



REVIEW

“Interventions to increase adherence to oral therapies in breast cancer patients: A systematic review based on the behavior change technique taxonomy”

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Abstract

Objective: High rates of non-adherence to oral medications in breast cancer (BC) patients have been reported. Here we provide an up-to-date systematic review of the interventions aimed at increasing adherence to oral medication in BC patients, with a particular focus on the content of the interventions.

Methods: PubMed, Scopus, Embase and Ovid databases and reference lists of relevant studies were searched through October 2022. Studies which (1) described an intervention aimed at increasing adherence to oral anticancer medication, (2) included (or planned to include) at least one sub-group of BC patients, (3) were written in English, and (4) with full-text available were included. The contents of the interventions were coded using the Behavior Change Technique Taxonomy. Quality assessment was conducted using Downs and Black scale.

Results: Thirty-six studies met the inclusion criteria and involved a total sample of 28,528 BC patients. Interventions were mainly delivered with eHealth devices ($n = 21$) and most of them used mobile app. Other studies used in-person modalities (e.g., CBT, relaxation technique) or written materials (e.g., psycho-educational booklet). The behavior change techniques most frequently implemented were “problem solving,” “social support,” “information about health consequences,” and “prompts/cues”. Quality assessment revealed that the higher risk of bias refers to the selection process.

Conclusions: The use of reminders, monitoring patients' medication-taking behaviors and giving feedback were the most frequently implemented techniques in those interventions that resulted significant. If these preliminary observations were to be confirmed by future comparative studies, they should be taken into account when developing new interventions.

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KEYWORDS

behavior change technique taxonomy, cancer, decision-making, endocrine therapy, medication adherence, oncology, oral anticancer medications

1 | BACKGROUND

The use of oral antineoplastic agents in cancer care has seen a rapid increase over the last two decades.¹ While this has led to an easier and more convenient administration of therapy, the issue of non-adherence to medication has become more pressing.² Unlike surgical interventions, radiotherapy, and intravenous treatments, which are administered by healthcare professionals in a clinical setting, oral medications such as endocrine therapy and oral chemotherapy, require a greater involvement of patients in their own treatment management. It is the patients' responsibility to know when, how frequently, and in which doses they should take their medication, often adding to a daily routine already made complex by other lifestyle changes required by a cancer diagnosis (e.g., new dietary requirements, consistent monitoring of symptoms, pressure to engage in physical activity). Moreover, the prolonged duration of the treatment cycle and the often severe side effects induced by the medication, pose additional barriers to an optimal medication adherence.³⁻⁵ Although several definitions with slightly different nuances have been proposed over the years, adherence is commonly described as "the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency."⁶ (p44)

The issue of non-adherence to oral medication is particularly relevant for breast cancer (BC) care, since approximately three quarters of BCs are hormone receptor positive, therefore requiring oral endocrine treatment.^{7,8} The oral endocrine therapy is indeed commonly prescribed for five to 10 years since the first treatment, but many studies⁹⁻¹¹ have shown that adherence to the prescription constantly decrease year by year. A recent review has reported that the rates of 5-year adherence to endocrine therapy in BC patients range from 33.3% to 88.6%, with an average drop of 25.5% from the first to the fifth year.⁴

Accruing evidence suggests that medication non-adherence has a critical impact on clinical outcomes. Indeed, when confronted with adherent patients, non-adherent BC patients have greater risk of developing metastases and BC recurrence, higher rates of mortality and worse disease-free survival.¹²⁻¹⁴ In addition, non-adherence has a significant economic impact: the general cost of non-adherence is estimated to be of approximately US\$100 billion a year in the USA and €125 billion in Europe.¹⁵⁻¹⁹ For what concerns BC, a study showed that the costs associated with low adherence are 26% higher when compared with adherent behaviors.²⁰ For these reasons, the identification of the factors affecting medication non-adherence is of crucial importance.

Adherence and non-adherence to medications are multifaceted behaviors, with complex underlying factors. The interaction of clinical, demographic, psychosocial and healthcare-related

factors are known to influence BC patients' medication-taking behaviors, and may act as barriers or as facilitators of adherence.³ One of the most frequently reported obstacles to adherence is the occurrence of unpleasant side effects caused by the medications (e.g., joint aches, hot flushes, vaginal dryness, weight gain, lack of energy, depression, mood swings,^{21,22} but other factors have also been reported, including concerns about long-term effects associated with medications (e.g., concerns of its toxicity, skepticism about benefits), a reduced perception of urgency in taking the prescribed medications, and not feeling sufficiently supported by health professionals.^{3,5}

Given the clinical and economic implications of non-adherence,^{12,15,17,19} the development and the implementation of interventions aiming at increasing adherence to oral therapies in BC patients is of great relevance. The interventions proposed so far vary greatly in methods and contents. Providing educational materials, developing mobile applications with reminders and other features, implementing different kind of supportive programs led by healthcare providers (e.g., nurses, dietitians and psychologists), are some of the strategies that already have been used to foster adherence to oral medications, but past systematic reviews have shown that despite the richness and variety of these interventions, their effects are modest and often not statistically significant.^{7,23,24}

In recent years many new interventions have been designed or implemented in order to tackle the issue of non-adherence, and, to our knowledge, these new efforts have not been yet systematically reviewed. Furthermore, past systematic reviews^{7,22,23} focused specifically on interventions aimed at increasing endocrine therapy adherence, thus excluding other forms of oral therapy prescribed for BC. In the present review we will provide a more complete overview of the available scientific literature by updating the work carried out in the past and including studies addressing adherence to oral therapies.^{7,23,24}

Consistently, the primary aim of the present work is to systematically review existing interventions aiming to improve BC patients' adherence to the oral medications. This will result in a thorough inventory that can be easily consulted by researchers and clinicians working in the field of medication adherence, offering an up-to-date overview of the state-of-the-art. The secondary aim of the present work is to thoroughly analyze the contents (the 'active components') of the interventions identifying the specific behavior change techniques (BCTs) implemented. Although comparing studies' effectiveness is beyond the scope of this work, the analysis of interventions' contents will allow to generate some preliminary hypotheses regarding which of the implemented techniques appear more promising in fostering medication adherence.

