improve medication adherence. Manias and Williams (2010) conducted
a meta-analysis of 46 trials across multiple diseases and found that counseling and education improved medication adherence. A small pilot study found that psychoeducational interventions were effective, but another found no effect on medication adherence rates (Demonceau et al., 2013; Manias & Williams, 2010).

Systematic reviews in patients with HIV, hypertension, and other chronic conditions demonstrated that psychoeducation improved adherence rates (Cutrona et al., 2010; Gwadry-Sridhar et al., 2013; Pellowsky & Kalichman, 2012); however, studies by Mathes, Antoine, Pieper, and Eikermann (2014) and Misono et al. (2010) did not find improvement. Cook, Emiliozzi, El-Hajj, and McCabe (2010) used counseling via telephone and found improvement in adherence rates. Using counseling and education in studies examining contraception, chronic conditions, and older adult patients, low effects to no effect were found on adherence rates (Halpern et al., 2013; Haynes et al., 2008; Higgins & Regan, 2004). RCTs in patients with asthma, diabetes, congestive heart failure, and prescribed five or more drugs found higher rates of adherence using counseling and education (Lawrence, Allison, Chen, & Demand, 2008; Schaffer & Tian, 2004; Wu et al., 2006, 2012; Young et al., 2012).

Seven RCTs in patients with HIV undergoing antiretroviral therapy, patients with hypertension and diabetes, patients with kidney disease, and two studies in patients with diabetes found no difference in adherence rates with educational interventions (Farrer, 2012; Fisher et al., 2011; Nietert et al., 2009; Odegard et al., 2005; Robbins et al., 2013; van Servellen & Lombardi, 2005; Williams, Manias, Liew, Gock, & Gorelik, 2012). A cohort studying patients with breast cancer and another studying patients using lipid-lowering drugs used an educational interventions and found higher rates of adherence, but no differences were found in a study with patients with breast cancer, a study with patients with colorectal cancer, or in four studies with patients with HIV undergoing antiretroviral therapy (Basso, Helena, Caraciolo, Paiva, & Nemes, 2013; Enriquez, Cheng, McKinsey, & Stanford, 2009; Kalichman et al., 2011; Parsons, Rosof, Punzalan, & Di Maria, 2005; Rosenzweig et al., 2011; Simons et al., 2011; Stuorman-Biezce et al., 2013). Studies in patients with gastrointestinal cancer, in patients using OMCs, and in patients with HIV did not report results on adherence (Konkle-Parker, Erlen, & Dubbert, 2010; Schneider, Adams, & Gosselin, 2014; Sommers, Miller, & Berry, 2012). Brennan et al. (2012) conducted a large observational study in patients with diabetes but did not report adherence rates. Mixed results were found, and effectiveness of psychoeducation to improve medication adherence could not be established.

Cognitive-behavioral therapy: A meta-analysis using cognitive-behavioral therapy to promote medication adherence demonstrated a positive effect. However, the intervention content and timing varied greatly (Manias & Williams, 2010).

Motivational interviewing: A single-site RCT in patients with HIV undergoing antiretroviral therapy found improved adherence when one face-to-face and two to five telephone sessions of motivational interviewing were provided (Dilorio et al., 2008). A cohort study with patients using statins found that 12-month medication possession rates and persistence were higher (Tai-tel, Jiang, Rudkin, Ewing, & Duncan, 2012). In addition, in a cohort study with patients with HIV undergoing antiretroviral therapy, nonadherence rates declined (Krummenacher et al., 2011). The Case Management Society of America (2010) recommended using motivational interviewing to promote medication adherence. RCTs found no difference in adherence rates when using motivational interviewing (Cook, Emiliozzi, & Pointer, 2009; Solomon et al., 2012; Williams et al., 2012). Studies were of small sample size, and findings were inconsistent.

