Review

Interventions to enhance adherence to oral anti-neoplastic agents: A Scoping Review

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Abstract

Background: As new targeted oral anti-neoplastic 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 anti-neoplastic 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. The majority of interventions were education and counseling-based and centered on provision of information about the drug and strategies to manage side effects. Only 8 studies used an mHealth tool and/or text messages to target non-adherence. Among studies with a comparison sample, fewer than 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 anti-neoplastic therapies has increased recently, few have been rigorously tested. The nascent literature suggests those that are pharmacist-directed and utilize 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 non-adherence to oral anti-neoplastic treatment.
Over the last two decades, administration of oral anti-neoplastic drugs has accelerated in both curative and palliative settings. A primary challenge of oral anti-neoplastic treatment is ensuring patients take their medication as indicated (i.e., adherence) and for the recommended duration (i.e., 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 non-adherent to their prescribed therapy are multi-factorial 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 non-adherence, including stopping treatment early (i.e., non-persistence) [7-11], although the association between experiencing symptoms or adverse effects and non-adherence 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 non-adherent if they a suffer from co-morbid conditions [17]. Access and costs are systems issues critical for some patients, with higher co-pays [18-20] and frequency of refills also impacting adherence [21]. In addition, simply not remembering to take ones' medication (e.g., unintentional non-adherence) has been identified as a contributor to sub-optimal 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
non-randomized 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 prior to 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 anti-cancer 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 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 anti-neoplastic 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.

Methods

Search strategy

Given the broad research objective, the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines
were followed [39]. The search strategy (Supplementary Methods) was designed to identify studies that evaluated interventions to improve adherence to oral anti-neoplastic 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 (SR and LN) 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 (AP) adjudicating articles without consensus agreement or questions about relevance. A single reviewer (SR) also reviewed reference lists of relevant review articles and of studies meeting inclusion criteria for additional studies. One reviewer (SR) independently assessed the quality of each included study with the Mixed Methods Appraisal Tool (MMAT) v2018, with approximately 20% selected for review by a second reviewer (LN). The MMAT allows for the evaluation of different study types, with each study graded on 7 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 (e.g., if limited to certain diagnoses/drugs vs. range of oral anti-cancer agents), sample size, a description of the intervention, methods of adherence assessment (e.g., self-report, prescription records) duration of study follow-up, and adherence results, defined as the proportion adherent/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. Of these, 52 met inclusion criteria, with an additional 4 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 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 5,000 breast cancer patients [44] and the smallest inclusive of 9 evaluable patients [45].

Eleven studies enrolled breast cancer patients prescribed ET [42-44, 46-54], 10 studies enrolled patients with hematologic malignancies [41, 45, 55-62], two studies included only non-small cell lung cancer patients [63, 64], two studies genitourinary cancer patients [65, 66], and two studies enrolled only gastrointestinal (GI) cancer
patients [67, 68]. For the remaining studies, multiple cancer diagnoses were eligible for inclusion. Among the non-breast cancer studies, the types of oral anti-neoplastic agent prescribed included tyrosine kinase inhibitors (TKIs), capecitabine, prednisone, and oral 6 mercaptopurine (6-MP), among other agents. With the exception of two studies that focused on adolescent and young adult (AYA) cancer patients [69, 70], 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 non-randomized studies of interventions with comparison data, there was 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 due to the lack of information about sampling strategy and representation. Additionally, a number of studies in this category that used self-report to assess adherence did not document the use of a validated measure.

Randomized trials (Table 1)

Two large RCTs enrolled post-menopausal women on aromatase inhibitors (AIs) for hormone-receptor positive breast cancer [42-44]. The Patient’s Anastrozole Compliance to Therapy (PACT) study randomized over 4,000 German women to an educational intervention which included mailed letters and pamphlets over the year following AI initiation, prompts each month to remind women to remain on therapy, as well as 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 to PACT, with CARIATIDE randomizing
over 2,700 women from 18 countries [42, 43]. The studies also had similar results: in PACT, compliance with treatment at one 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=0.81) [44]. In the CARIATIDE study, compliance, defined identically, was not different between the two arms at one year (82% in intervention vs. 81% in usual care, p=0.45) and at two 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 randomized 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 (COMPAS) was a three arm, single-institution trial conducted in Germany that randomized 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 to a control group that was provided with standard information [53]. At one-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 to the control arm (48.0%) [53]. However, the differences between the three arms were not statistically significant (p-value not reported) [53]. In a post-hoc analysis, the investigators grouped both interventions into a single arm and compared the combined-intervention arm vs. control, reporting a statistically significant difference (p=0.039) in this comparison [53]. Overall persistence was not statistically significantly different
between arms (p=0.082)[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 to a control group that only received pill monitoring by a nurse [71]. Adherence of 90-100% as measured by pill counts was similar between the arms (87% vs. 89%, p=0.807) among 158 evaluable patients after 8 weeks [71]. Another single-institution study randomized 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 two months (91.3% vs. 80% by self-report; 80.0% vs. 65.0% by refill rates) and at four 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 randomized 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 (MARS) [74] increased from 80% at study entry to 96.6% at the last follow-up (duration of follow-up not specified) in the intervention group, while in the control arm the proportion of adherent patients was the same (83.4%) at both time points (no p-values reported)[73].

A multi-site 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 to
standard care [56]. Among 68 evaluable patients who completed the trial, there was a statistically significant increase in adherence, measured by change in Morisky Medication Adherence Scale-8 (MMAS-8) scores [75] between baseline and follow-up at 9 months in the intervention group (p<0.0001), while this change was statistically non-significant in the standard care arm (p=0.593) [56].

A crossover trial of 25 patients with breast or GI cancer prescribed capecitabine randomized participants to either a pill box with sections for each individual dose or a standard pill bottle. Patients randomized to the pill box had similar levels of adherence compared to those randomized 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 [76].

An increasing number of interventions have involved technological approaches, including automatic reminders, to optimize adherence. Following a feasibility study that enrolled 30 patients [77], a larger randomized pilot study 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 (e.g., 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 [78]. Over the 10-week study, adherence, defined as taking ≥80% of medication in the past week, was not statistically different between groups [78].

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 [79, 80]. In the first trial, 80 participants were randomized to receive an SMT along with text messages each day for three 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 [79]. The average number of weeks adherent was identical in the intervention compared to control group (5.95 weeks, p=0.99) 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=0.26) which only received information and instructions about their treatment regimen [80]. There was also no statistically significant difference in self-reported adherence at the end of trial (86.7%, intervention vs. 79.2%, control, p=0.42) [80]. In contrast to the results of these two studies, a feasibility study that randomized 48 breast cancer patients prescribed AIs to a web-based application (“app”) that facilitated symptom self-reporting and provider notification for non-adherence or when symptoms reached an elevated level, or to the app alone, reported perfect adherence as assessed by the MMAS-4 in the group randomized to the app with reminders vs. 72.7% (p<0.05) in the app without reminders group [48].

