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Review

REVIEW

Interventions to Enhance Adherence to Oral Antineoplastic Agents: A Scoping Review

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Abstract

Background: As new targeted oral antineoplastic therapies have emerged in recent years, the development of effective strategies that promote optimal adherence to cancer medication regimens has become an important priority.

Methods: We conducted a scoping literature review to search for English language articles published through July 15, 2019, to identify studies that reported the testing and/or evaluation of interventions to improve adherence to oral antineoplastic agents.

Results: A total of 56 articles were selected for review. Of the studies evaluated, 14 were randomized trials. All interventions except two targeted adult patients. Thirty-three studies enrolled fewer than 100 patients. Most interventions were education- and counseling-based and centered on provision of information about the drug and strategies to manage side effects. Only eight studies used an mHealth tool and/or text messages to target nonadherence. Among studies with a comparison sample, fewer than one-half (44.7%) reported statistically significant improvements in adherence or persistence associated with the intervention; however, some pharmacist-directed programs, particularly those that integrated monitoring or routine follow-up with a provider, did demonstrate efficacy.

Conclusion: Although the development of adherence-promoting interventions for oral antineoplastic therapies has increased recently, few have been rigorously tested. The nascent literature suggests those that are pharmacist directed and use regular monitoring show promise, though additional prospective studies are needed. Study methodology, population selection, and potential challenges that may be encountered in the implementation and dissemination phases should be considered when developing new interventions to address nonadherence to oral antineoplastic treatment.

Over the last 2 decades, administration of oral antineoplastic drugs has accelerated in both curative and palliative settings. A primary challenge of oral antineoplastic treatment is ensuring patients take their medication as indicated (ie, adherence) and for the recommended duration (ie, persistence). Suboptimal adherence to oral regimens is associated with poorer outcomes in adult (1–4) and pediatric cancer populations (5,6). The reasons why individuals with cancer are nonadherent to their prescribed therapy are multifactorial and can be specific to the diagnosis, type and duration of therapy prescribed, associated toxicity, and patient characteristics, such as beliefs, knowledge, concerns, and behaviors. Side effects are a contributor for many patients and regimens to nonadherence, including stopping treatment early (ie, nonpersistence) (7–11), although the association between experiencing symptoms or adverse effects and nonadherence is not consistently seen in cancer populations (12–14). Favorable perceptions about the advantages of adhering to the medication and the need for the medication, higher levels of self-efficacy, and knowledge about diagnosis and treatment have all been found to be positively associated with adherence (7,12,14–16).

Patients are also more likely to be nonadherent if they suffer from comorbid conditions (17). Access and costs are systems issues critical for some patients, with higher copays (18–20) and frequency of refills also affecting adherence (21). In addition, simply not remembering to take one's medication (eg,

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unintentional nonadherence) has been identified as a contributor to suboptimal adherence in some settings (8,22,23).

Several reviews have considered studies of adherence to oral agents in cancer patients without a specific focus on interventions (24–29). Although there have been systematic reviews of adherence-promoting interventions in the chronic disease setting, inclusion criteria for these reviews has often meant that small studies or trials that are nonrandomized or lack a control group were excluded, resulting in few or no studies that included cancer patients (30–33). Furthermore, many of these reviews were published before the emergence of several targeted therapies and therefore fail to capture trials that have targeted relatively new agents. Of five more recent reviews that did focus on interventions for oral anticancer drugs, one was narrowly focused on behavioral interventions designed for improving endocrine therapy (ET) adherence in breast cancer patients (34); another was restricted to "controlled" studies, resulting in a total of six studies (35); a third study was designed as an evidence synthesis and was not limited to cancer patients (36); and a fourth reviewed only nurse-directed interventions (37). A recent review published by Zerillo and colleagues assessed oral chemotherapy interventions from a quality and safety perspective but did not include oral hormonal treatment or studies without a comparative arm or that used historical controls (38).

The objective of this review was to provide an updated, comprehensive summary of published studies of interventions designed with the intent of improving adherence to oral antineoplastic therapy. Evaluating these interventions can provide valuable information in describing both successful strategies and those that have failed. Understanding the limitations of prior studies is critical to improving the design and implementation of future interventions, recognizing that improved adherence will ultimately reduce morbidity and mortality from cancer.

REVIEW

Methods

Search Strategy

Given the broad research objective, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines were followed (39). The search strategy (Supplementary Methods, available online) was designed to identify studies that evaluated interventions to improve adherence to oral antineoplastic agents in adult or pediatric patient populations. Countway Library of Medicine at Harvard University assisted with the search process. PubMed, CINAHL, Embase, and Cochrane databases were searched through July 15, 2019 (no start date specified). Grey literature was not searched. Inclusion criteria included English language with adherence (or persistence) reported as a study outcome.

Screening and Quality Assessment

Titles and abstracts were screened by two reviewers (S. Rosenberg and L. Ngo) to assess relevance. Reviews, meta-analyses, abstracts, descriptions of study protocols, commentaries, and studies without a documented intervention or where there was no documentation of assessment of adherence or persistence were excluded. If initial screening indicated the development, testing, or implementation of an intervention or program related to oral anticancer medication with adherence as an outcome, the full article was retrieved and reviewed. Disagreements regarding inclusion were discussed and resolved by consensus, with a third reviewer (A. Partridge) adjudicating articles without consensus agreement or questions about relevance. A single reviewer (S. Rosenberg) also reviewed reference lists of relevant review articles and of studies meeting inclusion criteria for additional studies. One reviewer (S. Rosenberg) independently assessed the quality of each included study with the Mixed Methods Appraisal Tool v2018, with approximately 20% selected for review by a second reviewer (L. Ngo). The Mixed Methods Appraisal Tool allows for the evaluation of different study types, with each study graded on seven individual quality criteria (40).

Data Abstraction and Summary

Covidence (41) was used as the primary screening and data extraction tool. Elements captured from each selected study were country where the study was conducted, study design (including whether there was a comparison or control group), study population (eg, if limited to certain diagnoses or drugs vs range of oral anticancer agents), sample size, a description of the intervention, methods of adherence assessment (eg, self-report, prescription records), duration of study follow-up, and adherence results, defined as the proportion adherent or persistent as specified by each study at the end of follow-up, unless another metric was described.

Results

Summary of Study Characteristics

A total of 13 165 articles resulted from the combined search. After removing duplicate articles, reviews, abstracts, and other articles deemed irrelevant, 105 articles were selected for review.

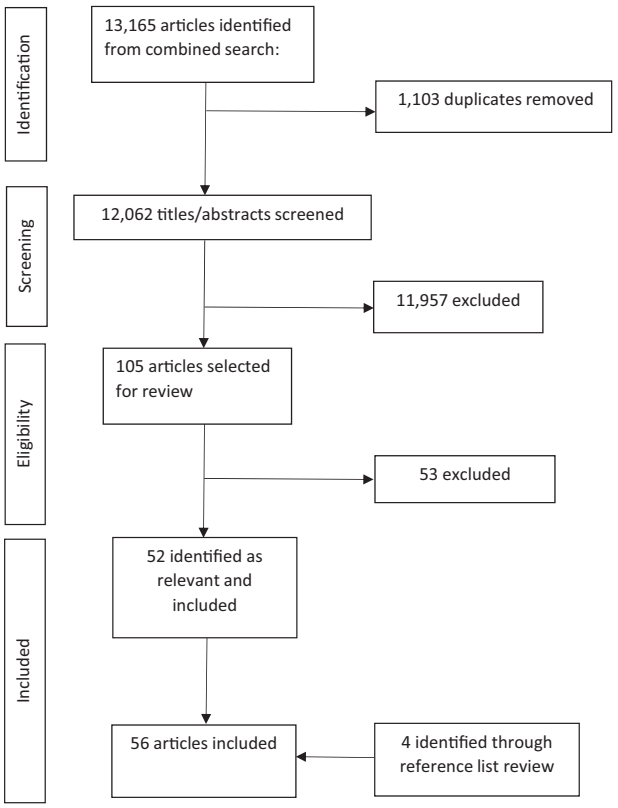

Figure 1. Search strategy flowchart.

Of these, 52 met inclusion criteria, with an additional four articles identified through a review of reference lists, resulting in a total of 56 articles (Figure 1).

The 56 articles [representing 55 different studies, with two articles identified inclusive of different data from the same study (42,43)] varied in design, cancer diagnosis, and intervention type. More than one-half (k = 32, 57.1%) were published between 2015 and 2019. Approximately one-quarter (k = 14, 25.5%) were randomized studies. Sample size varied widely, the largest being a randomized trial that enrolled nearly 5000 breast cancer patients (44) and the smallest inclusive of nine evaluable patients (45).