Packaging: A meta-analysis of 35 studies found that packaging interventions were effective (Conn et al., 2009). Two systematic reviews demonstrated that packaging improved adherence in patients with hypertension and diabetes and in older adult patients with chronic conditions; however, four studies were inconclusive (Banning, 2009; Fuangkan, Dhippayom, & Kongkaew, 2014; Higgins & Regan, 2004; Macintosh, Pond, Pond, Leung, & Siu, 2007; Mahtani, Heneghan, Glasziou, & Perera, 2011; Williams et al., 2008; Zedler et al., 2011). A qualitative study reported that it was difficult to get medications out of the packaging (Leconteurier, Cunningham, Campbell, & Copeland, 2011). Few studies produced results, effect sizes were small, and results were inconclusive in several studies.

Less frequent dosing: Higher rates of adherence were found in once-daily dosing compared to twice-daily dosing (Bae et al., 2012; Charpentier, Fleury, Dubroca, Vaur, & Clerson, 2005; Cooper et al., 2011). Single measures of adherence (medication possession rate from claims files and self-report) were used in each of these studies. One large-scale RCT found no difference in adherence rates with less frequent dosing (Udelson et al., 2009).

Reminders: AHRQ (2011) researched the use of GlowCaps and refill reminders; however, adherence rates were not reported. Conn et al. (2009) conducted a meta-analysis of 33 studies and found that interventions with a reminder to take the medication were more effective than those without. Six systematic reviews found improved adherence rates using various types of reminders (Banning, 2009; Halpern et al., 2013; Misono et al., 2010; Pellowsky & Kalichman, 2012; Revere & Dunbar, 2001; Vervloet, Linn, et al., 2012). Five multisite RCTs and two observational studies also found higher adherence rates. Evidence was mixed in several studies, and further research is needed (Belzer et al., 2014; Buckwalter, Wakefield, Hanna, & Lehmann, 2004; Derose et al., 2013; Heinrich & Kuiper, 2012; Vervloet, van Dijk, et al., 2012; Vollmer et al., 2011; Yard, Huh, King, & Simoni, 2011). In three RCTs in patients with HIV and heart disease and patients using multiple medications, no difference in adherence rates was found when reminders were used (Huang, Sangthong, et al., 2013; Kripanali, Schmotzer, & Jacobson, 2012; Nietert et al., 2009). Jansen, Andersen, and Brüning (2009) used reminders with allergy medications but did not report adherence rates. Christensen et al. (2010) found no difference in adherence rates using audiovisual reminders.

Automated dispensers: An observational study found overall dispensing rates of 99% with automated dispensers. A qualitative multisite study found that not all medications were taken on the prescribed day or at the correct time (Buckwalter et al., 2004; Larsen & Haugbolle, 2007).

Provider monitoring and feedback: A systematic review of 97 studies with patients with hypertension, two RCTs that provided physicians information on adherence rates or refills, and one study that provided daily adherence reports to physicians found no improvement in adherence rates (Gwadry-Sridhar et al., 2013;
Implications for Practice

- Promote adherence to oral agents for cancer by enacting patient feedback and monitoring, as well as multicomponent interventions.
- Use automated voice recordings and text messages and treat depression to promote adherence to oral agents.
- Implement evidence-based interventions in the clinical practice within the context of the institution to promote adherence to oral agents.

Nietert et al., 2009; Parker, Frampton, Blackwood, Shannon, & Moore, 2012; Tamblyn et al., 2010.

Decision aid: A multisite RCT on the use of a decision aid to overcome not taking medications in patients with diabetes or patients using statins found no difference between groups (Branda et al., 2013).

Calendar aid: A multisite RCT with patients using allergy medications did not report rates of adherence, and a qualitative study reported fewer disruptions in treatment when using a calendar to cue medicating taking (Jansen et al., 2009; Lecouturier et al., 2011).

Mail and online refills: Mail-order and online refill studies found higher rates of adherence, but effect sizes were small (Duru et al., 2010; Sarkar et al., 2014; Zhang et al., 2011). Measures of adherence were unable to account for reductions or stoppages in the script.

Institutional-level interventions: Effectiveness was not established in a large multisite cohort study in patients with HIV undergoing antiretroviral therapy. No differences were found in adherence rates in patients who tested provider training and facility monitoring (Boruett et al., 2013).