In order to achieve these aims, it was crucial to avail of a common, consensus-based, reliable framework for the classification of

the specific contents of behavior change interventions.²⁵ An interesting attempt to offer such a framework was found in the Behavior Change Technique Taxonomy (BCTT).²⁶ In fact, the BCTT offers a consensus-based nomenclature designed to specify and report the content of complex interventions.²⁷ This tool would help to better understand the main interventions' features and provide useful insights for the development of new and more personalized programs to change behavior. While BCTT has been successfully used in both primary research and systematic reviews addressing different types of behavior change interventions,^{28–30} to our knowledge this work is the first to apply this framework to the review of interventions specifically aimed at addressing adherence to oral therapies in BC.

2 | METHODS

2.1 | Search strategy

A search string combining keywords relating to core review terms was designed to identify all the relevant studies describing interventions to increase adherence to oral medication in BC patients. The words included in the string covered four core concepts: adherence, oral antineoplastic therapy, BC and intervention (see Appendix A for the full string). PubMed, Scopus, Embase and Ovid (Journals@Ovid) databases were searched for relevant records published until 17 October 2022. In addition, a manual search of the reference lists of relevant studies was conducted. The Preferred Reporting Items for Systematic Literature Reviews and Meta-Analysis,³¹ was followed throughout the reporting of this systematic review. This review was registered in the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42022298552. A protocol of the review was not prepared.

2.2 | Inclusion and exclusion criteria

Studies were considered eligible for inclusion in this review as long as (1) they described the proposal, testing or implementation of an intervention aimed at increasing oral anticancer agents adherence, (2) the sample included (or planned to include, in the case of study protocols) at least a sub-group of BC patients with relative specific results, (3) they were available in English, and (4) the full-text was available online. Conference papers, editorials and commentaries were excluded due to the lack of a specific description of the content of the interventions.

2.3 | Screening and quality assessment

Relevant reports were selected by two authors (MP and CM) that independently inspected titles and abstracts and applied the eligibility criteria. Reports were sorted as “accepted”, “rejected” or “for

discussion”, and the discrepancies were sent to a third author (LL) for the assessment; disagreements were settled by discussion until reaching a consensus. For the selected articles, the full-text version was then read by one of the authors (MP) to further confirm its relevance and its conformity to the eligibility criteria. When the full-text wasn't available online, it was requested to the corresponding author. The quality of the included studies was assessed with Downs and Black's methodological quality scale,³² a 27-item scale that provides a score on five different methodological quality dimensions: reporting bias (RB), external validity (EV), internal validity (IV), confounding (Selection Bias (SB)), and statistical power (P). The quality assessment was conducted by two authors (MP and CM), and disagreements were resolved by discussion until reaching a consensus.

Consistently with other previous reviews^{33,34} the statistical power evaluation was simplified: one point was assigned if the necessary sample size required to detect a significant difference had been calculated, and zero was assigned if it had not, or if the sample size was insufficient to reach adequate statistical power.

2.4 | Data extraction and summary

For each one of the included papers, the following information was extracted: authors, year of publication, country, patient sample, cancer stage, drug type, study design, mode of delivery, method of adherence measurement, brief description of the intervention and, if present, of the comparison/control group, time of assessment(s), and results. Data were extracted by one of the authors (MP), organized in an Excel spreadsheet, and checked by a second author (CM). The summary of the extracted data is reported in Tables 1 and 2.

Additionally, the interventions of the included studies were analyzed using the BCTT, a standardized and systematic way of categorizing the implemented BCTs. After completing the official BCTT online training (www.bct-taxonomy.com), one of the authors (MP) coded each described intervention using the taxonomy to analyze and classify the specific content of each study. Each included intervention was separately analyzed in its specific components, highlighting the techniques used to modify behavioral strategies and increase medication adherence. The taxonomy lists 93 distinct, precise and well-defined BCTs: these are clustered in 16 groups and constitute the “active ingredients” of behavioral change interventions, the specific contents that are supposed to bring about the desired change (e.g., increased medication adherence). The BCTs identified in each study are reported in Table 3.

3 | RESULTS

3.1 | Summary of study characteristics

The search returned a total of 3079 articles. After removing any duplicates, screening titles and abstracts, 49 articles were considered eligible. Of these, two articles were excluded since the corresponding

TABLE 1 Study characteristics.

First author, year	Country	Patient sample, cancer stage	Drug type	Study design	Mode of delivery	Method(s) of adherence
Arch, 2022	USA	88, early-stage I: 43 C: 45	ET (tamoxifen and aromatase inhibitors)	RCT ^a	eHealth (online self-paced intervention)	Self-report and EMM
Bhandari, 2019	USA	86, early-stage	ET (tamoxifen and aromatase inhibitors)	Single-arm study ^a	Other	Pill count
Bluethmann, 2021	USA	n/a, early-stage	ET (aromatase inhibitors)	RCT ^b	eHealth (videoconference)	Self-report and MPR
Chalela, 2018	USA	n/a	ET (tamoxifen and aromatase inhibitors)	RCT ^b	eHealth (mobile app)	Self-report and medical records
Eli, 2009	USA	237, early-stage I: 123 C: 114	ET (tamoxifen and aromatase inhibitors)	RCT	eHealth (written/telephone)	Pharmacy records
Ferraris, 2020	Italy	88, early-stage I: 44 C: 44	ET (tamoxifen)	RCT	Other	Self-report
Getachew, 2022	Ethiopia	162, all stages I: 87 C: 75	ET (tamoxifen)	RCT	In person (with also eHealth elements and written materials)	Self-report and MPR
Graetz, 2018	USA	48, early-stage I: 23 C: 25	ET (aromatase inhibitors)	RCT ^a	eHealth (mobile app)	Self-report
Hadji, 2013	Germany	4844, early-stage I: 2442 C: 2402	ET (aromatase inhibitors)	RCT	Educational/written material	Self-report and prescription data
Heisig, 2015	Germany	174, all stages	ET (tamoxifen and aromatase inhibitors)	Single-arm study	Educational/written material	Self-report

TABLE 1 (Continued)