Eleven studies enrolled breast cancer patients prescribed ET (42–44,46–54), 10 studies enrolled patients with hematologic malignancies (45,55–63), two studies included only non-small cell lung cancer (NSCLC) patients (64,65), two studies enrolled genitourinary cancer patients (66,67), and two studies enrolled only gastrointestinal (GI) cancer patients (68,69). For the remaining studies, multiple cancer diagnoses were eligible for inclusion. Among the non-breast cancer studies, the types of oral antineoplastic agent prescribed included tyrosine kinase inhibitors (TKIs), capecitabine, prednisone, and oral 6 mercaptopurine (6-MP), among other agents. Except for two studies that focused on adolescent and young adult (AYA) cancer patients (70,71), all other studies enrolled adults.

Overall study quality was mixed. Most randomized studies had minimal missing outcome data and reported comparable groups at baseline. However, it was unclear in most cases to what degree participants complied with the intervention. For nonrandomized studies of interventions with comparison data, there were also minimal missing outcome data and study measures were deemed adequate in almost all studies. However, a consistent weakness in this category was failure to adjust for confounding in the study design and analysis. Several single-arm studies with no comparison groups could not be conclusively evaluated because of the lack of information about sampling strategy and representation. Additionally, several studies in this category that used self-report to assess adherence did not document the use of a validated measure.

Randomized Trials

Two large randomized controlled trials (RCTs) enrolled postmenopausal women on aromatase inhibitors (AIs) for hormone receptor–positive breast cancer (42–44) (Table 1). The Patient's Anastrozole Compliance to Therapy (PACT) study randomly assigned more than 4000 German women to an educational intervention that included mailed letters and pamphlets during the year following AI initiation, prompts each month to remind women to remain on therapy, and small incentives (44). Both the study population and intervention in The Compliance of Aromatase Inhibitors Assessment in Daily Practice Through Educational Approach (CARIATIDE) study were comparable with PACT, with CARIATIDE randomizing more than 2700 women from 18 countries (42,43). The studies also had similar results: in PACT, compliance with treatment at 1 year, defined as taking all or almost all of their pills in the past year (based on self-report and corroborated with physician verification of the prescription), in the intervention and control groups was identical (88.8% vs 88.5%, $P = .81$) (44). In the CARIATIDE study, compliance, defined identically, was not different between the two arms at 1 year (82% in intervention vs 81% in usual care, $P = .45$) and at 2 years of follow-up (82% in both arms, P value not reported) (42,43). Persistence also did not differ between groups in both PACT and CARIATIDE (42–44). Negative findings were reported in a smaller study that randomly assigned breast and ovarian cancer patients to "structured patient navigation" vs standard clinical care augmented with additional education and assistance linking patients to supportive resources (47). Among 44 evaluable breast cancer patients who started hormonal therapy, adherence did not differ as assessed by prescription records (both groups combined: 59%, no P value reported) (47). The Compliance in Adjuvant Treatment of Primary Breast Cancer Study was a three-arm single-institution trial conducted in Germany that randomly assigned 181 breast cancer survivors prescribed ET to two different interventions including either supplemental letters sent periodically together with an informational pamphlet or periodic telephone calls made by a nurse compared with a control group that was provided with standard information (53). At 1 year of follow-up, adherence, as assessed by a composite self-report and a medication possession ratio (MPR) of 80% or greater, was higher in the telephone (62.7%) and letter (64.7%) groups compared with the control arm (48.0%) (53). However, the differences between the three arms were not statistically significant (P value not reported) (53). In a posthoc analysis, the investigators grouped both interventions into a single arm and compared the combined-intervention arm with control, reporting a statistically significant difference ($P = .039$) in this comparison (53). Overall persistence was not statistically significantly different between arms ($P = .082$) (53).

Several randomized trials included patients prescribed different types of oral agents for a range of solid tumors or hematologic malignancies. A study of 200 patients treated at a single institution tested a comprehensive educational intervention led by a pharmacist that incorporated cognitive-behavioral components compared with a control group that only received pill monitoring by a nurse (78). Adherence of 90–100% as measured by pill counts was similar between the arms (87% vs 89%, $P = .807$) among 158 evaluable patients after 8 weeks (78). Another single-institution study randomly assigned 48 patients to a standard care education program or standard care education supplemented with an individualized, nurse-implemented program that included weekly or biweekly telephone calls (72). Adherence, assessed by self-report and prescription refill rates, was higher numerically in the intervention vs usual care group at 2 months (91.3% vs 80% by self-report; 80.0% vs 65.0% by refill rates) and at 4 months of follow-up (95.1% vs 82.4% by self-report; 73.7% vs 68.8% by refill rates); however, none of these differences were statistically significant, a finding the authors attributed to the small sample size (72). A study conducted in India randomly assigned patients to receive an educational intervention at study entry (intervention) or at the last appointment (control) (73). Among 60 evaluable patients, adherence as measured by the Medication Adherence Rating Scale (79) increased from 80% at study entry to 96.6% at the last follow-up (duration of follow-up not specified) in the intervention group, whereas in the control arm the proportion of adherent patients was the same (83.4%) at both time points (no P values reported) (73).

A multisite randomized trial conducted in Finland enrolling chronic myeloid leukemia (CML) patients taking TKIs tested an educational intervention that included in-person trainings with a nurse, complemented with an educational video, pamphlet, and website, as well as text messages to prompt patients to take their drug compared with standard care (57). Among 68 evaluable patients who completed the trial, there was a statistically significant increase in adherence, measured by change in

Table 1. Summary of key study attributes: randomized trials

Author	Country	Study population	Total sample size (randomly assigned or enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results*
Hadji et al. 2013 (44)	Germany	Breast cancer patients prescribed AIs	4844 randomly assigned, 2740 evaluable	Education, including letters and pamphlets; monthly prompts; small tokens (eg, pill box, exercise advice)	Standard care	Self-report	1 y	Adherence: 88.8%, intervention vs 88.5%, control, $P = .81$ Persistence: 43%, intervention vs 40.5%, control, $P = .18$)
Neven et al. 2014 and Markopolous et al. 2015 (42,43)	International (18 countries)	Breast cancer patients prescribed AIs	2758 randomly assigned, 2543 evaluable at 1 y, 2242 evaluable at 2 y	Education, including letters and pamphlets	Standard care	Self-report	2 y	Adherence: 1 y: 82%, intervention vs 81%, control; $P = .4524$ 2 y: 82%, intervention vs 82%, control, P value not reported Persistence: 1 y: 86%, intervention vs 84%, control; $P = .1359$ 2 y: 88%, intervention vs 90%, control, P value not reported
Ziller et al. 2013 (53)	Germany	Breast cancer patients prescribed AIs	181 randomly assigned, 171 evaluable	Two intervention arms: 1: letters with details on how to reach nurse if needed and information booklets; 2: informational phone calls from nurse	Standard care (information given at visits only)	Self-report; prescription or medical records	1 y	Adherence: Self-report+MPR Three-arm comparison Arm 1: 64.7%, arm 2: 62.7%, vs control: 48%, P value not reported Posthoc comparison Combined arm 1 + arm 2 vs control, $P = .039$ Persistence: Prescription or medical records Mean weeks persistent: arm 1: 44.7% vs arm 2: 42.8% vs control: 38.6%, $P = .082$
Schneider et al. 2014 (72)	United States	Patients prescribed oral anticancer agents	48 enrolled, 45 evaluable	Chemotherapy education + phone calls from nurse (content personalized to patient based on baseline evaluation)	Standard care (chemotherapy education only)	Self-report; prescription records	4 mo	Adherence: 2 mo Self-report 91.3% intervention vs 80% control Prescription records 80% intervention vs 65% control, P value not reported 4 months Self-report 95.1% intervention vs 82.4% control Prescription records 73.7% intervention vs 68.8% control, P value not reported

(continued)

Table 1. (continued)