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 [69]. Compared to the control video game arm, patients in the intervention group had higher plasma 6-MP metabolite levels (p=0.002) at follow-up, although self-reported adherence (assessed by the Chronic Disease Compliance Instrument and the Medication Adherence Scale) was not different between groups [69].

Non-randomized studies with a comparison group (Table 2)
The ADHERE study tested a nurse-practitioner led in-person and telephone-based intervention for patients starting an oral anti-cancer treatment regimen [81]. The intervention included education, motivational interviewing, and a short cognitive-behavioral therapy component [81]. The adjusted mean number of weeks adherent did not differ between the intervention and usual care arms (5.45 vs. 5.26 weeks, p=0.73) [81].

A multi-site Korean study enrolled patients on imatinib for CML and assigned half to a nurse-directed education program that combined provision of information, telephone support, and reminder text messages [41]. When compared to patients who did not receive the intervention, persistence in the intervention arm was higher at one-year (96.9% vs. 86.6% p=0.002), two (97.5% vs. 84.5%, p=0.001), and three-year follow-up (96.4% vs. 82.0%, p=0.001), while adherence measured by doses (milligrams of imatinib taken vs. prescribed) was not statistically different between two groups at any assessment point [41].

Gebbia et al. implemented an oral treatment monitoring program for patients with advanced non-small cell lung cancer (NSCLC) prescribed erlotinib [63]. 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 [63]. When compared to 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 [82] (84% vs. 72%, p=0.042) and by pill counts, defined as proportion of drug taken vs. prescribed (87% vs. 78%, p=0.0021) in the intervention cohort [63]. A second self-report metric of adherence that used a Visual Analog Scale (VAS) was similar between groups (97%, intervention vs. 94%, control, p=0.067)[63].

Non-randomized 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 one year of follow-up (95.8% vs. 95.9%, p=0.95) 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 were used to identify women who were non-adherent, non-persistent, or who 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 discussion of ET with a physician; women were also informed that their plan fully covered ET [51]. Of the 36 women identified as non-adherent who were reached by a care manager, 22 (61%) subsequently had a prescription filled following this contact and 50% (11/22) were adherent after six months [51]. Among 31 women identified as non-adherent but who were never reached by a care manager, 16 subsequently filled a prescription (52%) and 25% (4/16) were adherent after six months[51]. The differences between groups (50% vs. 25%, p=0.11) was 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 to a standard care arm: education; a home visit by a nurse that incorporated various behavioral strategies; and “pill shaping”, which included comprehensive education as well as nurse monitoring while the patient was hospitalized [59, 61]. Overall adherence was low among all groups, although better allopurinol adherence was observed in the intervention groups compared to the control. Prednisone adherence remained suboptimal among the intervention groups [59, 61].

A more recent strategy to improve adherence to oral anti-neoplastic 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 prior to the CMP [83]. Adherence (as assessed by the MPR) after six months of follow-up was modestly higher numerically in the CMP cohort compared to the control group; however, the difference was not statistically significant (mean MPR: 44.8% vs. 41.5%, p=0.4016); persistence was statistically significantly higher in the CMP cohort vs. control (23.8% vs. 7.8%, p=0.0234) [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 anti-cancer therapies [84]. Compared to a pre-intervention cohort, there was numerically, but not statistically, higher adherence (MPR ≥80%) in the intervention group compared to historical controls (94.1% vs. 92.2%, p=0.199) [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=0.64) or never cutting back on their medication (69% vs. 77%, p=0.68) [85].

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 one month and six months after starting therapy aimed at addressing side effects and adherence [86]. Compared to historical controls, adherence
(MPR >90%) was similar in the two groups at one month (95.7%, intervention vs. 94.7%, historical control, p>0.05), but statistically significantly higher in the intervention cohort at six months (95.0%, vs. 87.7%, p=0.025) [86].

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 [57]. The proportion of participants who were adherent (MPR ≥90%) was higher in the intervention arm compared to the proportion among controls who received usual care (88.6% vs. 65.8%, p<0.0046) [57]. 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 to a standard care group (97.9% vs 90.5%, p=0.069); average adherence measured on each day was also greater in the intervention group (96.8% vs 87.2%, p=0.029) [87]. Persistence was also higher in the intervention group vs. standard care arm (83% vs. 48%, p=0.019) [87]. A Japanese study enrolling gastric cancer patients prescribed S1 chemotherapy reported statistically significantly higher persistence (ascertained from medical records) one year after the introduction of pharmacist-led education about the treatment and side effect management compared to historical controls (overall: 82.5% vs. 39.4%, p<0.0001; excluding patients who discontinued because of cancer recurrence or another reason, 91.7% vs. 55.2%, p<0.0001) [68].

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 [88]. Individuals where adherence was thought to
a problem were contacted by pharmacists or pharmacy nurses who delivered additional informational/supportive care content, services to help patients with costs, as well as connected patients with a doctor if needed [88]. When compared to a matched retail pharmacy control group, adherence, as assessed by the MPR, was higher in the intervention group (65.7% vs. 58%, p<0.001)[88].

A German study enrolled 78 patients on capecitabine treated at two different hospitals [89]. While those categorized as adherent received pharmaceutical care and adverse effect management, a subset (n=15) categorized as non-adherent (<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 non-adherence was intentional (e.g., if due to bothersome symptoms there was additional attention to symptom amelioration) or non-intentional (e.g., medication journals or “cue dosing” to address not remembering to take the drug) delivered by a pharmacist [89]. Following the introduction of the intervention, median daily adherence went from 85.7% (first cycle) to 97.6% (sixth cycle) in the non-adherent group while among the group that was classified as adherent at baseline (median daily adherence: 100%) remained highly adherent following the sixth cycle of treatment (100%) [89]. Persistence in both adherent and non-adherent patients (excluding those whose treatment was stopped early by a doctor) was 100% [89].

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 (RCC) prescribed pazopanib enrolled in the intervention arm, statistically significantly (p<0.001) higher than the 62% reported among the 13 historical controls [66]. 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=0.7) in a study inclusive of 33 patients with RCC, prostate, or angiolipoma of the kidney [65].

**Single arm studies with pre-post comparison (Table 3)**

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 [62]. Evaluable patients included those who filled out the diary (n=44). Although median time using the diary varied (median of 246 days), adherence (measured with prescription records) was higher with the diary when matched and compared to time periods before and after the diary was used (86.5% vs. 93.6%, p=0.0007) [62]. In a single institution Australian study of 23 patients, pharmacists met weekly with patients following their stem cell transplants for six weeks to manage medication issues; adherence was assessed at each week with a 4-item version of the MMAS [55]. There was a statistically significant decrease in average MMAS score (1.53, 95% CI 1.12-1.94, p<0.0001) 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 [55].