First author, year	Country	Patient sample, cancer stage	Drug type	Study design	Mode of delivery	Method(s) of adherence
Hershman, 2020	USA	724, early-stage I: 360 C: 364	ET (aromatase inhibitors)	RCT	eHealth (text messaging)	Self-report and urine assays
Jacob, 2015	Germany	4915, n/a I: 1874 C: 3041	ET (tamoxifen and aromatase inhibitors)	Retrospective cohort study	Other	Electronic medical records
Jacobs, 2022	USA	100, early-stage I: 50 C: 50	ET	RCT ^a	eHealth (videoconference)	Self-report and EMM
Komatsu, 2020	Japan	155, metastatic I: 78 C: 77	Capecitabine, lapatinib and tegafur/gimeracil/oteracil	RCT	In person	MPR
Krok-Schoen, 2019	USA	39, early-stage	ET (tamoxifen and aromatase inhibitors)	Single-arm study ^a	eHealth (mobile app)	Self-report
Lee, 2020	USA	7867, early-stage I: 4287 C: 3580	ET (tamoxifen and aromatase inhibitors)	Retrospective cohort study	Educational/written material	MPR
Mamguem Kanga, 2020	France	n/a, early-stage	ET	RCT ^b	eHealth (tablet)	Self-report
Markopoulos, 2015	International (18 countries)	2757, early-stage I: 1379 C: 1378	ET (aromatase inhibitors)	RCT	Educational/written material	Self-report and provider report
Meguerditchian, 2016	Canada	n/a, early-stage	ET (tamoxifen and aromatase inhibitors)	Non-randomized controlled study ^b	eHealth (eHealth tool for providers)	MPR
Moon, 2019	UK	41, early-stage	ET (tamoxifen)	Single-arm study ^a	Educational/written material	Self-report
Mougalian, 2017	USA	200, early-stage I: 100 C: 100	ET (tamoxifen and aromatase inhibitors)	Non-randomized controlled study ^a	eHealth (mobile app)	Self-report

(Continues)

TABLE 1 (Continued)

First author, year	Country	Patient sample, cancer stage	Drug type	Study design	Mode of delivery	Method(s) of adherence
Myers, 2022	Canada	27, early-stage	ET (tamoxifen and aromatase inhibitors)	Single-arm study ^a	eHealth (videoconference)	Self-report
Paladino, 2019	USA	n/a, early-stage	ET (tamoxifen and aromatase inhibitors)	RCT ^b	eHealth (mobile app)	Self-report and EMM
Park, 2021	South Korea	61, early-stage I: 31 C: 30	ET (tamoxifen and aromatase inhibitors)	RCT	eHealth (mobile app)	EMM
Ream, 2021	USA	135, early-stage I1: 44 I2: 49 C: 42	ET	RCT	In person	Self-report
Riis, 2020	Denmark	134, early-stage I: 65 C: 69	ET	RCT ^a	Other	Electronic medical records
Sanft, 2021	USA	n/a, early-stage	ET (tamoxifen and aromatase inhibitors)	RCT ^b	In person	Self-report and urine assays
Shelby, 2019	USA	n/a, early-stage	ET	RCT ^b	eHealth (telephone)	Self-report and EMM
Smith, 2022	UK	n/a, early-stage	ET (tamoxifen, raloxifene, and aromatase inhibitors)	RCT ^b	eHealth (videoconference)	Self-report
Tan, 2020	Singapore	244, early-stage I: 123 C: 121	ET (aromatase inhibitors)	RCT	eHealth (text messaging)	Self-report
Von Blanckenburg, 2013	Germany	n/a, early-stage	ET (tamoxifen and aromatase inhibitors)	RCT ^b	In person	Self-report
Wagner, 2016	USA	230, early-stage I: 36 C1: 163 C2: 31	ET	Cohort study ^a	eHealth (telephone)	MPR
Yanez, 2022	USA	n/a	ET	RCT ^b	eHealth (online tool)	Self-report, EMM and medical/pharmaceuticals records

TABLE 1 (Continued)

First author, year	Country	Patient sample, cancer stage	Drug type	Study design	Mode of delivery	Method(s) of adherence
Yu, 2012	China	516, early-stage I: 252 C: 264	ET (aromatase inhibitors)	Non-randomized controlled study	Educational/written material	MPR
Yu, 2021	China	4475, early-stage I: 648 C1: 2966 C2: 861	ET	Retrospective cohort study	eHealth (mobile app)	Self-report
Ziller, 2013	Germany	181, all stages I1: 57 I2: 57 C: 57	ET (aromatase inhibitors)	RCT	eHealth (written/telephone)	Self-report and MPR

Abbreviations: C, control group; EMM, electronic medication monitor; ET, endocrine therapy; I, intervention group; MPR, medication possession ratio; n/a, not available; RCT, randomized controlled trial.
^aPilot study.

^bStudy Protocol.

TABLE 2 Intervention characteristics.

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Arch, 2022	Values intervention + adjuvant endocrine therapy education (REACH - resources and education for adherence to cancer hormonal therapy)	Adjuvant endocrine therapy education	Baseline, 1 week, 3 and 6 months (self-report) and each month for 6 months (EMM)	Significantly higher adherence in intervention group (adherence rate: 87.8 vs. 96.3%, $p = 0.027$), but only in the first month
Bhandari, 2019	Daily blister pack (bubble packaging)	n/a	1 year	Adherence was higher than that in historical studies (adherence rate: 97%)
Bluethmann, 2021	An evidence-based physical activity program that includes bi-weekly, supervised exercise sessions plus 30 min of education. It included: 8 weeks of supervised sessions plus 8 weeks of self-guided home sessions with periodic phone coaching	Enhanced standard care (written materials and assessment visits)	Baseline, 4, 6 and 12 months	n/a
Chalela, 2018	App + patient navigation	Standard care	Baseline, 3 and 6 months	n/a

(Continues)

TABLE 2 (Continued)