Author	Country	Study population	Total sample size (randomly assigned or enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results*
Ramesh et al. 2015 (73)	India	Patients prescribed oral anticancer agents	97 enrolled, 80 randomly assigned, 60 evaluable	Education, including pamphlet at initial visit	Usual care (received education and pamphlet at end of study)	Self-report	Not evaluable†	Adherence: Change from first to last visit, 80% to 96.6% (intervention); no change (83.4% at first and last visit) in control group, *P* values not reported
Kekale et al. 2016 (57)	Finland	CML patients prescribed TKIs	86 randomly assigned, 68 evaluable	In-person meeting with nurse; educational pamphlets, video, and website; text message reminders	Standard care	Self-report	9 mo	Adherence (change from baseline to 9 mo): Intervention % with high MMAS-8 score 23%, baseline vs 51%, 9 mo % with medium MMAS-8 score 54%, baseline vs 46%, 9 mo % with low MMAS-8 score 23%, baseline vs 3%, 9 mo Overall, 49% improved from baseline, change from baseline to 9 mo, $P < .0001$ Control % with high MMAS-8 score 21%, baseline vs 20%, 9 mo % with medium MMAS-8 score 67%, baseline vs 61%, 9 mo % with low MMAS-8 score 12%, baseline vs 18%, 9 mo Overall, 18% improved from baseline, change from baseline to 9 mo, $P = .593$
Macintosh et al. 2007 (74)	Canada	Patients prescribed capecitabine for breast or GI cancer	25 randomly assigned, 24 evaluable after cycle 1, 18 with complete follow-up	Pill boxes with individual sections for doses	Conventional pill bottles	Self-report (diaries); pill counts	42 d; 2 cycles of treatment	Adherence‡: 81% intervention vs 86% control, *P* values not reported
Spoelstra et al. 2013 (75)	United States	Patients prescribed oral anticancer agents	119 randomly assigned, 119 evaluable, 91 evaluable at exit interview	3 intervention arms: 1) AVR system + SMT; 2) AVR + SMT + nurse-led adherence counseling by phone; 3) AVR + SMT + nurse-led symptom management and adherence counseling by phone	None	Self-report; prescription or medical records	10 wk	Adherence: Self-report Overall rate of 58% reported as similar across groups Prescription or medical records Overall rate of 67% reported (difference between groups not specified)

(continued)

Table 1. (continued)

Author	Country	Study population	Total sample size (randomly assigned or enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results*
Spoelstra et al. 2015 (76)	United States	Patients prescribed oral anticancer agents	80 randomly assigned, 68 evaluable at exit interview	Text messages + SMT + usual care	Usual care (SMT provided at end of study)	Self-report; prescription or medical records	10 wk	Adherence: Self-report Mean no. of weeks adherent: 5.95 wk intervention vs 5.95 wk control, $P = .99$ Exit interview 81% intervention vs 76% control, P value not reported Prescription or medical records RDI: 1.06 intervention vs 0.74 control, $P = .13$
Spoelstra et al. 2016 (77)	United States	Patients prescribed oral anticancer agents	75 randomly assigned, 69 evaluable at exit interview	Text messages + usual care (education by providers about medication regimen, including adherence, adverse effects and symptom management, how to reach provider if needed)	Usual care	Self-report; prescription or medical records	10 wk	Adherence: Self-report Mean no. of weeks adherent: 6.5 wk intervention, vs 7.2 wk control, $P = .26$ Exit interview 86.7% intervention vs 79.2% control, $P = .42$ Prescription or medical records Data collected but not evaluated
Kato et al. 2008 (70)	International (United States, Canada, Australia)	AYA patients (aged 13–39 y) with acute leukemia and non-Hodgkin's lymphoma§	375 randomly assigned, 304 evaluable, 54 evaluable for oral chemotherapy endpoint	Video game about issues of cancer treatment and care in adolescents and young adults	Commercial video game	Self-report ; 6-MP levels	3 mo	Adherence: Self-report (includes antibiotic regimen) Mean CDCI: 81 intervention vs 78.4 control, $P = .78$ Mean MAS: 2.9 vs 3.0, $P = .503$ Mean 6-MP levels 8499.1 intervention vs 8087.0 control, $P = .002$ (adjusted P)
Ell et al. 2009 (47)	United States	Breast cancer patients prescribed ET‖	237 breast cancer patients randomly assigned, 44 evaluable for tamoxifen, AI endpoint	Structured patient navigation included education, psychosocial support, and navigation to promote treatment access and adherence	"Enhanced" usual care: standard clinical care, assistance linking patients to financial and social support resources, brochure about depression and cancer	Prescription records	1 y	Adherence: 59% (both groups combined), no difference reported between groups

(continued)

Table 1. (continued)

Author	Country	Study population	Total sample size (randomly assigned or enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results*
Graetz et al. 2018 (48)	United States	Breast cancer patients prescribed AIs	48 randomly assigned, 43 evaluable	App (facilitating sharing of symptoms with providers and provider notification for high symptom levels or nonadherence) + email or text reminders	App only	Self-report	6–8 wk	Adherence: 100% intervention vs 72.7% control, $P < .05$
Krikorian et al. 2019 (78)	United States	Patients prescribed oral anticancer agents	200 randomly assigned, 173 evaluable at week 4, 158 evaluable at week 8	Pharmacist-directed individualized education, included in-person sessions that incorporated cognitive-behavioral components focused on potential contributors to nonadherence, managing side effects; printed information about medication regimen; phone follow-up	Nurse-conducted pill count	Pill counts; self-report; prescription records	8 wk	Adherence: Pill counts: Week 4 Intervention 90% vs 89% control, $P = .807$ Week 8 Intervention 87% vs 89% control, $P = .807$

*Unless other metric (eg, mean weeks or mean change in score) or timing specified, results represent the proportion adherent or persistent as defined by each study at the end of follow-up. AIs = aromatase inhibitors; AVR = automated voice response; AYA = adolescent and young adult; CDCI = chronic disease compliance instrument; CML = chronic myeloid leukemia; ET = endocrine therapy; GI = gastrointestinal; MAS = Medication Adherence Scale; MMAS = Morisky Medication Adherence Scale; 6-MP = 6-mercaptopurine; MPR = medication possession ratio; RDI = relative dose intensity; SMT = symptom management toolkit; TKI = tyrosine kinase inhibitor.
†Follow-up not reported, or study specified enrollment and/or assessment timing but duration of follow-up or timing of adherence assessment not explicitly described.
‡Summary measure of adherence outcome representing cumulative adherence between cycle 1 + 2; not specified whether based on self-report or pill counts.
§Overall sample includes patients with other hematologic and solid tumor diagnoses.
‖Overall sample includes breast and gynecologic cancer patients.

Morisky Medication Adherence Scale-8 (MMAS-8) scores (80) between baseline and follow-up at 9 months in the intervention group ($P < .0001$), whereas this change was statistically nonsignificant in the standard care arm ($P = .593$) (57).

A crossover trial of 25 patients with breast or GI cancer prescribed capecitabine randomly assigned participants to either a pill box with sections for each individual dose or a standard pill bottle. Patients randomly assigned to the pill box had similar levels of adherence compared with those randomly assigned to a standard pill bottle (81% for pill box vs 86% for standard bottle, *P* value not reported), though the pill boxes were well received and rated favorably by patients (74).

An increasing number of interventions have involved technological approaches, including automatic reminders, to optimize adherence. Following a feasibility study that enrolled 30 patients (81), a larger randomized pilot study randomly assigned 119 patients with different diagnoses and oral regimens to one of three intervention arms: a combination symptom management toolkit (SMT) and automated voice response (AVR) phone intervention; SMT+AVR and a nurse-led intervention (eg, sharing of behavior modification strategies) to help with symptoms and increase adherence; or an SMT+AVR and a nurse-led intervention only to increase adherence (75). During the 10-week study, adherence, defined as taking at least 80% of medication in the past week, was not statistically different between groups (75).

Two other randomized studies conducted by Spoelstra and colleagues tested a text messaging intervention for patients prescribed oral agents for a range of solid tumors and hematologic malignancies (76,77). In the first trial, 80 participants were randomly assigned to receive an SMT along with text messages each day for 3 weeks following enrollment (with an optional fourth week) reminding them to take their medicine and asking them to text back if they took it; an additional text was sent regarding symptom management each week of the trial (76). The average number of weeks adherent was identical in the intervention compared with control group (5.95 weeks, $P = .99$) and proportion adherent was marginally higher in the intervention vs control group (81% vs 76%, no *P* value reported) at the conclusion of the 10-week study. The second 10-week trial included 75 patients with the average number of weeks adherent (assessed by self-report) similar between the text messaging intervention group (6.5 weeks) and usual care group (7.2 weeks, $P = .26$) that only received information and instructions about their treatment regimen (77). There was also no statistically significant difference in self-reported adherence at the end of trial (86.7%, intervention vs 79.2%, control, $P = .42$) (77). In contrast to the results of these two studies, a feasibility study that randomly assigned 48 breast cancer patients prescribed AIs to a web-based application (app) that facilitated symptom self-reporting and provider notification for nonadherence or when symptoms reached an elevated level, or to the app alone, reported perfect adherence as assessed by the MMAS-4 in the group randomly assigned to the app with reminders vs 72.7% ($P < .05$) in the app without reminders group (49).

A trial designed for AYA cancer patients tested the impact of a cancer treatment-focused video game on several outcomes, including adherence to oral 6-MP in a subset of 54 patients with leukemia and or non-Hodgkin's lymphoma (70). Compared with the control video game arm, patients in the intervention group had higher plasma 6-MP metabolite levels ($P = .002$) at follow-up, although self-reported adherence (assessed by the Chronic Disease Compliance Instrument and the Medication Adherence Scale) was not different between groups (70).