A study testing a mobile health (mHealth) app that facilitated scheduling of medication reminders and adherence tracking enrolled 23 AYA patients prescribed oral anti-cancer and/or supportive care agents for the treatment of hematologic malignancies or solid tumors [70]. Adherence was measured with electronic monitoring caps each week and was not different throughout the 8-week intervention when compared to adherence measured during the 4 weeks prior to the intervention (p>0.05) [70].

The Israeli multi-site TAKE-IT study used a pre-post design to evaluate a multi-level 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 [58]. While patients who were adherent (≥90% assessed by MEMS) prior to the introduction of the intervention remained adherent post-intervention (97.1% vs. 98.1%, p-value not reported), among those classified as non-adherent (<90%) pre-intervention, there was improvement when assessed post-intervention (71.2% vs. 79.6%, p=0.04) [58].

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=0.0135) from 65.2% pre-intervention to 100% adherence when measured 4 months after introduction of education and monthly pharmacist monitoring [60]. A feasibility study conducted in the United Kingdom targeted breast cancer patients identified as non-adherent with a 4-6 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 non-significant (p=0.391) change in MARS 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 (Table 4)**

A nurse-led intervention for patients beginning treatment on erlotinib for NSCLC utilized the Multinational Association for Supportive Care in Cancer Oral Agent Teaching Tool (MOATT) as part of a combination in-clinic and telephone-based educational intervention [64]. 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 [64]. 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 [67]. Almost all patients (95.8%) reported perfect adherence to their medication among those enrolled in a small pilot study where nurses utilized the electronic medical record to track symptoms, all oral medications, dosing, and adherence [90]. Among participants of the Italian-based “Active Home Care” program, where patients received their oral anti-neoplastic drugs from a nurse who visited each week, all were reported adhering to their regimen as prescribed [91, 92].

Heisig et al. enrolled over 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 three months of follow-up, 6.6% were classified as “non-adherent”, defined as taking <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 non-adherence 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 or not they took their medication; at the end of the pilot, adherence (≥90%) was 66.7% among the 9 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% [93] and another where average adherence (calculated based on number of pills not taken) was 98.9% [94]. 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 [95] with a follow-up study reporting a persistence (ascertained by medical record review) rate of 78% among 41 patients [96]. An Australian study that assessed self-reported adherence (missed dose due to forgetting or any other reason) mid-cycle and at the end of the second cycle of treatment reported an adherence of 77.8% among 18 and 9 patients prescribed different oral agents, who were evaluable at each time point, respectively [97]. The pharmacist-led intervention in Japan for patients on S-1 chemotherapy which demonstrated improved persistence compared to historical controls [68] documented “good” adherence (93.2%) among 44 patients surveyed about the intervention in a separate study [98]. 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%; MPR: 93.9%) among those who participated in a pharmacy program also described by Morgan et al. [85, 99].

Discussion
Numerous observational studies have sought to improve the understanding of the problem of non-adherence to oral anti-cancer agents, detailing the prevalence of and factors associated with non-adherence 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 pre-specified adherence outcome [48, 56, 69] and a fourth study reported a statistically significant effect in a post-hoc analysis where two different intervention arms were combined [53]. Findings from RCTs with large sample sizes were disappointing, including from two trials that enrolled post-menopausal 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 anti-neoplastic 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 [100]. While 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 to historical controls, the success of these interventions may be attributed to the intensive monitoring and/or serial follow-up where providers (e.g., 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 [100]. Systematic monitoring of adherence also supports a targeted approach by identifying, through clinic or pharmacy records, individuals who are non-adherent or are
at risk for non-adherence who are likely to benefit most from intensive follow-up. Importantly, we only identified 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 [71]. 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 8 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 [41] and another on adherence [56]; a third study reported improved adherence associated with an app with email/text reminders compared to the app alone [48]. In contrast, those that enrolled patients representing a spectrum of different diagnoses did not report statistically significant improvements [70, 79, 80]. While 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. While text messages generally serve as reminders to take a medication and address one barrier to adherence, designing a more comprehensive application that targets intentional non-adherence 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. While an mHealth intervention tested in a small group of AYA survivors did not statistically significantly improve adherence [70], a video game designed for AYA patients demonstrated a measurable and statistically significant impact on adherence as indicated by 6MP
metabolite levels in that population. 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 [69]. 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 [101].

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 non-adherence [102-105]. In theory, these associations support the development of interventions based on widely used conceptual models and frameworks [103, 106]. 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 [107]. The authors concluded that while those interventions grounded in theory did have a statistically significant effect on adherence outcomes, they described this effect as “modest” [107]. Of the 14 randomized studies in this review, 7 described a theoretical or conceptual framework that influenced or informed the intervention [47, 53, 69, 72, 78-80]. Of these, Kato et al. [69] and Ziller et al. (in a post-hoc analysis) [53] reported statistically significant improvements in the intervention arms. The complex and multi-factorial contributors to non-adherence clearly make selecting an appropriate conceptual model and formulating an intervention based on that model challenging and represents 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 both in the design and analytic plans of randomized and non-randomized
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 impact intervention design, implementation, and potential for efficacy. Given several of the studies we reviewed were conducted internationally, these contextual factors should be considered when interpreting study outcomes.

Non-adherence 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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**Notes**
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References


45. Pereira-Salgado A, Westwood JA, Russell L, et al. Mobile Health Intervention to Increase Oral Cancer Therapy Adherence in Patients With Chronic Myeloid Leukemia