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Elli, 2009	Written information + patient navigation	Enhanced standard care (written materials)	6 and 12 months	No significant differences in adherence between the groups; $d = 0.132$
Ferraris, 2020	One oral tablet/day containing 80 mg of red clover extract for 24 months + diet-lifestyle intervention	Placebo + diet-lifestyle intervention	24 months	The adherence of the total sample was higher than reported in literature (proportion of adherent patients: 89%)
Getachew, 2022	A nurse-delivered comprehensive package of services including education, provision of written material, reminder with phone call, additional empathetic counseling and monitoring of medication refill	Standard care	Baseline, 6 and 12 months	Participants in the intervention group reported significantly higher adherence at 12 months (proportion of adherent patients: 70 vs. 44.8%, $p = 0.036$); $d = 0.580$
Graetz, 2018	App + reminder (weekly reminders to use the app)	App (no reminders)	Baseline and 6–8 weeks	Participants in the app + reminder group reported significantly higher adherence (proportion of adherent patients: 100 vs. 72.7%, $p < 0.05$); $d = 1.684$
Hadji, 2013	Standard care + educational materials	Standard care	Baseline, 12 and 24 months	No significant differences in adherence between the groups; $d = 0.016$
Heisig, 2015	Enhanced information	n/a	Baseline and 3 months	Post-intervention adherence was higher, but the difference wasn't statistically significant; $d = 0.169$
Hershman, 2020	Text messaging (twice a week over 36 months)	No text messaging	Baseline and every 3 months up to 36 months	No significant differences in adherence between the groups; $d = 0.229$
Jacob, 2015	Disease management program (DMP)	Standard care	3 years	The rate of therapy discontinuation at 3 years was lower in DMP patients (32.7 vs. 39.6%, $p < 0.001$); $d = 0.166$
Jacobs, 2022	A patient-centered, evidence-based, small-group, videoconference intervention (symptom-targeted randomised intervention for distress and adherence to adjuvant endocrine therapy—STRIDE)	Medication monitoring control group	Baseline, 12 and 24 weeks	No significant differences in adherence between the groups; $d = 0.07$
Komatsu, 2020	Nurse-led self-management intervention	Standard care	Baseline and 3 months	No significant differences in adherence between the groups; $d = 0.048$
Krok-Schoen, 2019	A smartphone, text-based reminder system to increase adherence, coupled with an interactive smartphone app	n/a	Baseline and 3 months	Significant improvements in adherence rate ($p = 0.015$); $d = 0.493$
Lee, 2020	Health system outreach program	Pre-outreach cohort	Every 12 months after prescription	Adherence (+4.9%; $d = 0.125$) and discontinuation rates (–4%) improved modestly

TABLE 2 (Continued)

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Mamgum Kanga, 2020	Systematic HRQoL assessment (using a tablet, prior to each consultation, with presentation of scores to clinicians) coupled with therapeutic information	Standard care	Baseline and 12 months	n/a
Markopoulos, 2015	Educational materials	Standard care	Baseline, 1 and 2 years	Compliance did not improve; $d = 0.004$
Meguerditchian, 2016	A patient-specific, real-time eHealth alert delivered at point-of-care	Standard care	Baseline and 18 months	n/a
Moon, 2019	A self-management intervention via a paper booklet	n/a	Baseline and completion of the intervention (2–12 weeks)	Unintentional non-adherence was lower after the intervention, but the difference wasn't statistically significant; $d = 0.15$
Mougalian, 2017	A bidirectional text-message application that tracks adherence, records symptoms, and alerts the clinical team	Historical control	Every week for 3 months	Intervention group reported high adherence (proportion of adherent patients: 93.3%)
Myers, 2022	A virtual supervised strength and aerobic exercise program (BE-FIT - breast cancer endocrine therapy fitness)	n/a	Baseline and 6 weeks	Post-intervention adherence was higher, but the difference wasn't statistically significant; $d = 0.333$
Paladino, 2019	1: App and weekly reminders to use it; 2: App, weekly reminders and feedback on the use of the app	Standard care	12 months (EMM) and 12, 18, 24, 30, 36 months (self-report) when possible	n/a
Park, 2021	A smart pill bottle paired with the Pillsy mobile application	Standard care	28 days	Significantly higher adherence rate in intervention group (97.3 vs. 88.33%, $p = 0.004$); $d = 0.787$
Ream, 2021	1: a CBT intervention comprising cognitive-behavioral components of CBSM; 2: A relaxation training modeled after the relaxation component of CBSM	Health education	Baseline, post intervention (5 weeks), 6 and 12 months and 8 years	Significantly higher adherence in intervention group 2
Riis, 2020	Individualized follow-up care	Standard follow-up care	Baseline and every 3 months for 2 years	No significant differences in adherence between the groups; $d = 0.301$
Sanft, 2021	A yearlong, 16 session, nutrition and exercise intervention	Standard care	Baseline, post-chemotherapy, 1 and 2 years	n/a
Shelby, 2019	A telephone-based coping skills training that teaches patients adherence skills and techniques for coping with problematic symptoms (CST-AET)	Health education	Baseline, 3, 6, 12, and 18 months	n/a

(Continues)

TABLE 2 (Continued)

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Smith, 2022	An ACT intervention including an individual session and three group sessions + access to a website containing evidence-based methods for self-managing side-effects	Standard care	Baseline, 3 and 6 months	n/a
Tan, 2020	Text-messaging reminder	Standard care	Self-report: Baseline, 6 months and 1 year; hormone level: Baseline and 1 year	Significantly higher adherence in intervention group (proportion of adherent patients: 72.4 vs. 59.5%, $p = 0.034$) at 6 months; $d = 0.318$
Von Blanckenburg, 2013	Side-effect prevention training (SEPT)	Control group: Standard care; Attention control group: Supportive therapy	Baseline, post-treatment, 3 and 6 months	n/a
Wagner, 2016	Outreach conducted by health plan care managers	1 (adherent group): Standard care; 2 (not contacted): Standard care	Baseline and 6 months	Adherence in the intervention group was higher, but the difference wasn't statistically significant; $d = 0.557$
Yanez, 2022	An online, mindfulness-based program (MyJourney) designed to improve adherence to endocrine therapy	Health education website	Baseline, 4 and 8 weeks, 6 and 12 months	n/a
Yu, 2012	A patient support program comprising educational support material and a follow-up reminder service	Standard care	1 year	No significant differences in persistence between the groups; $d = 0.016$
Yu, 2021	An app enabling communication between patients and medical workers and providing personalized management	1 (pre-app): Standard care; 2 (app non-used): Standard care	Every 3 months within the first 2 years after surgery, every 6 months between 3 and 5 years, and once a year after 5 years	The use of the app was not significantly associated with treatment compliance; $d = 0.331$
Ziller, 2013	1: Reminder letters and information booklet; 2: Telephone reminder and information	Standard care	12 months	Adherence in the intervention groups was higher, but the difference wasn't statistically significant (1: $d = 0.311$; 2: $d = 0.274$)

Abbreviation: n/a, not available.

TABLE 3 Techniques identified in each intervention using the behavior change technique (BCT) taxonomy.