Nonrandomized Studies With a Comparison Group

The ADHERE study tested a nurse practitioner–led in-person and telephone-based intervention for patients starting an oral anticancer treatment regimen (82) (Table 2). The intervention included education, motivational interviewing, and a short cognitive-behavioral therapy component (82). The adjusted mean number of weeks adherent did not differ between the intervention and usual care arms (5.45 vs 5.26 weeks, $P = .73$) (82).

A multisite Korean study enrolled patients on imatinib for CML and assigned one-half to a nurse-directed education program that combined provision of information, telephone support, and reminder text messages (55). When compared with patients who did not receive the intervention, persistence in the intervention arm was higher at 1-year (96.9% vs 86.6% $P = .002$), 2-year (97.5% vs 84.5%, $P = .001$), and 3-year follow-up (96.4% vs 82.0%, $P = .001$), whereas adherence measured by doses (milligrams of imatinib taken vs prescribed) was not statistically different between the two groups at any assessment point (55).

Gebbia et al. implemented an oral treatment monitoring program for patients with advanced NSCLC prescribed erlotinib (64). In addition to education about the drug and potential side effects, patients and their caregivers were told to contact their care team if they experienced any side effects or issues; a fast track visit system was also provided to facilitate evaluation, if needed (64). Compared with a retrospectively identified control group that had not been offered this program, adherence (≥95%) was higher as assessed by the Basel Assessment of Adherence Scale adapted for TKIs (91) (84% vs 72%, $P = .042$) and by pill counts, defined as proportion of drug taken vs prescribed (87% vs 78%, $P = .0021$) in the intervention cohort (64). A second self-report metric of adherence that used a visual analog scale was similar between groups (97%, intervention vs 94%, control, $P = .067$) (64).

Nonrandomized studies evaluating interventions aimed at improving adherence to ET in breast cancer survivors have demonstrated mixed results. Mean persistence (assessed by prescription refill rates) was high in both the information-based intervention and standard care groups after 1 year of follow-up (95.8% vs 95.9%, $P = .95$) in a study of breast cancer survivors on AIs (52). A quality improvement study targeting hormone receptor–positive breast cancer survivors enrolled in Medicaid used pharmaceutical records to identify women who were nonadherent, were nonpersistent, or had never started ET (51). The intervention involved a phone call from a Medicaid care plan manager in which ET recommendations were discussed and guidance regarding ET discussion with a physician; women were also informed that their plan fully covered ET (51). Of the 36 women identified as nonadherent who were reached by a care manager, 22 (61%) subsequently had a prescription filled following this contact and 50% (11 of 22) were adherent after 6 months (51). Among 31 women identified as nonadherent but who were never reached by a care manager, 16 subsequently filled a prescription (52%) and 25% (4 of 16) were adherent after 6 months (51). The differences between groups (50% vs 25%, $P = .11$) were not statistically significant, likely due to the small sample size (51).

Using a sequential cohort design, Levine et al. and Richardson et al. enrolled patients diagnosed with different hematologic cancers taking allopurinol and prednisone and compared the following different combinations with a standard care arm: education; a home visit by a nurse that incorporated various behavioral strategies; and "pill shaping," which included

Table 2. Summary of key study attributes: nonrandomized studies with a comparison group

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)*	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results†
Spoelstra et al. 2017 (82)	United States	Patients prescribed oral anticancer agents	61 consented, 54 evaluable, 40 evaluable at exit interview	In-person counseling with nurse practitioner at treatment initiation, follow-up phone calls addressing adherence, symptom management + usual care (education by providers about medication regimen, adverse effects and symptom management, medication reminder strategies, how to reach provider if needed)	Usual care	Self-report	8 wk	Adherence: Mean number of weeks adherent: 5.45 intervention vs 5.26 control, $P = .73$
Moon et al. 2012 (55)	Korea	CML patients prescribed imatinib	114 enrolled, 100 evaluable at year 3	Phone counseling by nurse, daily dose reminder texts, letters	Standard care	Prescription records	3 y	Adherence: Year 1: 96.4% intervention vs 96.9% control, $P = .387$ Year 2: 96.2% intervention vs 96.6% control, $P = .488$ Year 3: 96.5% intervention vs 96.6% control, $P = .958$ Persistence: Year 1: 96.9% intervention vs 86.6% control, $P = .002$ Year 2: 97.5% intervention vs 84.5% control, $P = .001$ Year 3: 96.4% intervention vs 82.0% control, $P = .001$
Yu et al. 2012 (52)	China	Breast cancer patients prescribed AIs	516 enrolled, 503 evaluable, 489 with complete follow-up	Education about breast cancer and oral hormonal treatment, periodic newsletters, reminder phone calls +standard care	Standard care	Prescription records	1 y	Persistence: Mean of 95.8% intervention vs mean of 95.9% control, $P = .95$
Wagner et al. 2016 (51)	United States	Nonmetastatic hormone receptor–positive breast cancer patients enrolled in New York State Medicaid	230 included in study cohort, 194 evaluable‡	For women identified as nonadherent or nonpersistent or had never initiated ET: Phone call from a Medicaid care plan manager where ET recommendations were discussed, guidance about discussing ET with their physician, and letting women know their plan fully covered ET	1) Women classified as adherent 2) Women eligible for phone call but could not be reached or did not finish all call content with care manager	Prescription records	6 mo	Adherence: 50% women who started out nonadherent but were reached by a care manager adherence vs 25% women not reached vs 86% women who started out as adherent, $P = .11$

(continued)

Table 2. (continued)

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)*	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results†
Gebbia et al. 2013 (64)	Italy	Non-small cell lung cancer patients prescribed erlotinib	217 screened, 150 evaluable	Oral treatment monitoring program: education for patient + caregiver; patients and their caregivers were told to contact their care team via phone, fax, or email if they experienced unexpected side effects or issues; a "fast track visit system" was also provided to facilitate evaluation	Usual care (education about side effects)	Self-report Pill counts	2 mo	Adherence: Self-report BAAS: 84% intervention vs 72% control; $P = .042$ VAS: 97% intervention vs 94% control, $P = .067$ Pill counts 87% intervention vs 78% control, $P = .0021$
Khandelwal et al. 2012 (83)	United States	Patients prescribed sorafenib, sunitinib, or erlotinib	754 enrolled and evaluable	Oral chemotherapy CMP: telephone-based education and support, conducted by nurses and pharmacists	Nonparticipation in program (historical controls)	Prescription records	6 mo	Adherence: Month 6: Mean MPR: 44.8% intervention vs 41.5% control, $P = .4016$ Persistence: Month 6: 23.8% intervention vs 7.8% control, $P = .0234$
Middendorff et al. 2018 (84)	United States	Patients prescribed abiraterone, capecitabine, dasatinib, erlotinib, everolimus, imatinib, pazopanib, regorafenib, sorafenib, or temozolomide	96 enrolled and evaluable	Specialty pharmacy case management program: financial help, pharmacist-led education, symptom management, and phone support provided by both nurses and pharmacists	Nonparticipation in case management program (historical controls)	Prescription or medical records	6 mo	Adherence: Mean MPR: 94.1% intervention vs 92.2% control, $P = .199$
Ribed et al. 2016 (85)	Spain	Patients prescribed dasatinib, nilotinib, sorafenib, pazopanib, gefitinib, erlotinib, imatinib, sunitinib, abiraterone, lenalidomide, thalidomide, or everolimus	249 enrolled, 215 evaluable at 1 mo, 112 evaluable at 6 mo	Pharmacist-led education and symptom management program	Nonparticipation in case management program (historical controls)	Prescription records	6 mo	Adherence: 1 month: 95.7% intervention vs 94.7% control, $P > .05$ 6 months: 95% intervention vs 87.7% control, $P = .025$
Lam and Cheung 2016 (58)	United States	CML patients prescribed TKIs	281 enrolled, 269 evaluable§	Oncology pharmacist-managed oral anticancer therapy program	Usual care	Prescription or medical records	Mean in intervention arm: 31.9 mo	Adherence: 88.6% intervention vs 65.8% control, $P < .0046$

(continued)

Table 2. (continued)