### Table 1. Summary of key study attributes: Randomized Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study population</th>
<th>Total sample size (Randomized or enrolled/evaluable at end of follow-up)</th>
<th>Intervention</th>
<th>Control/Comparison group (if applicable)</th>
<th>Method of adherence/persistence measurement</th>
<th>Duration of study follow-up</th>
<th>Results*</th>
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</thead>
<tbody>
<tr>
<td>Hadji et al. 2013</td>
<td>Germany</td>
<td>Breast cancer patients prescribed AIs</td>
<td>4,844 randomized/2,740 evaluable</td>
<td>Education, including letters and pamphlets; monthly prompts; small tokens (e.g., pill box, exercise advice)</td>
<td>Standard care</td>
<td>Self-report</td>
<td>1 year</td>
<td>Adherence: 88.8%, intervention vs. 88.5%, control, p=0.81  Persistence: 43%, intervention vs. 40.5%, control, p=0.18</td>
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<tr>
<td>Neven et al. 2014</td>
<td>International (18 countries)</td>
<td>Breast cancer patients prescribed AIs</td>
<td>2,758 randomized/2,543 evaluable at 1 year 2,242 evaluable at 2 years</td>
<td>Education, including letters and pamphlets</td>
<td>Standard care</td>
<td>Self-report</td>
<td>2 years</td>
<td>Adherence: 1 year: 82%, intervention vs. 81%, control; p=0.4524 2 year: 82%, intervention vs. 82%, control, p-value not reported Persistence: 1 year: 86%, intervention vs. 84%, control; p=0.1359 2 year: 88%, intervention vs. 90%, control, p-value not reported</td>
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<tr>
<td>Ziller et al. 2013</td>
<td>Germany</td>
<td>Breast cancer patients prescribed AIs</td>
<td>181 randomized/171 evaluable</td>
<td>Two intervention arms: #1: letters with details on</td>
<td>Standard care (information given at visits)</td>
<td>Self-report Prescription/medical records</td>
<td>1 year</td>
<td>Adherence: Self-report+MPR Three arm</td>
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<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Method</td>
<td>Outcomes</td>
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<td>Schneider et al. 2014</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents 48 enrolled/45 evaluable</td>
<td>Chemotherapy education + phone calls from nurse (content personalized to patient based on baseline evaluation)</td>
<td>Standard care (chemotherapy education only) Self-report Prescriptions records 4 months Adherence: 2 months Self-report 91.3%, intervention, vs. 80%, control Prescription records 80%, intervention vs. 65%, control, p-value not reported</td>
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<tr>
<td>Ramesh et al. 2015</td>
<td>India</td>
<td>Patients prescribed oral anti-cancer agents 97 enrolled/60 evaluable</td>
<td>Education, including pamphlet at initial visit</td>
<td>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</td>
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<td>Study</td>
<td>Country</td>
<td>Intervention</td>
<td>Patients described</td>
<td>Follow-up</td>
<td>Medication adherence</td>
<td>Self-report method</td>
<td>Duration</td>
<td>Adherence (Change from baseline to 9 months):</td>
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</table>
| Kekale et al. 2016 [56]     | Finland | CML patients prescribed TKIs | 86 randomized/68 evaluable | In person meeting with nurse, educational pamphlets/video/website; text message reminders | Standard care       | Self-report | 9 months | intervention % with high MMAS-8 score 23% to 51%, % with medium MMAS-8 score 54% to 46%, % with low MMAS-8 score 23% to 3%; Overall, 49% improved from baseline, p<0.0001,  
control % with high MMAS-8 score 21% vs. 20%, % with medium MMAS-8 score 67% to 61%, % with low MMAS-8 score 12% to 18%; Overall, 18% improved from baseline, p=0.593  |
<p>| Macintosh et al. 2007 [76]  | Canada  | Patients prescribed capecitabine for breast or GI cancer | 25 randomized/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 days/2 cycles of treatment | Adherence:‡: 81%, intervention vs. 86%, control, no p-values reported |
| Spoelstra et al. 2013 [78]  | United States | Patients prescribed oral anti-cancer agents | 119 randomized/119 evaluable/91 evaluable at exit interview | 3 intervention arms: 1) AVR system + SMT; 2) AVR + SMT + nurse led | None | Self-report Prescription/medical records | 10 weeks | Adherence: Self-report  Overall rate of 58% reported as similar across groups |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Intervention</th>
<th>Measure</th>
<th>Adherence</th>
<th>Duration</th>
<th>Effect Size</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Spoelstra et al. 2015 [79]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>80 randomized /68 evaluable at exit interview</td>
<td>Text messages + SMT + usual care</td>
<td>Usual care (SMT provided at end of study)</td>
<td>Self-report</td>
<td>Prescription/medical records</td>
<td>Overall rate of 67% reported (difference between groups not specified)</td>
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<tr>
<td>Spoelstra et al. 2016 [80]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>75 randomized/69 evaluable at exit interview</td>
<td>Text messages + usual care (education by providers about medication regimen, including adherence, adverse effects and symptom management, how to reach provider if needed)</td>
<td>Usual care</td>
<td>Self-report</td>
<td>Prescription/medical records</td>
<td>10 weeks</td>
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<tr>
<td>Study</td>
<td>Location</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Duration</td>
<td>Data collected but not evaluated</td>
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<td>Kato et al. 2008 [69]</td>
<td>International (United States, Canada, Australia)</td>
<td>AYA patients (age 13-29) with acute leukemia and non-Hodgkin's lymphoma§</td>
<td>Video game about issues of cancer treatment and care in adolescents and young adults</td>
<td>Commercial video game</td>
<td>3 months</td>
<td>Self-report, 6-MP levels</td>
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<td>Eli et al. 2008 [47]</td>
<td>United States</td>
<td>Breast cancer patients prescribed endocrine therapy</td>
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<td>Structured patient navigation which included education, psychosocial support, and navigation to promote treatment access and adherence</td>
<td>&quot;Enhanced&quot; usual care: standard clinical care, assistance linking patients to financial and social support resources, brochure about depression and cancer</td>
<td>Prescription records</td>
<td>1 year</td>
<td>Self-report, includes anti-biotic regimen, 6-MP levels, 8499.1, intervention vs. 8087.0, control, p=0.002 (adjusted p-value)</td>
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<tr>
<td>Graetz et al. 2018 [48]</td>
<td>United States</td>
<td>Breast cancer patients prescribed AIs</td>
<td>App (facilitating sharing of symptoms with providers and provider notification for high symptom levels or non-adherence) + email or text reminders</td>
<td>App only</td>
<td>6-8 weeks</td>
<td>100%, intervention vs. 72.7%, control, p&lt;0.05</td>
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<tr>
<td>Krikorian et al. 2019[71]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>200 randomized/173 evaluable at week 4/158 evaluable at week 8</td>
<td>Pharmacist directed individualized education, included in person sessions that incorporated cognitive-behavioral components focused on potential contributors to non-adherence, managing side effects; printed information about medication regimen; phone follow-up</td>
<td>Nurse-conducted pill count</td>
<td>Pill counts Self-report Prescription records</td>
<td>8 weeks</td>
<td>Adherence: Pill counts: Week 4 Intervention, 90%, vs. 89%, control, p=0.807 Week 8 Intervention, 87%, vs. 89%, control, p=0.807</td>
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</table>

Abbreviations: AIs, Aromatase Inhibitors; AVR, Automated voice response; SMT, symptom management toolkit; RDI, relative dose intensity; 6-MP, 6-mercaptopurine; CDCI, Chronic Disease Compliance Instrument; MAS, Medication Adherence Scale; CML, Chronic Myeloid Leukemia; TKI, tyrosine kinase inhibitor; MPR, medication possession ratio; MMAS, Morisky Medication Adherence Scale; GI, gastrointestinal; AYA, adolescent and young adult
*Unless other metric (e.g., mean weeks or mean change in score) or timing specified, results represent the proportion adherent/persistent as defined by each study at the end of follow-up
†Follow-up not reported or study specified enrollment and/or assessment timing but duration of follow-up/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
Table 2. Summary of key study attributes: Non-randomized studies with a comparison group