Author	Year	1.1	1.2	1.4	2.1	2.2	2.3	3.1	3.3	4.1	5.1	5.2	6.1	6.2	7.1	7.3	8.1	9.1	9.2	10.4	11.2	12.5	12.6	13.2	13.4	14.8
Arch	2022	X								X					X					X						X
Bhandari	2019				X																	X				
Bluethmann	2021							X																		
Chalela	2018	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Elli	2009	X						X	X	X	X										X					
Ferraris	2020																									
Getachew	2022				X			X		X	X				X			X								
Graetz	2018					X	X																			
Hadji	2013							X		X	X				X						X					
Heisig	2015									X	X							X								
Hershman	2020							X		X	X				X			X								
Jacob	2015									X	X															
Jacobs	2022	X			X			X		X	X							X			X			X	X	
Komatsu	2020	X						X		X	X							X								
Krok-Schoen	2019	X						X		X	X				X					X						
Lee	2020					X									X											
Manguem Kamga	2020									X	X				X			X								
Markopoulos	2015									X	X										X					
Meguerditchian	2016				X																					
Moon	2019	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	
Mougalian	2017	X						X		X					X											
Myers	2022																						X			
Paladino (1)	2019						X																			
Paladino (2) ^a						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Park	2021					X		X							X						X					
Ream (1)	2021						X																	X		

(Continues)

TABLE 3 (Continued)

Author	Year	1.1	1.2	1.4	2.1	2.2	2.3	3.1	3.3	4.1	5.1	5.2	6.1	6.2	7.1	7.3	8.1	9.1	9.2	10.4	11.2	12.5	12.6	13.2	13.4	14.8	
Ream (2) ^a							X														X		X				
Riis	2020						X																				
Sanft	2021	X						X																			
Shelby	2019	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smith	2022	X					X										X				X						
Tan	2020			X										X													
Von Blanckenburg	2013	X					X			X								X				X		X			
Wagner	2016						X										X										
Yanez	2022						X			X										X		X					
Yu	2021					X									X												
Yu	2012									X																	
Ziller (1)	2013						X			X				X													
Ziller (2) ^a			X					X		X				X				X									

Note: 1.1 = Goal setting (behavior); 1.2 = Problem solving; 1.4 = Action planning; 2.1 = Monitoring of behavior by others without feedback; 2.2 = Feedback on behavior; 2.3 = Self-monitoring of behavior; 3.1 = Social support (unspecified); 3.3 = Social support (emotional); 4.1 = Instruction on how to perform the behavior; 5.1 = Information about health consequences; 5.2 = Saliency of consequences; 6.1 = Demonstration of the behavior; 6.2 = Social comparison; 7.1 = Prompts/cues; 7.3 = Reduce prompts/cues; 8.1 = Behavioral practice/rehearsal; 9.1 = Credible source; 9.2 = Pros and cons; 10.4 = Social reward; 11.2 = Reduce negative emotions; 12.5 = Adding objects to the environment; 12.6 = Body changes; 13.2 = Framing/reframing; 14.8 = Reward alternative behavior.

^aStudies in which more than one intervention is proposed are reported twice.

full-text was not available, while 11 were excluded after assessing the eligibility of the full-text (see Figure 1 for a detailed flowchart of the selection process).

All the examined studies were published between 2009 and 2022. Of these, 19 studies were conducted in North America,³⁵⁻⁵³ 10 were conducted in Europe,⁵⁴⁻⁶³ one was an international study in which data were collected in 18 different countries,⁶⁴ one was conducted in Africa,⁶⁵ and the remaining five took place in Asia.⁶⁶⁻⁷⁰

With regards to the design, the examined studies consisted of 24 randomized controlled trials (RCT), of which nine were protocols, and four were pilot studies; the other 12 studies were retrospective and prospective cohort studies, single-arm studies, and non-randomized controlled studies, of which six were pilot studies and one was a protocol.

Following the classification proposed by Osterberg,¹⁶ only two studies included a direct objective measure of adherence collecting urine assays,^{40,48} while the other 34 studies included indirect measures (e.g., self-report, pill count). Specifically, in 10 papers adherence was assessed only using prescription data, pill count or electronic medication monitors (EMM). While the remaining studies measured adherence with different tools: 26 papers assessed adherence using self-report questionnaires alone ($n = 13$) or paired with other measures (e.g., prescription data, provider report, urine assays).

All the examined studies considered adherence to oral endocrine therapy (e.g., tamoxifen, aromatase inhibitors), except for one study addressing oral chemotherapy (i.e., capecitabine and tegafur/gimeracil/oteracil) and targeted therapy (i.e., lapatinib).⁶⁶

The interventions were explicitly based upon different theoretical frameworks and models in more than one third ($n = 15$) of the

included studies. Among these, social cognitive theory⁷¹ was the more frequently applied,^{36,37,46,48,49} followed by Cognitive Behavioral Therapy.^{47,52,62,72-74} Other interventions were based on the models of concordance and shared decision making,^{66,75} the theory of planned behavior,^{59,68,76} the health belief model,^{38,53,77} the common-sense model of self-regulation,^{59,78} the Acceptance and Commitment Therapy,^{51,61,79} the Mindfulness-Based Stress Reduction,^{53,80} and the self-affirmation theory.^{51,81}

Across the articles examined, the sample size varied between 27 and 7867, with a total of 28,528 BC patients. Only one sample was composed entirely of metastatic BC patients,⁶⁶ while other three studies recruited both early-stage and metastatic patients.^{56,63,65} Two studies did not specify patients' cancer stage^{37,57} and all the others included only early-stage BC patients.

The characteristics of the included studies are synthesized in Table 1.

3.2 | Type of intervention

The interventions described in the studies examined vary both in format and in content. Further, the interventions were delivered in person, via electronic devices (i.e., computer, tablet, telephone/smartphone), via written materials or in different combinations of these tools. The following paragraphs synthesize the delivery mode of interventions, while the specific contents are described in the BCTs paragraph.

An in-depth description of the interventions is provided in Table 2.