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)*	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results†
Simons et al. 2011 (86)	Germany	Colorectal and breast cancer patients prescribed capecitabine	50 enrolled, 48 evaluable	Pharmacist-led educational intervention that included information and addressed need for optimal adherence to medication; pamphlet with side effect management information; follow-up by phone	Standard care	Electronic pill monitoring	Mean in intervention arm: 89.7 d; Range: 9.0–137.5 Mean in control arm: 69.4 d; Range: 13.0–128.0	Adherence: Mean: 97.9 intervention vs 90.5% control, $P = .069$ Mean daily: 96.8% intervention vs 87.2% control, $P = .029$ Persistence: 83% intervention vs 48% control, $P = .019$
Tschida et al. 2012 (87)	United States	Patients prescribed oral anticancer agents	928 enrolled and evaluable‖	Specialty pharmacy program including educational component, notifications when a prescription was due to be refilled, and adherence monitoring; telephone follow-up	Retail pharmacy program	Prescription records	1 y	Adherence: Mean weighted MPR: 65.7% intervention vs 58% control, $P < .001$
Krolop et al. 2013 (88)	Germany	Patients prescribed capecitabine	78 enrolled, 73 evaluable	Pharmaceutical care and assistance with adverse effect management+ pharmacist-led intervention that used personalized approach to address individual patient challenges, expectations with adherence for patients classified as nonadherent	Pharmaceutical care and assistance with adverse effect management only for patients classified as adherent	Electronic pill monitoring	6 cycles of treatment	Adherence: In those categorized as nonadherent: Median daily adherence: 85.7% (first cycle) to 97.6% (sixth cycle) Mean daily adherence: 80.8% (first cycle) to >90% (sixth cycle) In those categorized as adherent: Median daily adherence: all cycles 100% Mean daily adherence: 98.9% (first cycle) to 97.3% (sixth cycle) Persistence: 100% (all patients) P values not reported
Levine et al. 1987 (60)	United States	Hematologic malignancy patients prescribed allopurinol and/or prednisone	108 enrolled and evaluable	3 intervention arms: 1) education + home visit by nurse that incorporated various behavioral strategies, including accounting for patient routines, prompts, and a contract involving patient and a relative who committed to aiding patient with adhering	Standard care	Self-report serum drug levels	6 mo	Adherence: Allopurinol Serum levels Arm 1: 45%, arm 2: 47.2% vs arm 3: 44.4% vs control: 16.8%, $P < .01$ Self-report

(continued)

Table 2. (continued)

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)*	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results†
				to treatment; 2) education + instruction on taking medication ("pill shaping"); 3) education + home visit + pill shaping				Arm 1: 92%, arm 2: 90% vs arm 3: 92.6% vs control: 53.8%, $P < .01$ Prednisone¶ Serum levels Arm 1: 38%, arm 2: 32.7% vs arm 3: 37.8% vs control: 26.8%, $P \geq .01$
Richardson et al. 1987 (62)	United States	Hematologic malignancy patients prescribed allopurinol and/or prednisone	92 enrolled and evaluable	3 intervention arms: 1) education + home visit by nurse that incorporated various behavioral strategies, including accounting for patient routines, prompts, and a contract involving patient and a relative who committed to aiding patient with adhering to treatment; 2) education + instruction on taking medication ("pill shaping"); 3) education + home visit + pill shaping	Standard care	Self-report serum drug levels	6 mo	Adherence: Allopurinol Serum levels Arm 1: 49.9%, arm 2: 49.5% vs arm 3: 45.2% vs control: 16.1%, $P < .05$ Self-report Intervention arms ranged from 90% to 93% vs control: 48%, $P < .01$ Prednisone¶ Serum levels Arm 1: 33.8%, arm 2: 36.1% vs arm 3: 35.8% vs control: 31.2%, $P \geq .05$
Kimura et al. 2017 (69)	Japan	Gastric cancer patients prescribed S-1 chemotherapy	134 enrolled	In-person pharmacist; education about medication, checking adherence and symptoms; advice about symptom management; supportive care given if necessary; pharmacist available by phone if needed	Nonparticipation in program (historical controls)	Medical records	1 y	Persistence Overall: 82.5% intervention vs 39.4%, $P < .0001$ Excluding those who discontinued because of recurrence or other reason: 91.7% intervention vs 55.2%, $P < .0001$
Conliffe et al. 2019 (66)	United States	Patients with genitourinary cancer prescribed oral anticancer agents	33 enrolled and evaluable	Oral agent monitoring program; pharmacist-led education and follow-up	Nonparticipation in program (historical controls)	Not specified	3 mo	Persistence: 73% intervention vs 59% control, $P = .7$
Todo et al. 2019 (67)	Japan	Renal cell carcinoma patients prescribed pazopanib	50 enrolled and evaluable	Pharmacist-directed monitoring program, in-person with phone follow-up with focus on addressing side effects, supportive care given if necessary, availability of phone consultation with pharmacist if needed	Nonparticipation in program (historical controls)	Self-report (drug diary)	Not evaluable#	Adherence: 100% intervention vs 62% control, $P < .001$

(continued)

Table 2. (continued)

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)*	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results†
Morgan et al. 2018 (89)	United States	Patients prescribed oral anticancer agents	122 enrolled and evaluable for self-report, 66 evaluable for prescription records	Pharmacist-directed oral chemotherapy management program including educational component, addressing side effects and adherence challenges, enhanced follow-up by pharmacy including phone reminders about refills	Nonparticipation in program (historical controls)	Self-report Prescription records	Not evaluable#	Adherence: Prescription records (no comparison group): Mean MPR: 92% Median MPR: 96% Self-report: Never forgetting to take medication: Intervention 76% vs 70% control, $P = .64$ Never cutting back on medication: Intervention 69% vs 77% control, $P = .68$

*For nonrandomized studies with comparison group, sample size represents totally analytic sample (eg, inclusive of historical controls). AIs = aromatase inhibitors; BAAS = Basel Assessment of Adherence Scale; CML = chronic myeloid leukemia; CMP = cycle management program; ET = endocrine therapy; MPR = medication possession ratio; TKI = tyrosine kinase inhibitor; VAS = visual analog scale.
†Unless other metric (eg, mean weeks or mean change in score) or timing specified, results represent the proportion adherent or persistent as defined by each study at the end of follow-up.
‡Sample size includes women initially classified as adherent (n = 163), women classified as nonadherent but were not reached (n = 31), and women classified as nonadherent and reached (n = 36).
§Includes usual care controls (n = 225) from previous study (90); included all TKIs but adherence in intervention arm only assessed in evaluable patients on imatinib (n = 44).
‖Propensity-matched sample (n = 464 in each arm).
¶Serum levels of prednisone evaluated in subset.
#Follow-up not reported or study specified enrollment and/or assessment timing but duration of follow-up timing of adherence assessment not explicitly described.

comprehensive education as well as nurse monitoring while the patient was hospitalized (60,62). Overall adherence was low among all groups, although better allopurinol adherence was observed in the intervention groups compared with the control. Prednisone adherence remained suboptimal among the intervention groups (60,62).

A more recent strategy to improve adherence to oral antineoplastic drugs involves implementing pharmacy-monitoring programs, several of which have focused on improving adherence among patients prescribed newer targeted therapies. A chemotherapy cycle management program (CMP) study reported by Khandelwal et al. included comprehensive and integrated telephone-based education and support conducted by nurses and pharmacists available to patients on sorafenib, sunitinib, or erlotinib (83). If the patient experienced a grade 2 or 3 adverse event, the patient's doctor was notified. The program was evaluated retrospectively using data from a national payer database, with a historical control cohort of patients enrolled before the CMP (83). Adherence (as assessed by the MPR) after 6 months of follow-up was modestly higher numerically in the CMP cohort compared with the control group; however, the difference was not statistically significant (mean MPR = 44.8% vs 41.5%, $P = .4016$); persistence was statistically significantly higher in the CMP cohort vs control (23.8% vs 7.8%, $P = .0234$) (83). In a pharmacy claims analysis, Middendorff et al. evaluated the effectiveness of a similar program that also included integrated pharmacist and nurse education and support, management of symptoms, and financial help for patients prescribed a wide range of oral anticancer therapies (84). Compared with a preintervention cohort, there was numerically, but not statistically, higher adherence (MPR $\geq$ 80%) in the intervention group compared with historical controls (94.1% vs 92.2%, $P = .199$) (84). In a study by Morgan et al., patients who used an oral chemotherapy specialty pharmacy program were not statistically significantly more likely than historical controls to report never forgetting to take their medication (76% vs 70%, $P = .64$) or never cutting back on their medication (69% vs 77%, $P = .68$) (89).

A Spanish tertiary care center introduced a pharmaceutical care program, aligned with American Society of Clinical Oncology guidelines, in which pharmacists educated patients at the start of an oral regimen, subsequently following up with two additional interactions at 1 month and 6 months after starting therapy aimed at addressing side effects and adherence (85). Compared with historical controls, adherence (MPR > 90%) was similar in the two groups at 1 month (95.7%, intervention vs 94.7%, historical control, $P > .05$) but statistically significantly higher in the intervention cohort at 6 months (95.0%, vs 87.7%, $P = .025$) (85).