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study population</th>
<th>Total sample size (Randomized or enrolled/evaluable at end of follow-up)</th>
<th>Intervention</th>
<th>Control/Comparison group (if applicable)</th>
<th>Method of adherence/persistence measurement</th>
<th>Duration of study follow-up*</th>
<th>Results†</th>
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</thead>
<tbody>
<tr>
<td>Spoelstra et al. 2017</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>61 consented/54 evaluable/40 evaluable at exit interview</td>
<td>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)</td>
<td>Usual care</td>
<td>Self-report</td>
<td>8 weeks</td>
<td>Adherence: Mean number of weeks adherent: 5.45, intervention vs. 5.26, control, p= 0.73</td>
</tr>
<tr>
<td>Moon et al. 2012</td>
<td>Korea</td>
<td>CML patients prescribed imatinib</td>
<td>114 enrolled/100 evaluable at year 3</td>
<td>Phone counseling by nurse, daily dose reminder texts, letters</td>
<td>Standard care</td>
<td>Prescription records</td>
<td>3 years</td>
<td>Adherence: Year 1: 96.4%, intervention vs. 96.9%, control, p=0.387 Year 2: 96.2%, intervention vs. 96.6%, control, p=0.488 Year 3: 96.5%, intervention vs. 96.6%, control, p=0.958</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Group Description</td>
<td>Follow-up</td>
<td>Intervention Details</td>
<td>Control Details</td>
<td>Outcome Measures</td>
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<td>Yu et al. 2012 [52]</td>
<td>China</td>
<td>Breast cancer patients prescribed AIs</td>
<td>1 year</td>
<td>Education about breast cancer and oral hormonal treatment, periodic newsletters, reminder phone calls + standard care</td>
<td>Standard care</td>
<td>Persistence: Year 1: 96.9%, intervention vs. 86.6%, control, p=0.002 Year 2: 97.5%, intervention vs. 84.5%, control, p=0.001 Year 3: 96.4%, intervention vs. 82.0%, control, p=0.001</td>
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<tr>
<td>Wagner et al. 2016 [51]</td>
<td>United States</td>
<td>Non-metastatic hormone-receptor positive breast cancer patients enrolled in New York State Medicaid</td>
<td>6 months</td>
<td>For women identified as non-adherent/non-persistent or had never initiated endocrine therapy: Phone call from a Medicaid care plan manager where endocrine therapy recommendations were discussed, guidance about discussing endocrine therapy with their physician, and letting women know their plan fully covered 1) Women classified as adherent 2) Women who were eligible for a phone call but could not be reached or did not finish all of call content with the care manager</td>
<td>Prescription records</td>
<td>Adherence: 50%, women who started out non-adherent but were reached by a care manager adherence vs. 25%, women not reached vs. 86%, women who started out as adherent, p=0.11</td>
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<td>Study</td>
<td>Country</td>
<td>Patient Characteristics</td>
<td>Screened/Evaluable</td>
<td>Intervention Details</td>
<td>Control Details</td>
<td>Time Frame</td>
<td>Adherence</td>
<td>Metrics</td>
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<tr>
<td>Gebbia et al. 2013 [63]</td>
<td>Italy</td>
<td>Non-small-cell lung cancer patients prescribed erlotinib</td>
<td>217 screened/150 evaluable</td>
<td>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.</td>
<td>Usual care (education about side effects)</td>
<td>2 months</td>
<td>Adherence: Self-report BAAS: 84%, intervention vs. 72%, control: p=0.042 VAS: 97%, intervention vs. 94%, control, p=0.067</td>
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<tr>
<td>Khandelwal et al. 2012 [83]</td>
<td>United States</td>
<td>Patients prescribed sorafenib, sunitinib, or erlotinib</td>
<td>754 enrolled/evaluable</td>
<td>Oral chemotherapy cycle management program: telephone-based education and support, conducted by nurses and pharmacists</td>
<td>Non-participation in program (historical controls)</td>
<td>6 months</td>
<td>Adherence: Month 6: Mean MPR: 44.8% intervention vs. 41.5%, control, p=0.4016 Persistence: Month 6: 23.8%, intervention vs. 7.8%, control, p=0.0234</td>
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<tr>
<td>Middendorff et al. 2018 [84]</td>
<td>United States</td>
<td>Patients prescribed abiraterone, capecitabine, dasatinib, erlotinib, everolimus, imatinib, pazopanib, regorafenib, sorafenib, or temozolomide</td>
<td>96 enrolled/evaluable</td>
<td>Specialty pharmacy case management program: financial help, pharmacist-led education, symptom management, and phone support provided by both nurses and pharmacists</td>
<td>Non-participation in case management program (historical controls)</td>
<td>6 months</td>
<td>Adherence: Mean MPR: 94.1%, intervention vs. 92.2%, control, p=0.199</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Patient Population</td>
<td>Number of Patients</td>
<td>Pharmacist-led Components</td>
<td>Evaluation</td>
<td>Outcome Measures</td>
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<tr>
<td>Ribed et al. 2016 [86]</td>
<td>Spain</td>
<td>Patients prescribed dasatinib, nilotinib, sorafenib, pazopanib, gefitinib, erlotinib, imatinib, sunitinib, abiraterone, lenalidomide, thalidomide or everolimus</td>
<td>249 enrolled/ 215 evaluable at 1 month/ 112 evaluable at 6 months</td>
<td>Non-participation in case management program (historical controls)</td>
<td>Prescription records</td>
<td>6 months: 1.95%, intervention, vs. 94.7%, control, p=0.05 6 months: 95%, intervention, 87.7%, control, p=0.025</td>
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<tr>
<td>Lam and Cheung 2016 [57]</td>
<td>United States</td>
<td>CML patients prescribed TKIs</td>
<td>281 enrolled/269 evaluable</td>
<td>Oncology pharmacist-managed oral anticancer therapy program</td>
<td>Usual care</td>
<td>Mean in intervention arm: 31.9 months Adherence: 88.6%, intervention vs. 65.8%, control, p&lt;0.0046</td>
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<tr>
<td>Simons et al. 2011 [87]</td>
<td>Germany</td>
<td>Colorectal and breast cancer patients prescribed capecitabine</td>
<td>50 enrolled/ 48 evaluable</td>
<td>Pharmacist-led educational intervention that included information as well as addressed need for optimal adherence to the medication; pamphlet with side effect management information; follow-up by phone</td>