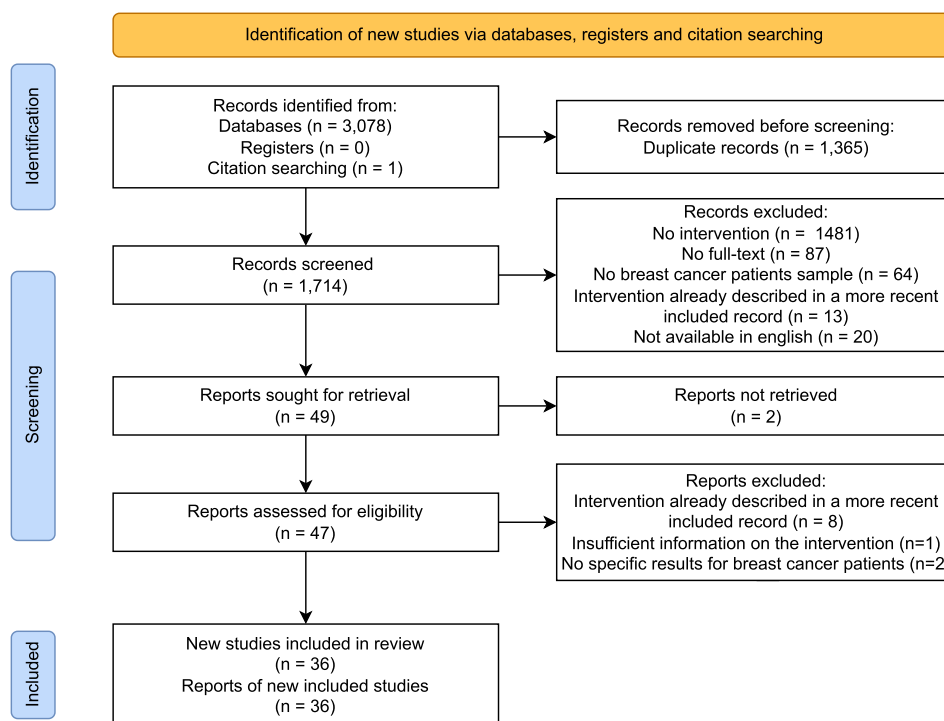


FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow.

3.2.1 | eHealth interventions

The majority of the interventions ($n = 21$) were delivered through electronic devices (i.e., computer, tablet, telephone/smartphone), and several of these ($n = 7$) used mobile applications. Five studies involving eHealth technologies have reported significant results in term of medication adherence.^{39,41,51,67,68} The interventions described in these studies rely on the use of bespoke mobile applications featuring adherence tracking tools and reminder systems, with the exception of one study in which a text message reminders system was tested,⁶⁸ and another one in which a brief values intervention was delivered online together with educational contents.⁵¹ The other 16 eHealth interventions here examined adopted the following modalities: the use of phone calls to deliver patient navigation, outreach programs or simple information and reminders,^{38,50,63} the use of mobile app designed to facilitate communication between outpatients and medical workers,⁷⁰ the use of videoconferences to deliver different group or individual interventions,^{45,52} and the use of text messages to track adherence and symptoms or deliver educational material.^{40,44} These interventions did not lead to significant improvements in patients' adherence levels. Among the reviewed studies, there were also eight protocols^{36,37,43,46,49,53,58,61} containing the description of interventions implementing eHealth-based strategies to improve medication adherence.

3.2.2 | In-person interventions

The interventions described in five studies were delivered in person by healthcare professionals (i.e., nurses, clinical psychologists and dietitians) or psychology students.^{47,48,62,65,66} Among these studies, two RCTs reported significant results.^{47,65} In Ream and colleagues' study⁴⁷ the research team compared three interventions: one of them consisted of different components of Cognitive Behavioral Stress Management (CBSM), another provided a relaxation training modeled after the relaxation components of CBSM, and the other one was a health education program. In the other mentioned study a comprehensive package of nurse-delivered services to increase adherence to tamoxifen was tested against standard care.⁶⁵ Other interventions delivered through in-person modalities consisted in a nurse-led self-management program, a side-effect prevention training, and a nutrition and exercise intervention aiming at preventing adverse treatment-related side-effects.^{48,62,66}

3.2.3 | Interventions delivered through written material

In six of the examined studies the provision of different kinds of written material (i.e., letters, self-management booklets, leaflets) can be considered the main core of the proposed interventions. Among these studies, Lee et al.⁴² investigated an outreach program

consisting in mailed reminder letters (and, eventually, telephone follow-up calls) which led to significantly increased adherence.

The other interventions involved the delivery of written educational material pertaining the mechanisms of anticancer medications, their benefits and side effects, alone^{55,56,64} or in combination with a telephone follow-up reminder service.⁶⁹ Another study tested a self-management psycho-educational booklet containing information about medication and their side-effects and providing different Cognitive Behavioral Therapy-based activities (e.g., goal setting, problem solving).⁵⁹

3.2.4 | Other interventions

The remaining interventions could not be classified in any of the previous categories. One of these aimed at increasing patients' adherence by filling their prescriptions in the form of daily blister packs,³⁵ while another study tested the effects of dietary supplement and lifestyle changes in reducing treatment side effects and consequently increasing adherence.⁵⁴ Finally, two types of individualized programs were tested: in the first, follow-up care was individualized according to electronic patient reported outcomes⁶⁰; the other study tested the impact of the disease management program (i.e., patient-centered, multidisciplinary programs designed to improve quality of care) in increasing adherence levels.⁵⁷

3.3 | Behavior change techniques

The content of the interventions was coded and classified following the BCTT.²⁶ In the examined interventions, 25 out of the 93 BCTs outlined in the taxonomy were identified. The number of BCTs found in each intervention varied from 0 (where the intervention was only indirectly affecting adherence, being therefore impossible to classify it following this taxonomy) to 17. The BCTs implemented in each intervention are reported in Table 3.

The techniques most often implemented in these interventions were: "problem solving" ($n = 14$), "social support" ($n = 20$), "information about health consequences" ($n = 22$), and "prompts/cues" ($n = 16$). Among the interventions that yielded statistically significant results in improving adherence, the most implemented BCTs were "feedback on behavior" ($n = 4$), "information about health consequences" ($n = 4$) and "prompts/cues" ($n = 6$). For a description of these BCTs see Michie et al., 2013.²⁶

3.4 | Risk of bias

The Downs and Black's methodological quality scale³² is composed of 27 questions, and it allows the evaluation of the study on five different dimensions (i.e., reporting bias - RB, external validity - EV, internal validity - IV, selection bias - SB, and power - P). The results of the methodological quality assessment are reported on Table 4