Several other pharmacist-directed education interventions have demonstrated some efficacy in improving adherence. One study retrospectively evaluated CML patients who participated in a program that included an educational component as part of a consult with a pharmacist and then regular follow-up conducted by the pharmacist to check adherence and side effects (58). The proportion of participants who were adherent (MPR $\geq$ 90%) was higher in the intervention arm compared with the proportion among controls who received usual care (88.6% vs 65.8%, $P < .0046$) (58). Average total adherence, measured by Medication Event Monitoring System (MEMS) pill bottles among breast and colorectal cancer patients taking capecitabine who participated in a pharmacist-directed educational intervention that included provision of information as well as follow-up by phone, was slightly higher compared with a standard care group (97.9% vs 90.5%, $P = .069$); average adherence measured on each day was also greater in the intervention group (96.8% vs 87.2%, $P = .029$) (86). Persistence was also higher in the intervention group vs standard care arm (83% vs 48%, $P = .019$) (86). A Japanese study enrolling gastric cancer patients prescribed S-1 chemotherapy reported statistically significantly higher persistence (ascertained from medical records) 1 year after the introduction of pharmacist-led education about the treatment and side effect management compared with historical controls (overall: 82.5% vs 39.4%, $P < .0001$; excluding patients who discontinued because of cancer recurrence or another reason, 91.7% vs 55.2%, $P < .0001$) (69).

Another study assessed a specialty pharmacist program that included education, phone calls, notifications when a prescription was due to be refilled, and an adherence evaluation for pharmacy beneficiaries (87). Individuals for whom adherence was thought be a problem were contacted by pharmacists or pharmacy nurses who delivered additional informational and supportive care content, services to help patients with costs, as well as connected patients with a doctor if needed (87). Compared with a matched retail pharmacy control group, adherence, as assessed by the MPR, was higher in the intervention group (65.7% vs 58%, $P < .001$) (87).

A German study enrolled 78 patients on capecitabine treated at two different hospitals (88). While those categorized as adherent received pharmaceutical care and adverse effect management, a subset (n = 15) categorized as nonadherent (<90% adherence as assessed by MEMS following the first cycle of chemotherapy) received pharmaceutical care, adverse effect management, plus a tailored intervention delivered by a pharmacist based on whether nonadherence was intentional (eg, if due to bothersome symptoms, there was additional attention to symptom amelioration) or nonintentional (eg, medication journals or "cue dosing" to address not remembering to take the drug) delivered by a pharmacist (88). Following the introduction of the intervention, median daily adherence went from 85.7% (first cycle) to 97.6% (sixth cycle) in the nonadherent group, and the group that was classified as adherent at baseline (median daily adherence = 100%) remained highly adherent following the sixth cycle of treatment (100%) (88). Persistence in both adherent and nonadherent patients (excluding those whose treatment was stopped early by a doctor) was 100% (88).

Two studies with similar pharmacist-led monitoring programs that enrolled patients with genitourinary malignancies had mixed results. Todo et al. reported perfect adherence (self-reported in drug diaries) in the 37 patients with renal cell carcinoma prescribed pazopanib enrolled in the intervention arm, statistically significantly ($P < .001$) higher than the 62% reported among the 13 historical controls (67). In contrast, persistence (method of assessment not specified) was numerically but not statistically significantly higher in the intervention group vs historical controls (73% vs 59%, $P = .7$) in a study inclusive of 33 patients with renal cell carcinoma, prostate cancer, or angiolipoma of the kidney (66).

Single-Arm Studies With Pre and Post Comparison

In an Italian study, a pharmacist provided 123 patients prescribed TKIs with a drug diary along with information about side effects and instructions regarding what to do if a dose was skipped (63) (Table 3). Evaluable patients included those who filled out the diary (n = 44). Although median time using the diary varied (median = 246 days), adherence (measured with prescription records) was higher with the diary when matched and

Table 3. Summary of key study attributes: single arm pre and post comparison

Author	Country	Study population	Total sample size (enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence or persistence measurement	Duration of study follow-up	Results*
Chieng et al. 2013 (56)	Australia	Patients who received allogeneic stem cell transplant	23 enrolled, 17 evaluable	Weekly in-person pharmacist consultations	N/A	Self-report	6 wk	Adherence: 100% Mean change in MMAS score from wk 0–6: 1.53, $P < .0001$
Santoleri et al. 2019 (63)	Italy	CML patients prescribed TKIs	123 received intervention, 44 evaluable (used diary)	Pharmacist provided drug diary + information about side effects as well as instructions regarding what to do if a dose is skipped	N/A	Self-report (drug diary) Prescription records	Median of 246 d using intervention (diary)	Adherence: Self-report (time period with diary only): 97.4% Prescription records: 86.5% without diary vs 93.6% with diary, $P = .0007$
Moon et al. 2019 (49)	United Kingdom	Breast cancer patients prescribed tamoxifen: all nonadherent at baseline	41 consented, 27 evaluable	Education about tamoxifen, potential side effects, communication and supportive resources; cognitive-behavioral therapy component and SMART goal setting	N/A	Self-report	Mean of 7 wk (range = 2–12 wk)	Adherence: Mean MARS score 22.8 pre vs 23.1 post, $P = .391$ 0% pre vs 9% post *P* value not reported
Leader et al. 2018 (59)	Israel	CML patients prescribed TKIs	58 enrolled and 45 evaluable	Multilevel intervention; Motivational interviewing conducted by nurse; peer support group for patients; educational seminar for patients in group-based setting; pharmacist education about potential drug interactions and how to correctly take the medication	N/A	Electronic pill monitoring	7 mo	Adherence: Adherent patients at baseline: 97.1% pre vs 98.1% post, *P* value not reported Nonadherent patients at baseline: 71.2% pre vs 79.6% post, $P = .04$
Linder et al. 2019 (71)	United States	AYA patients (aged 15–29 y) prescribed oral anticancer and/or supportive care agents	23 enrolled and evaluable	App with features that facilitated scheduling of medication reminders, adherence tracking	N/A	Electronic pill monitoring	3 mo	Adherence: No statistically significant change pre- to postintervention, $P > .05$
Moulin et al. 2017 (61)	Brazil	CML patients prescribed TKIs	23 enrolled and evaluable	Monthly pharmacist monitoring, education about CML, TKIs, and importance of adhering to treatment	N/A	Self-report	4 mo	Adherence: 65.2% pre vs 100% post, $P = .0135$

*Unless other metric (eg, mean weeks or mean change in score) or timing specified, results represent the proportion adherent or persistent as defined by each study at the end of follow-up. AYA = adolescent and young adult; CML = chronic myeloid leukemia; MARS = Medication Adherence Rating Scale; MMAS = Morisky Medication Adherence Scale; N/A = not applicable; SMART = Specific, Measurable, Attainable, Relevant and Time-bound; TKI = tyrosine kinase inhibitor.

compared with time periods before and after the diary was used (86.5% vs 93.6%, $P = .0007$) (63). In a single-institution Australian study of 23 patients, pharmacists met weekly with patients following their stem cell transplants for 6 weeks to manage medication issues; adherence was assessed each week with a four-item version of the MMAS (56). There was a statistically significant decrease in average MMAS score (1.53, 95% confidence interval = 1.12 to 1.94, $P < .0001$) from week 1 to week 6, and of the 17 evaluable patients at the 6-week assessment point, all had an MMAS score of 0, indicating high adherence (56).

A study testing a mobile health (mHealth) app that facilitated scheduling of medication reminders and adherence tracking enrolled 23 AYA patients prescribed oral anticancer and/or supportive care agents for the treatment of hematologic malignancies or solid tumors (71). Adherence was measured with electronic monitoring caps each week and was not different throughout the 8-week intervention compared with adherence measured during the 4 weeks before the intervention ($P > .05$) (71).

The Israeli multisite TAKE-IT study used a prepost design to evaluate a multilevel intervention that included motivational interviewing conducted by a nurse, a patient support group, educational seminar, and pharmacist education about potential drug interactions and how to correctly take the medication among CML patients prescribed TKIs (59). Patients who were adherent (≥90% assessed by MEMS) before the introduction of the intervention remained adherent postintervention (97.1% vs 98.1%, P value not reported), and among those classified as nonadherent (<90%) preintervention, there was improvement when assessed postintervention (71.2% vs 79.6%, $P = .04$) (59).