<td>Standard care</td>
<td>Mean in intervention arm: 89.7 days, Range: 9.0-137.5 Mean in control arm: 69.4 days, Range: 13.0-128.0 Adherence: 97.9%, intervention vs. 90.5%, control, p=0.069 mean daily: 96.8%, intervention vs. 87.2%, control, p=0.029 Persistence: 83%, intervention vs. 48% control, p=0.019</td>
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<tr>
<td>Tschida et al. 2012 [88]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>928 enrolled/ evaluable</td>
<td>Specialty pharmacy program including educational component, notifications when a prescription was due to be refilled, and adherence monitoring; telephone follow-up</td>
<td>Retail pharmacy program</td>
<td>Adherence: Mean weighted MPR: 65.7%, intervention vs. 58% control, p&lt;0.001</td>
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<tr>
<td>Krolop et al. 2013 [89]</td>
<td>Germany</td>
<td>Patients prescribed capecitabine</td>
<td>78 enrolled/73 evaluable</td>
<td>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 non-adherent</td>
<td>Pharmaceutical care and assistance with adverse effect management only for patients classified as adherent</td>
<td>Electronic pill monitoring</td>
<td>6 cycles of treatment</td>
<td>Adherence: In those categorized as non-adherent: Median daily adherence: 85.7% (first cycle) to 97.6% (sixth cycle) Mean daily adherence: 80.8% (first cycle) to &gt;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</td>
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<tr>
<td>Levine et al. 1987 [59]</td>
<td>United States</td>
<td>Hematologic malignancy patients prescribed allopurinol and/or prednisone</td>
<td>108 enrolled/evaluable</td>
<td>3 intervention arms: 1) education + a home visit by a nurse that incorporated various behavioral strategies, including accounting for patient routines, prompts and a contract involving patient and a relative who committed to aiding the patient with adhering to treatment; 2) Standard care</td>
<td>Self-report Serum drug levels</td>
<td>6 months</td>
<td>Adherence: Allopurinol Serum levels Arm #1: 45%, Arm #2: 47.2%, vs. Arm #3: 44.4% vs. control: 16.8%, p&lt;0.01 Self-report Arm #1: 92%, Arm #2: 90%, vs. Arm #3: 92.6% vs. control: 53.8%, p&lt;0.01 Prednisone Serum levels Arm #1: 38%, Arm #2: 32.7%, vs. Arm #3: 37.8% vs. control:</td>
<td></td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Population</td>
<td>Sample Size</td>
<td>Intervention Description</td>
<td>Control Description</td>
<td>Outcomes</td>
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<tr>
<td>Richardson et al. 1987 [61]</td>
<td>United States</td>
<td>Hematologic malignancy patients prescribed allopurinol and/or prednisone</td>
<td>92</td>
<td>3 intervention arms: 1) education + a home visit by a nurse that incorporated various behavioral strategies, including accounting for patient routines, prompts and a contract involving patient and a relative who committed to aiding the patient with adhering to treatment; 2) education + instruction on taking the medication (“pill shaping”); 3) education + home visit + pill shaping</td>
<td>Standard care</td>
<td>Adherence: Allopurinol Serum levels Arm #1: 49.9%, Arm #2: 49.5%, vs. Arm #3: 45.2% vs. control: 16.1%, p&lt;0.05</td>
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<td>Self-report Serum drug levels</td>
<td></td>
<td>Self-report Intervention arms ranged from 90-93% vs. control: 48%, p&lt;0.01</td>
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<td>Prednisone† Serum levels Arm #1: 33.8%, Arm #2: 36.1%, vs. Arm #3: 35.8% vs. control: 31.2%, p≥0.05</td>
<td></td>
<td>Prednisone† Serum levels Arm #1: 33.8%, Arm #2: 36.1%, vs. Arm #3: 35.8% vs. control: 31.2%, p≥0.05</td>
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<tr>
<td>Kimura et al. 2017 [68]</td>
<td>Japan</td>
<td>Gastric cancer patients prescribed S1 chemotherapy</td>
<td>134</td>
<td>In person pharmacist; education about medication, checking of adherence and symptoms; advice about symptom management; supportive care given if necessary; pharmacist available by</td>
<td>Non-participation in program (historical controls)</td>
<td>Medical records Overall: 82.5%, intervention vs. 39.4%, p&lt;0.0001 Excluding those who discontinued because of recurrence or other reason): 91.7%, intervention vs. 55.2%, p&lt;0.0001</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Population</td>
<td>Follow-up</td>
<td>Setting</td>
<td>Education and follow-up</td>
<td>Non-participation in program (historical controls)</td>
<td>Method</td>
<td>Adherence</td>
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<tr>
<td>Conliffe et al. 2019 [65]</td>
<td>United States</td>
<td>Patients with genitourinary cancer prescribed oral anti-cancer agents</td>
<td>33 enrolled/evaluable</td>
<td>Oral agent monitoring program; pharmacist-led education and follow-up</td>
<td>Not specified</td>
<td>3 months</td>
<td>Pharmacy consultation with pharmacist if needed</td>
<td>Self-report</td>
</tr>
<tr>
<td>Todo et al. 2019 [66]</td>
<td>Japan</td>
<td>Renal cell carcinoma patients prescribed pazopanib</td>
<td>50 enrolled/evaluable</td>
<td>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</td>
<td>Self-report (drug diary)</td>
<td>Non-participation in program (historical controls)</td>
<td>Self-report</td>
<td>Adherence: 100% intervention vs. 62% control, p&lt;0.001</td>
</tr>
<tr>
<td>Morgan et al. 2018 [85]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>122 enrolled/evaluable for self-report/ 66 evaluable for prescription records</td>
<td>Pharmacist directed oral chemotherapy management program including educational component, addressing side-effects and adherence challenges, enhanced follow-up</td>
<td>Self-report Prescription records</td>
<td>Non-participation in program (historical controls)</td>
<td>Self-report</td>
<td>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=0.64</td>
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<tr>
<td>up by pharmacy including phone reminders about refills</td>
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<td>Neve cutoff back on medication: Intervention, 69% vs. 77% control, p=0.68</td>
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</tbody>
</table>