TABLE 4 Risk of bias assessment—Downs & Black's methodological quality scale.³²

First author, year	RB (0–11)	EV (0–3)	IV (0–7)	SB (0–6)	P (0–1)	Tot (0–28)
Arch, 2022	9	3	6	6	1	25
Bhandari, 2019	8	2	4	0	0	14
Eil, 2009	7	2	6	5	0	20
Ferraris, 2020	10	1	7	5	1	24
Getachew, 2022	9	2	4	1	1	17
Graetz, 2018	8	2	5	4	0	19
Hadji, 2013	9	2	4	6	1	22
Heisig, 2015	9	2	4	1	0	16
Hershman, 2020	9	2	5	6	1	23
Jacob, 2015	7	3	3	2	0	15
Jacobs, 2022	9	2	5	6	1	23
Komatsu, 2020	9	2	5	6	0	22
Krok-Schoen, 2019	9	2	3	0	0	14
Lee, 2020	9	3	5	3	0	20
Markopoulos, 2015	8	2	4	6	1	21
Moon, 2019	9	2	4	1	0	16
Mougalian, 2017	9	2	5	2	0	18
Myers, 2022	10	2	5	1	0	18
Park, 2021	9	2	5	5	0	21
Ream, 2021	9	2	5	4	0	20
Riis, 2020	9	2	5	5	0	21
Tan, 2020	9	2	5	6	0	22
Wagner, 2016	9	2	5	3	0	19
Yu, 2012	9	2	5	2	1	19

(Continues)

TABLE 4 (Continued)

First author, year	RB (0–11)	EV (0–3)	IV (0–7)	SB (0–6)	P (0–1)	Tot (0–28)
Yu, 2021	9	2	3	2	1	17
Ziller, 2013	9	2	6	5	1	23
Means	8.81	2.08	4.73	3.58	0.38	19.58
SD	0.69	0.39	0.96	2.14	0.50	3.07
Protocols						
Bluethmann, 2021	6	1	3	4	1	15
Chalela, 2018	6	1	3	4	1	15
Manguem Kamga, 2020	7	1	3	3	1	15
Meguerditchian, 2016	7	0	3	0	1	11
Paladino, 2019	8	2	3	4	1	18
Sanft, 2021	6	1	3	4	1	15
Shelby, 2019	6	2	3	4	0	15
Smith, 2022	7	2	3	4	1	17
Von Blanckenburg, 2013	6	1	4	4	1	16
Yanez, 2022	6	1	3	4	1	15
Means	6.5	1.2	3.1	3.5	0.9	15.2
SD	0.71	0.63	0.32	1.27	0.32	1.81

Abbreviations: EV, External Validity; IV, Internal Validity; P, Power; RB, Reporting Bias; SB, Selection Bias; SD, Standard Deviation.

(lower scores indicate higher risk of bias). Given the differences in availability of data between study protocols and all the other included records, their methodological quality scores have been reported in two separated sections of Table 4.

For what concerns those studies describing the implementation of an intervention and its results (i.e., all the studies with the exclusion of study protocols, $n = 26$), “selection bias” is the dimension with higher risk of bias score, with a mean of 3.58 (SD = 2.14, range = 0–6). “Internal validity” and “external validity” received medium scores, with means of respectively 4.73 (SD = 0.96, range = 0–7) and 2.08 (SD = 0.39, range = 0–3), while the RB dimension resulted to be the one with lower risk of bias, with a mean of 8.81 (SD = 0.69, range = 0–11).

Only 10 of the 26 studies with available results scored one on the dimension of statistical power.

Protocols had lower total scores on average (15.2 against 19.58), as lower were the single dimensions scores: RB = 6.5 (SD = 0.71), EV = 1.2 (SD = 0.63), IV = 3.1 (SD = 0.32), SB = 3.5 (SD = 1.27). The only exception was the statistical power dimension: in contrast with the other types of studies, only one out of 10 protocols did not mention a power analysis.

4 | DISCUSSION

The negative effects of medication non-adherence and the increasing diffusion of oral anti-cancer therapies justify the surging interest in adherence enhancing interventions for BC patients, as testified by the large number of studies addressing this issue. Indeed, the number of studies proposing or testing these interventions has substantially increased: 25 out of 36 of the included studies were published between 2018 and 2022.

All the included studies were focused on adherence to endocrine therapy (e.g., tamoxifen, aromatase inhibitors), except one, focusing on oral chemotherapy (i.e., capecitabine and tegafur/gimeracil/oteracil) and targeted therapy (i.e., lapatinib).⁶⁶ The greater attention given to endocrine therapy adherence may be explained by the different duration of these treatments: indeed endocrine treatments are usually taken for five to 10 years, while other oral treatments are usually prescribed for shorter duration.⁸² A greater duration of treatment may facilitate the emergence of adherence issues, as testified by the fact that non-adherence commonly increases with time from treatment initiation.⁴ The smaller extent of non-adherence to oral chemotherapy and targeted therapy seems supported by the results of the included study by Komatsu et al;⁶⁶ the researchers conducted a RCT testing the effect of a self-management support program on metastatic BC patients' adherence to oral chemotherapy and targeted therapy. The intervention did not result in improved adherence, since both the groups (control group and intervention group) reported high levels of medication adherence (>90% medication possession ratio). Nonetheless, including this study in our analysis gave us the possibility to observe and highlight the disparity of attention given to adherence pertaining to different

categories of drugs, thus allowing us to offer a broader overview of this field of research.

The studies here examined showed a variety of different approaches to reduce medication non-adherence, highlighting the heterogeneity that characterizes this field of research. Despite this variability, the predominance of eHealth interventions clearly emerges from the data here collected. In fact, the interventions were delivered mainly through Internet and/or communication technologies in the majority of the studies here reviewed (21 out of 36 studies), testifying the increasing relevance of this intervention modality in cancer care.^{83–86}

The included studies differ not only for the specific intervention characteristics, but also for the use of different adherence measures, for the different duration of subjects' assessment and follow-up, and for the various study designs. Notably, 10 study protocols were included; despite the lack of relevant information pertaining interventions' efficacy, their inclusion led to a broader overview of the state-of-the-art pertaining adherence increasing interventions, offering a larger and updated picture of this field of research. The heterogeneity of the studies retrieved strongly reduces the comparability of studies' results, thus the comparison of interventions' effectiveness is not within the scope of this work. Nonetheless, the thorough analysis of interventions' characteristics and contents here conducted allows to draw some preliminary observations and to generate some hypotheses that may be further tested in future research. In this perspective, some of these hypotheses are outlined and commented below.

First of all, the analysis of interventions' specific contents and the variety of interventions' results seems to support the idea of non-adherence as a complex phenomenon with a multifactorial origin, requiring therefore complex solutions.⁴ Furthermore, statistically significant improvements in adherence were reported in only nine out of the 26 studies for which the results were available. A similar outcome has been explained in another review by the reduced length of follow-ups: authors highlighted that since adherence decreases over time, short follow-ups may not entirely capture interventions' impact.²³ Moreover, the mere fact to participate in a study measuring adherence could in itself foster the propensity for following the physician's prescriptions. Nonetheless, these possible explanations may not be enough to justify these findings: thus the importance of finding significant strategies and interventions targeting medication adherence in this particular clinical population is still very relevant.^{7,23,24} It is therefore crucial to identify those BCTs that seem to be more promising in increasing adherence to medication. In this vein, coding the different techniques with BCTT allowed to analyze and classify each intervention with more precision, rigor and clarity, and thus led to the following preliminary observations. Notably, although the BCTT was applied to all the included studies, the following observations have been drawn focusing on those 26 studies reporting the results of the interventions (therefore excluding study protocols).