Other interventions have demonstrated mixed results. A single-institution Brazilian study that enrolled 23 CML patients prescribed TKIs also reported a statistically significant improvement ($P = .0135$) from 65.2% preintervention to 100% adherence when measured 4 months after introduction of education and monthly pharmacist monitoring (61). A feasibility study conducted in the United Kingdom targeted breast cancer patients identified as nonadherent with a 4- to 6-week intervention that combined education about tamoxifen, side effects, and supportive resources, a cognitive-behavioral therapy component, and phone follow-up (49). Among 27 evaluable patients, there was a statistically nonsignificant ($P = .391$) change in Medication Adherence Rating Scale scores from 22.8 (pre) to 23.1 (post), with the proportion adherent increasing from 0 to 9% (49).

Single-Arm Studies With No Comparison

A nurse-led intervention for patients beginning treatment on erlotinib for NSCLC used the Multinational Association for Supportive Care in Cancer Oral Agent Teaching Tool as part of a combination in-clinic and telephone-based educational intervention (65) (Table 4). Self-reported adherence (assessed 6–8 weeks following the start of treatment) among 27 evaluable patients enrolled in this single-arm feasibility study was high with an average MMAS-8 score of 7.12 (65). Following the completion of the first cycle of treatment, self-reported adherence was high (mean MMAS-8 score = 7.89) in a similarly designed feasibility study that included 30 patients with GI cancer that introduced both oral and print education from either a doctor or nurse practitioner, with telephone follow-up and additional teaching by a nurse (68). Almost all patients (95.8%) reported perfect adherence to their medication among those enrolled in a small pilot study where nurses used the electronic medical record to track symptoms, all oral medications, dosing, and adherence (98). Among participants of the Italian-based "Active Home Care" program, where patients received their oral antineoplastic drugs from a nurse who visited each week, all were reported adhering to their regimen as prescribed (92,93).

Heisig et al. enrolled more than 100 German breast cancer survivors on tamoxifen or an aromatase therapy and provided them with a pamphlet with "enhanced information" relevant to their therapy, including benefits of ET and symptoms associated with ET (54). After 3 months of follow-up, 6.6% were classified as "nonadherent," defined as taking less than 80% of therapy (54). Barlow et al. conducted a qualitative study that evaluated the impact of a 10-week "spiritual healing" holistic medicine intervention among breast cancer survivors experiencing side effects while on ET. All women said they had not contemplated stopping their medication during the 10 weeks (46). A pilot study targeting ET adherence in breast cancer survivors tested a text messaging intervention that included reminders in combination with messages that addressed adherence challenges, side effect monitoring, refill notifications, and provider notification if a patient demonstrated a pattern of nonadherence or was experiencing a high symptom burden (50). Among all 100 women enrolled, adherence (≥80% adherent) was 85.1%; among 89 women who finished the 3-month study, adherence was 93.3% (50). A 10-week pilot study enrolling CML patients prescribed imatinib also included text messages to remind patients about taking their medication along with tailored information based on side effect profile and nurse phone follow-up that used motivational interviewing to encourage adherence and utilization of strategies to manage side effects (45). Adherence was assessed based on participant response to a text about whether they took their medication; at the end of the pilot, adherence (≥90%) was 66.7% among the nine evaluable patients (45).

Several pharmaceutical management and monitoring interventions, generally inclusive of some combination of education, instruction about adherence and symptom management strategies, in combination with phone and/or in person follow-up, have been evaluated in small samples with no standard care or historical control comparison. Adherence to oral medications in these studies was fairly high, including one study where adherence (assessed by prescription records) was 82.4% (94) and another where average adherence (calculated based on number of pills not taken) was 98.9% (95). In a third study, 70% of a cohort of 30 patients followed for 3 months after the incorporation of an oral chemotherapy management program reported never skipping their medication (96), with a follow-up study reporting a persistence (ascertained by medical record review) rate of 78% among 41 patients (101). An Australian study that assessed self-reported adherence (missed dose because of forgetting or any other reason) midcycle and at the end of the second cycle of treatment reported an adherence of 77.8% among 18 and nine patients prescribed different oral agents who were evaluable at each time point, respectively (99). The pharmacist-led intervention in Japan for patients on S-1 chemotherapy that demonstrated improved persistence compared with historical controls (69) documented "good" adherence (93.2%) among 44 patients surveyed about the intervention in a separate study (97). Overall self-reported adherence was 89%, with patients with breast or GI cancer less adherent (self-report = 86%, MPR = 85%) than those with hematological malignancies (self-report = 94.7%,

Table 4. Summary of key study attributes: single-arm studies, no comparison

Author	Country	Study population	Total sample size (Enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence persistence measurement	Duration of study follow-up	Results*
Decker et al. 2009 (81)	United States	Patients prescribed oral anticancer agents	30 enrolled and evaluable	AVR system + SMT; follow-up phone call from nurse if patient identified as nonadherent or experiencing high symptom burden	N/A	Self-report; Prescription or medical records	10 wk	Adherence: Prescription records: 76.7%
Boucher et al. 2015 (65)	United States	Non-small cell lung cancer patients prescribed erlotinib	30 enrolled, 27 evaluable	In-person and phone nurse-directed education that used MASCC-MOATT materials	N/A	Self-report	6–8 wk	Adherence: Mean MMAS score at study completion: 7.12 (SD = 1.01)
Sommers et al. 2012 (68)	United States	GI cancer patients prescribed ≥1 oral anticancer agent	30 enrolled and evaluable	Oral and print education, nurse-initiated educational phone call	N/A	Self-report	One cycle of treatment	Adherence: Mean MMAS score at study completion: 7.89 (SD: 0.55)
Heisig et al. 2014 (54)	Germany	Breast cancer patients prescribed ET	174 enrolled, 137 evaluable	Supplementary education about ET	N/A	Self-report	3 mo	Adherence: 93.4%,
Bordonaro et al. 2012 (92)	Italy	Patients prescribed capecitabine, vinorelbine, imatinib, sunitinib, sorafenib, temozolomide, or ibandronate	30 enrolled and evaluable	Home-based program: treatment brought to patient's home; adherence or toxicity monitoring; phone number for patients to call if needed	N/A	Self-report; Provider observation	Not evaluable†	Adherence: 100%
Bordonaro et al. 2014 (93)	Italy	Patients prescribed capecitabine, vinorelbine, imatinib, sunitinib, sorafenib, temozolomide, or ibandronate	62 enrolled and evaluable	Home-based program: treatment brought to patient's home; adherence or toxicity monitoring; phone number for patients to call if needed	N/A	Self-report	Not evaluable†	Adherence: 100%
Battis et al. 2017 (94)	United States	Patients prescribed abiraterone, capecitabine, chlorambucil, crizotinib, dasatinib, enzalutamide, hydroxyurea, ibrutinib, imatinib, nilotinib, pazopanib, sorafenib, sunitinib, temozolomide, or topotecan	68 enrolled and evaluable	Pharmacist-directed oral chemotherapy monitoring clinic; education and instruction about adherence, symptoms, dose schedules, additional interaction with patients if identified as nonadherent	N/A	Prescription records	Not evaluable†	Adherence: 82.4%
Riu et al. 2018 (95)	Spain	Patients prescribed oral anticancer agents	83 enrolled and evaluable	Integrated pharmaceutical care program; education about taking medication, taking other medications, adherence; symptom management	N/A	Pill counts	Not evaluable†	Adherence: Mean = 98.9%
	United States				N/A	Self-report	3 mo	Adherence: 70%

(continued)

Table 4. (continued)

Author	Country	Study population	Total sample size (Enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence persistence measurement	Duration of study follow-up	Results*
Wong et al. 2014 (96)		Patients prescribed capecitabine, erlotinib, everolimus, hydroxyurea, lapatinib, lenalidomide, neratinib, or tamoxifen	30 enrolled and evaluable	Pharmacist-directed oral chemotherapy management program; included in person and phone follow-up, education about the medication and side effects, tailored information about handling side effects				Persistence: 70%
Kimura et al. 2017 (97)	Japan	Patients prescribed regorafib; trifluridine or tipiracil; tegafur; gimeracil, oteracil potassium, or lenvatinib‡	47 enrolled, 44 evaluable	Pharmacist-directed education about medication, side effects (including checking side effects); advice about symptom management; general lifestyle recommendations; phone consults available	N/A	Self-report	1 mo	Adherence: 93.2%
Rodriguez et al. 2017 (98)	United States	GI, breast, hematology, neurology patients	71 enrolled and evaluable	Nurse-led tracking of symptoms, oral medications, dosing, and adherence via the electronic medical record	N/A	Self-report (documented by nurses)	Not evaluable†	Adherence: 95.8%
Pereira-Salgado et al. 2017 (45)	Australia	CML patients prescribed imatinib	10 consented, 9 evaluable	Multilevel intervention including mHealth component with text message to remind patients about taking their medication and information based on the patients' side effect profile in combination with nurse phone follow-up that used motivational interviewing to encourage adherence and as well as use of strategies to manage side effects	N/A	Self-report	10 wk	Adherence: 66.7%
Mougalian et al. 2017 (50)	United States	Breast cancer patients prescribed ET	100 enrolled and evaluable, 89 evaluable for complete data at end of study	Text message reminders and messages addressing adherence challenges, side effect monitoring; notifications to refill medication; notifications to provider if pattern of nonadherence identified or if high levels of side effects reported	N/A	Self-report	3 mo	Adherence: Overall: 85.1% Among patients who finished study: 93.3%