Abbreviations: CML, Chronic Myeloid Leukemia; AIs, Aromatase Inhibitors; BAAS, Basel Assessment of Adherence Scale; VAS, Visual Analog Scale; TKI, tyrosine kinase inhibitor; MPR, medication possession ratio

* For non-randomized studies with comparison group, sample size represents totally analytic sample (e.g., inclusive of historical controls)
† Unless other metric (e.g., mean weeks or mean change in score) or timing specified, results represent the proportion adherent/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 non-adherent but were not reached (n=31) and women classified as non-adherent and reached (n=36)
§ Includes usual care controls (n=225) from previous study [108]; 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
## Table 3. Summary of key study attributes: single arm pre-post comparison

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study population</th>
<th>Total sample size (Randomized or enrolled/evaluable at end of follow-up)</th>
<th>Intervention</th>
<th>Control/Comparison group (if applicable)</th>
<th>Method of adherence/persistence measurement</th>
<th>Duration of study follow-up</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chieng et al. 2013 [55]</td>
<td>Australia</td>
<td>Patients who received an allogeneic stem cell transplant</td>
<td>23 enrolled/17 evaluable</td>
<td>Weekly in-person pharmacist consultations</td>
<td>N/A</td>
<td>Self-report</td>
<td>6 weeks</td>
<td>Adherence:100% Mean change in MMAS score from week 0-week 6: 1.53, p=0.0001</td>
</tr>
<tr>
<td>Santoleri et al. 2019 [62]</td>
<td>Italy</td>
<td>CML patients prescribed TKIs</td>
<td>123 received intervention/44 evaluable (used diary)</td>
<td>Pharmacist provided drug diary + information about side effects as well as instructions regarding what to do if a dose is skipped</td>
<td>N/A</td>
<td>Self-report (drug diary) Prescription records</td>
<td>Median of 246 days using intervention (diary)</td>
<td>Adherence: Self-report (time period with diary only): 97.4% Prescription records: 86.5%, without diary vs. 93.6%, with diary, p=0.0007</td>
</tr>
<tr>
<td>Moon et al. 2019 [49]</td>
<td>United Kingdom</td>
<td>Breast cancer patients prescribed tamoxifen – all non-adherent at baseline</td>
<td>41 consented/27 evaluable</td>
<td>Education about tamoxifen, potential side effects, communication and supportive resources; cognitive behavioral therapy component and SMART goal setting</td>
<td>N/A</td>
<td>Self-report</td>
<td>Mean of 7 weeks (range: 2-12 weeks)</td>
<td>Adherence: Mean MARS score 22.8, pre vs. 23.1, post, p=0.391 0%, pre vs 9%, post No p-value reported</td>
</tr>
<tr>
<td>Leader et al. 2018 [58]</td>
<td>Israel</td>
<td>CML patients prescribed TKIs</td>
<td>58 enrolled/45 evaluable</td>
<td>Multi-level intervention; Motivational interviewing conducted by nurse; peer support group for patients; educational seminar for patients in group-</td>
<td>N/A</td>
<td>Electronic pill monitoring</td>
<td>7 months</td>
<td>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=0.04</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Baseline Characteristics</td>
<td>Intervention</td>
<td>Follow-up</td>
<td>Adherence</td>
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<tr>
<td>Linder et al. 2019</td>
<td>United States</td>
<td>AYA patients (age 15-29) prescribed oral anti-cancer and/or supportive care agents</td>
<td>23 enrolled/evaluable</td>
<td>App with features that facilitated scheduling of medication reminders, adherence tracking</td>
<td>3 months</td>
<td>Adherence: No statistically significant change pre to post intervention, p&gt;0.05</td>
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</tr>
<tr>
<td>Moulin et al. 2017</td>
<td>Brazil</td>
<td>CML patients prescribed TKIs</td>
<td>23 enrolled/evaluable</td>
<td>Monthly pharmacist monitoring, education about CML, TKIs, and importance of adhering to treatment</td>
<td>4 months</td>
<td>Adherence: 65.2%, pre vs 100%, post, p=0.0135</td>
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</tbody>
</table>

Abbreviations: N/A, not applicable; CML, Chronic Myeloid Leukemia; TKI, tyrosine kinase inhibitor; MMAS, Morisky Medication Adherence Scale; MARS, Medication Adherence Rating Scale; SMART, Specific, Measurable, Attainable, Relevant and Time-bound; AYA, adolescent and young adult

*Unless other metric (e.g., mean weeks or mean change in score) or timing specified, results represent the proportion adherent/persistent as defined by each study at the end of follow-up
†Follow-up not reported or study specified enrollment and/or assessment timing but duration of follow-up/timing of adherence assessment not explicitly described.
Table 4. Summary of key study attributes: single-arm studies, no comparison