Supportive interventions: A meta-analysis of patients in Africa found that community education improved adherence rates; however, the study had poor design and was not generalizable to other settings (Fuangchan et al., 2014). A systematic review of studies of patients using antihypertensive medications found that patients who used support groups had higher self-management, but the study did not differentiate between medication management and other types of care (Gwadry-Sridhar et al., 2013). A single-site RCT found no difference in adherence rates in patients with HIV undergoing antiretroviral therapy using a caregiver to prompt adherence; however, the study was underpowered (Kunutsor et al., 2011). A small pilot study was encouraging because higher adherence rates were found when health coaches were used to prompt adherence (Leung et al., 2012). A multisite observational study with patients with lung cancer found higher adherence rates by pill count when monthly phone calls were provided for support; however, the duration and timing of adherence measures were unclear (Gebbia et al., 2013). A qualitative study with companions providing support during antiretroviral therapy reported improved adherence (Foster et al., 2010). The evidence on effectiveness of support is encouraging but not of the rigor to recommend for practice, and further study is needed.

Workplace care delivery: A large, multisite cohort study found that intervention group adherence rates were higher than the covered population when services were delivered in the workplace rather than in a pharmacy (Sherman et al., 2009). Medication possession rate was the single measure of adherence, and no consideration was given to other factors in this study.

Intervention to improve provider communication: A systematic review of 13 studies on health information technology interventions to facilitate patient and provider communication found a small effect on adherence rates (Misono et al., 2010). Studies with more rigorous design or with more intense intervention doses may be needed to establish effectiveness.

Cost and co-pay reduction: A systematic review of 68 studies found no difference in adherence with co-payment reduction (Viswanathan et al., 2012b). Three large-scale medication possession rates studies found higher adherence rates when co-payments were reduced, waived, or rebated; however, these studies had no control group for comparison (Chernew et al., 2008; Farley, Wansink, Lindquist, Parker, & Maciejewski, 2012; Kostev et al., 2013). The Case Management Society of America (2010) consensus-based guidelines stated that reimbursement needs to be maximized to affect adherence. Findings were mixed, and studies lacked rigorous design.

Implications for Nursing Practice and Research

The review of the evidence indicates that ongoing research on adherence to OACs is warranted. The literature supports use of monitoring of adherence rates with patient feedback and multicomponent interventions. The literature also indicates that text message and AVR interventions, as well as treatment of depression, are likely to be effective at promoting medication adherence. To date, the evidence is insufficient to support many interventions, such as education, calendars, packaging, refill cues, cognitive-behavioral therapy, motivational interviewing, dispensing tools, decision aids, or improving communication with providers. Oncology nurses have a critical role in implementing the available evidence, conducting research, and developing new evidence on OAC adherence. In addition, given the high rate of depression among patients with chronic disease, depression should be routinely assessed, and treatment should be coordinated when warranted because depressive symptoms are known to increase risk for poor adherence (Ciesla & Roberts, 2001; Hartzell, Janke, & Weintrob, 2008). However, the authors of the current article acknowledge that the majority of this evidence is in populations other than patients with cancer, and these interventions may not work for the population of patients with cancer. Care for patients prescribed OACs and the technology to support medication adherence is evolving rapidly, and many of these studies were completed several years ago.

Future research should use more rigorous studies with larger sample sizes in varied cancer types. More research is needed in diverse ethnic populations. Intervention components should be clearly defined, and interventions that show promise should be replicated in populations of patients with cancer to make results more generalizable. Interventions showing the most potential are AVRs, text messages, and depression management, as well as educational interventions, interventions that conduct monitoring and feedback, and interventions that use refill cues.
Conclusions

To date, no standard exists for the management of OAC adherence. Evidence for interventions to manage this significant clinical problem has been lacking in patients with cancer. Future researchers should consider focusing on intervention approaches that show promise. Oncology nurses are crucial to overseeing and guiding patients to self-manage OAC treatment. Nurses should be aware of the evidence-based interventions, or lack thereof, when caring for patients prescribed OACs, and use that information to guide decision making in clinical practice.

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