(continued)

Table 4. (continued)

Author	Country	Study population	Total sample size (Enrolled and evaluable at end of follow-up)	Intervention	Control or comparison group (if applicable)	Method of adherence persistence measurement	Duration of study follow-up	Results*
Barlow et al. 2013 (46)	United Kingdom	Breast cancer patients prescribed ET	12 enrolled and evaluable	"Spiritual healing" holistic medicine intervention	N/A	Self-report	10 wk	Adherence: 100%
Byrne et al. 2018 (99)	Australia	Patients prescribed capecitabine, temozolomide, pazopanib, olaparib, etoposide, afatinib, everolimus, vinorelbine, or abiraterone	29 consented, 18 evaluable at end of cycle 1, 9 evaluable at the end of cycle 2	Pharmacist-directed education that used MASCC-MOATT materials; phone or in-person follow-up to address side effects, additional education if needed	N/A	Self-report	2 cycles of treatment	Adherence: 77.8% (at end of both cycle 1 and cycle 2)
Muluneh et al. 2018 (100)	United States	Patients prescribed bosutinib, imatinib, nilotinib, ibrutinib, idelalisib, sorafenib, dasatinib, bexarotene, capecitabine, everolimus, lapatinib, regorafenib, or temozolomide	107 enrolled and evaluable	Pharmacist-directed oral chemotherapy program management including educational component, adherence monitoring, side effect, drug interaction management	N/A	Self-report Prescription records	Not evaluable†	Adherence: Overall Self-report: 89% Hematological malignancies: Self-report: 94.7% Prescription records: 93.9% Breast/GI cancer: Self-report: 86% Prescription records: 85%
Wong et al. 2016 (101)	United States	Patients prescribed capecitabine, erlotinib, everolimus, lenalidomide, neratinib, hydroxyurea, pazopanib, letrozole, anastrozole, tamoxifen, abiraterone, imatinib, sorafenib, sunitinib, lapatinib, or bosutinib	86 enrolled, 41 evaluable	Pharmacist-directed oral chemotherapy management program; including in-person and phone follow-up, education about the medication and side effects	N/A	Medical record	3 mo	Persistence: 78%

*Unless other metric (eg, mean weeks or mean change in score) or timing specified, results represent the proportion adherent or persistent as defined by each study at the end of follow-up. AVR = Automated voice response; CML = chronic myeloid leukemia; ET = endocrine therapy; GI = gastrointestinal; MASCC-MOATT = Multinational Association of Supportive Care in Cancer Oral Agent Teaching Tool; MMAS = Morisky Medication Adherence Scale; MPR = medication possession ratio; N/A = not applicable; SMT = symptom management tool kit.

†Follow-up not reported, or study specified enrollment and/or assessment timing but duration of follow-up or timing of adherence assessment not explicitly described.

‡Part of larger study that also included adherence to supportive care prescriptions; subset only includes patients prescribed oral anticancer agents.

MPR = 93.9%) among those who participated in a pharmacy program also described by Morgan et al. (89,100).

Discussion

Numerous observational studies have sought to improve the understanding of the problem of nonadherence to oral anticancer agents, detailing the prevalence of and factors associated with nonadherence to treatment for a variety of types of cancers (24–26). The present review documents the increasing number of interventions developed to enhance adherence to these agents in more recent years. However, few are RCTs. Among the 14 randomized trials, only three reported a positive effect of the intervention on a prespecified adherence outcome (48,57,70), and a fourth study reported a statistically significant effect in a posthoc analysis where two different intervention arms were combined (53). Findings from RCTs with large sample sizes were disappointing, including from two trials that enrolled postmenopausal women prescribed AIs following a diagnosis of hormone receptor–positive breast cancer, suggesting that simply providing women with information is insufficient (42–44).

The implementation of pharmaceutical monitoring programs to improve adherence with oral antineoplastic agents appeared to be successful in some settings, which is consistent with findings from studies of medication adherence interventions tested in other diseases, where pharmaceutical-directed approaches have been found to be the most effective (102). Although the efficacy of the pharmacist-directed programs we identified in our review should be considered in the context of their evaluation, which in many cases was in comparison with historical controls, the success of these interventions may be attributed to the intensive monitoring and/or serial follow-up where providers (eg, pharmacists and/or nurses) were able to check in with patients. Anticipation of a weekly call from a nurse or pharmacist may help a patient remember to take their medication. Individualized attention may help patients manage acute problems while supporting patient goal-setting and encouraging patients to remain focused on these goals (102). Systematic monitoring of adherence also supports a targeted approach by identifying, through clinic or pharmacy records, individuals who are nonadherent or are at risk for nonadherence who are likely to benefit most from intensive follow-up. Importantly, we identified only one pharmacist-directed intervention that was tested in a randomized trial, with results of this study showing no difference between the intervention and control arms (78). However, this was a single-institution study, and given that pharmacist monitoring has demonstrated some efficacy, additional prospective, randomized studies are warranted to evaluate these types of interventions more conclusively.

The wide penetration of mobile technologies has led to the emergence of new platforms for adherence intervention delivery. In total, we identified eight studies that used an mHealth tool and/or text messages. Of the studies we identified that incorporated text messaging, those enrolling one disease type appeared to be more effective, with one reporting a positive impact on persistence (55) and another on adherence (57); a third study reported improved adherence associated with an app with email or text reminders compared with the app alone (48). In contrast, those that enrolled patients representing a spectrum of different diagnoses did not report statistically significant improvements (71,76,77). Although there are commonalities that span across disease types and patient populations, a "one-size-fits-all" approach to adherence interventions in cancer patient populations may not be an ideal model. Although text messages generally serve as reminders to take a medication and address one barrier to adherence, designing a more comprehensive application that targets intentional nonadherence may be more effective.

Interventions should also be tailored to the needs of patient populations that may experience specific challenges, such as young cancer patients. Whereas an mHealth intervention tested in a small group of AYA survivors did not statistically significantly improve adherence (71), a video game designed for AYA patients demonstrated a measurable and statistically significant impact on adherence as indicated by 6-MP metabolite levels in that population (70). The authors did note another challenge: compliance with the intervention itself, with only 28% of patients playing the game each week for a full hour as intended (70). Clearly, intervention implementation can be difficult even in well-controlled research studies. Strategies to promote engagement may enhance their ability to improve adherence and associated disease outcomes (103).

Studies to evaluate medication adherence in oncology and other chronic disease settings have often identified potentially modifiable factors, such as beliefs, perceptions, and knowledge, as contributors to nonadherence (104–107). In theory, these associations support the development of interventions based on widely used conceptual models and frameworks (105,108). In a meta-analysis that quantified the impact of theory-driven interventions on adherence, of 683 eligible articles that described an intervention, only 18% were associated with a specific theory or model (109). The authors concluded that although those interventions grounded in theory did have a statistically significant effect on adherence outcomes, they described this effect as "modest" (109). Of the 14 randomized studies in this review, seven described a theoretical or conceptual framework that influenced or informed the intervention (47,53,70,72,75–77). Of these, Kato et al. (70) and Ziller et al. (in a posthoc analysis) (53) reported statistically significant improvements in the intervention arms. The complex and multifactorial contributors to nonadherence clearly make selecting an appropriate conceptual model and formulating an intervention based on that model challenging and represent an area in need for further attention.

The focus of this review was not to evaluate the methods of adherence assessment; however, the variability of measures and definitions of adherence can make it challenging to compare outcomes across studies. Additionally, it is critical to address heterogeneity regarding cancer type, prognosis, age, and oral regimen within study samples in both the design and analytic plans of randomized and nonrandomized trials. Other issues for consideration are the potential for causal inference, generalizability, scalability, dissemination, and sustainability. There is also the potential for social or cultural factors to affect intervention design, implementation, and potential for efficacy. Given that several of the studies we reviewed were conducted internationally, these contextual factors should be considered when interpreting study outcomes.

Nonadherence to oral treatment spans across diagnoses and regimens, thus developing, testing, and delivering interventions that help the increasing number of cancer patients who will be prescribed oral drugs as part of their treatment is critical. Understanding what strategies are useful, how these strategies work, and for whom they are most effective should be a priority to ensure that all patients achieve maximum therapeutic benefit.

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