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study population</th>
<th>Total sample size (Randomized or enrolled/evaluable at end of follow-up)</th>
<th>Intervention</th>
<th>Control/Comparison group (if applicable)</th>
<th>Method of adherence/persistence measurement</th>
<th>Duration of study follow-up</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decker et al. 2009 [77]</td>
<td>United States</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>30 enrolled/evaluable</td>
<td>AVR system + SMT; follow-up phone call from nurse if patient identified as non-adherent or experiencing high symptom burden</td>
<td>N/A</td>
<td>Self-report; Prescription/medical records</td>
<td>10 weeks</td>
<td>Adherence: Prescription records: 76.7%</td>
</tr>
<tr>
<td>Boucher et al. 2015 [64]</td>
<td>United States</td>
<td>Non-small cell lung cancer patients prescribed erlotinib</td>
<td>30 enrolled/27 evaluable</td>
<td>In person and phone nurse-directed education that used MASCC-MOATT materials</td>
<td>N/A</td>
<td>Self-report</td>
<td>6-8 weeks</td>
<td>Adherence: Mean MMAS score at study completion: 7.12 (SD: 1.01)</td>
</tr>
<tr>
<td>Sommers et al. 2012 [67]</td>
<td>United States</td>
<td>GI cancer patients prescribed ≥1 oral anti-cancer agent</td>
<td>30 enrolled/evaluable</td>
<td>Oral and print education, nurse-initiated educational phone call</td>
<td>N/A</td>
<td>Self-report</td>
<td>One cycle of treatment</td>
<td>Adherence: Mean MMAS score at study completion: 7.89 (SD: 0.55)</td>
</tr>
<tr>
<td>Heisig et al. 2014 [54]</td>
<td>Germany</td>
<td>Breast cancer patients prescribed endocrine therapy</td>
<td>174 enrolled/137 evaluable</td>
<td>Supplementary education about endocrine therapy</td>
<td>N/A</td>
<td>Self-report</td>
<td>3 months</td>
<td>Adherence: 93.4%,</td>
</tr>
<tr>
<td>Bordonaro et al. 2012 [92]</td>
<td>Italy</td>
<td>Patients prescribed capecitabine, vinorelbine, imatinib, sunitinib, sorafenib, temozolomide, or ibandronate</td>
<td>30 enrolled/evaluable</td>
<td>Home-based program: Treatment brought to patient’s home; adherence/toxicity monitoring; phone number for patients to call if needed</td>
<td>N/A</td>
<td>Self-report Provider observation</td>
<td>Not evaluable†</td>
<td>Adherence: 100%</td>
</tr>
<tr>
<td>Bordonaro et al. 2014 [91]</td>
<td>Italy</td>
<td>Patients prescribed capecitabine, vinorelbine, imatinib, sunitinib, sorafenib, temozolomide, or ibandronate</td>
<td>62 enrolled/evaluable</td>
<td>Home-based program: Treatment brought to patient’s home; adherence/toxicity monitoring; phone number for</td>
<td>N/A</td>
<td>Self-report</td>
<td>Not evaluable†</td>
<td>Adherence: 100%</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Patients prescribed</td>
<td>Enrolled/Evaluable</td>
<td>Monitoring Method</td>
<td>Adherence</td>
<td>Persistence</td>
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<tr>
<td>Battis et al. 2017</td>
<td>United States</td>
<td>Patients prescribed abiraterone, capecitabine, chlorambucil, crizotinib, dasatinib, enzalutamide, hydroxyurea, ibrutinib, imatinib, nilotinib, pazopanib, sorafenib, sunitinib, temozolomide, or topotecan</td>
<td>68 enrolled/evaluable</td>
<td>Pharmacist-directed oral chemotherapy monitoring clinic; education and instruction about adherence, symptoms, dose schedules, additional interaction with patients if identified as non-adherent</td>
<td>N/A</td>
<td>Not evaluable†</td>
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<tr>
<td>Riu et al. 2018</td>
<td>Spain</td>
<td>Patients prescribed oral anti-cancer agents</td>
<td>83 enrolled/evaluable</td>
<td>Integrated pharmaceutical care program; education about taking medication, taking other medications, adherence; symptom management</td>
<td>N/A</td>
<td>Not evaluable†</td>
<td>Adherence: Mean: 98.9%</td>
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<tr>
<td>Wong et al. 2014</td>
<td>United States</td>
<td>Patients prescribed capecitabine, erlotinib, everolimus, hydroxyurea, lapatinib, lenalidomide, neratinib, or tamoxifen</td>
<td>30 enrolled/evaluable</td>
<td>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</td>
<td>N/A</td>
<td>Self-report</td>
<td>3 months</td>
<td>Adherence: 70%  Persistence:70%</td>
</tr>
<tr>
<td>Kimura et al. 2017</td>
<td>Japan</td>
<td>Patients prescribed regorafib, trifluridine/tipiracil, tegafur/gimeracil/oteracil</td>
<td>47 enrolled/44 evaluable</td>
<td>Pharmacist-directed education about medication, side effects</td>
<td>N/A</td>
<td>Self-report</td>
<td>1 month</td>
<td>Adherence: 93.2%</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Patient Group</td>
<td>Sample Size</td>
<td>Intervention</td>
<td>Follow-Up</td>
<td>Adherence</td>
<td>Additional Notes</td>
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<tr>
<td>Rodriguez et al. 2017 [90]</td>
<td>United States</td>
<td>GI, breast, hematology, neurology patients</td>
<td>71 enrolled/evaluable</td>
<td>Nurse-led tracking of symptoms, oral medications, dosing, and adherence via the electronic medical record</td>
<td>N/A</td>
<td>Self-report (documented by nurses)</td>
<td>Not evaluable†</td>
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<tr>
<td>Pereira-Salgado et al. 2017 [45]</td>
<td>Australia</td>
<td>CML patients prescribe imatinib</td>
<td>10 consented/9 evaluable</td>
<td>Multi-level 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 utilization of strategies to manage side effects</td>
<td>N/A</td>
<td>Self-report</td>
<td>10 weeks</td>
<td>Adherence: 66.7%</td>
</tr>
<tr>
<td>Mougalian et al. 2017 [50]</td>
<td>United States</td>
<td>Breast cancer patients prescribed endocrine therapy</td>
<td>100 enrolled/evaluable/ 89 evaluable for complete data at end of study</td>
<td>Text message reminders and messages addressing adherence challenges, side</td>
<td>N/A</td>
<td>Self-report</td>
<td>3 months</td>
<td>Adherence: Overall: 85.1% Among patients who finished study: 93.3%</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Diagnosis/Therapy</td>
<td>Enrollment</td>
<td>Intervention</td>
<td>Data Source</td>
<td>Follow-up</td>
<td>Adherence</td>
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<tr>
<td>Barlow et al. 2013</td>
<td>United Kingdom</td>
<td>Breast cancer patients prescribed endocrine therapy</td>
<td>12 enrolled/evaluable</td>
<td>&quot;Spiritual Healing&quot; holistic medicine intervention</td>
<td>N/A</td>
<td>Self-report</td>
<td>10 weeks</td>
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</tr>
<tr>
<td>Byrne et al. 2018</td>
<td>Australia</td>
<td>Patients prescribed capecitabine, temozolomide, pazopanib, olaparib, etoposide, afatinib, everolimus, vinorelbine, or abiraterone</td>
<td>29 consented/18 evaluable at the end of cycle 1/ 9 evaluable at the end of cycle 2</td>
<td>Pharmacist-directed education that used MASCC-MOATT materials; phone or in-person follow-up to address side effects, additional education if needed</td>
<td>N/A</td>
<td>Self-report</td>
<td>2 cycles of treatment</td>
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</tr>
<tr>
<td>Muluneh et al. 2018</td>
<td>United States</td>
<td>Patients prescribed bosutinib, imatinib, nilotinib, ibritinib, idelalisib, sorafenib, dasatinib, bexarotene, capecitabine, everolimus, lapatinib, regorafenib, or temozolomide</td>
<td>107 enrolled/evaluable</td>
<td>Pharmacist directed oral chemotherapy program management including educational component, adherence monitoring, side-effect, drug interaction management</td>
<td>N/A</td>
<td>Self-report</td>
<td>Not evaluable†</td>
<td></td>
</tr>
<tr>
<td>Wong et al. 2016</td>
<td>United States</td>
<td>Patients prescribed capecitabine, erlotinib, everolimus, lenalidomide, neratinib.</td>
<td>86 enrolled/41 evaluable</td>
<td>Pharmacist-directed oral chemotherapy management program;</td>
<td>N/A</td>
<td>Medical record</td>
<td>3 months</td>
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</table>

Wong et al. 2016 [96]  United States  Patients prescribed capecitabine, erlotinib, everolimus, lenalidomide, neratinib.  86 enrolled/41 evaluable  Pharmacist-directed oral chemotherapy management program;  N/A  Medical record  3 months  Persistence: 78%
| | hydroxyurea, pazopanib, letrozole, anastrozole, tamoxifen, abiraterone, imatinib, sorafenib, sunitinib, lapatinib, or bosutinib | including in person and phone follow-up, education about the medication and side effects |  |

Abbreviations: AVR, Automated voice response; SMT, symptom management toolkit; MASCC-MOATT, Multinational Association of Supportive Care in Cancer Oral Agent Teaching Tool; CML, Chronic Myeloid Leukemia; MPR, medication possession ratio; MMAS, Morisky Medication Adherence Scale; GI, gastrointestinal; N/A, not applicable; SD, standard deviation

*Unless other metric (e.g., mean weeks or mean change in score) or timing specified, results represent the proportion adherent/persistent as defined by each study at the end of follow-up
†Follow-up not reported or study specified enrollment and/or assessment timing but duration of follow-up/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 anti-cancer agents
Figure 1. Search strategy flow chart.
Figure 1.

13,165 articles identified from combined search:
1,103 duplicates removed

12,062 titles/abstracts screened

11,957 excluded

105 articles selected for review

53 excluded

52 identified as relevant and included

56 articles included

4 identified through reference list review