The fact that the BCT “feedback on behavior” (i.e., monitoring and providing feedback on the desired behavior's performance) was

identified in four of the nine interventions that resulted in significantly better adherence rates, and in only one of the 18 with statistically non-significant results, may suggest that this technique can have some efficacy in increasing medication adherence.^{87,88}

Although equally frequent in the interventions resulted significant ($n = 4$), the same consideration cannot be drawn for the technique “information about health consequences”, which in our case consists in giving information to the patients about the consequences of adhering or not adhering to their prescribed oral medication. In fact, this BCT is even more frequent in those interventions that failed to significantly improve participants' adherence rates (present in 11 out of 18 interventions). This seems to suggest that providing information in favor of the desired behavior, although may be useful, may not be in itself sufficient to improve adherence outcomes. The observation that providing educational material alone may not constitute an effective behavior change strategy has already been put forward in literature^{23,89} and the results here reported seem to further corroborate this hypothesis. This is consistent with the characterization of non-adherence as a complex phenomenon, originating from the interaction of multiple factors rather than being simply the result of lack of information.^{3,4,89}

Another promising technique often implemented in significant interventions is “prompts/cues”. This BCT was indeed present in six out of nine of the studies reporting significant results (while it was implemented only in seven out of 18 of the interventions which didn't lead to significant results). “Prompts/cues” usually takes the form of reminders delivered with different frequencies (e.g., daily, weekly, monthly), often availing of appositely designed mobile applications. Prompting or cueing the medication-taking behavior may be especially relevant in reducing non-intentional non-adherence, which is the form of non-adherence led by forgetfulness or misunderstanding of provider's indications, rather than by intentional decision-making.⁹⁰

Finally, while a recent review⁴ indicated social support as one of the factors affecting adherence to endocrine treatment in BC patients, applying the BCT “social support” led to a significant increase in adherence rates only three out of the 15 times it was implemented in studies reporting results of interventions. This further confirms the complexity of the interactions of medication taking behaviors' determinants, and the resulting difficulties in influencing those determinants in order to increase adherence.⁴

4.1 | Study limitations

This review has some limitations that should be considered. Firstly, there is a possibility that not all the pertinent studies may have been captured by the search string. A thorough search strategy was applied to four different databases, however the exclusion of conference abstracts and gray literature, which was justified by the necessity of comprehensive descriptions of the interventions, may have led to the exclusion of relevant material. Furthermore, it is possible that some of the specific contents of the interventions were bypassed

by the BCTT classification: although some of the techniques may have been present, they may not have been coded due to incomplete or generic intervention descriptions. Following BCTT coding instructions (www.bct-taxonomy.com), only those techniques whose implementation was explicitly stated and clearly described were coded. It is also worth mentioning again that adherence measurement was not homogeneous among the included studies: not only the methods of measurement were different (e.g., self-report, EMM, urine assays), but also the way in which adherence measures were used varied greatly. Indeed, while some researchers chose to use adherence as a continuous variable,^{38,39,41} others used it as a dichotomous value (i.e., adherent vs. non-adherent) and set different thresholds: most of them considered adherent those subjects who took at least 80% of their prescribed medication,^{36,37,44} others set the threshold at 90%⁶⁶ or at 75%,⁴⁸ and others used the cut-off scores of self-report measures.^{58,59} Furthermore, in some studies different terms were used with slightly different meanings or nuances (i.e., persistence—taking the medication for the prescribed length of time, discontinuation—stopping taking the prescribed medication before time, compliance—synonymous of adherence),^{55,57,58,63,64,69} yet all of them are encompassed in the broader concept of adherence. Yet, the lack of a common nomenclature and the variety of the ways in which adherence is measured and quantified may reduce results' interpretability. These considerations, together with the difference pertaining to study designs, the timing of assessments and the length of follow-up, highlight once again the preliminary nature of the observations pertaining to different BCTs efficacy outlined in this work. Further, the frequencies of each technique in significant interventions may not be enough to guarantee its efficacy. Additionally, the reliance on statistical significance in summarizing evidence may be problematic given that the papers included pilot and single-arm studies. Future studies have to be designed in order to test our preliminary hypotheses.

Finally, although the review inclusion criteria were designed to capture intervention addressing adherence to all types of oral anti-cancer medication, all the included studies but one⁶⁶ focused on endocrine therapy. As such, the observations here reported reflect mainly non-adherence to those specific treatments, and cannot be generalized to other types of oral therapies.

4.2 | Clinical implications

The information here reported and commented lead to preliminary but potentially relevant observations. Further testing of the hypotheses outlined in this work through specifically designed comparative studies may be a starting point for the development of evidence-based guidelines to be taken in consideration while designing future interventions aiming at increasing adherence levels in BC patients. Specifically, BCTs “feedback on behavior” and “prompts/cues” effectiveness should be further tested, and, if it were confirmed, interventions designer should consider including such techniques in adherence increasing interventions.

5 | CONCLUSIONS

This systematic review offers an up-to-date overview of the interventions proposed to increase medication adherence in BC patients. Further research is needed in order to better understand the mechanisms behind medication taking behaviors, thus explaining why some interventions actually increase adherence levels while many others do not. In this vein, future comparative studies may further investigate the effect of BCTs “feedback on behavior” and “prompts/cues” in increasing adherence levels among BC patients. In order to ensure the replicability of the interventions and facilitate the analysis that may be conducted on their results, it is advisable for future studies to include detailed descriptions of the proposed interventions, possibly utilizing a standardized nomenclature such as the one offered by the BCTT. This will enhance primary as well as secondary research.²⁷

AUTHOR CONTRIBUTIONS

Massimo Pezzolato: Conceptualization, investigation, data curation, visualization, formal analysis, writing – original draft; **Chiara Marzorati:** Conceptualization, investigation, data curation, writing – review & editing; **Lucilla Lanzoni:** Investigation, data curation, writing – review & editing; **Dario Monzani:** Conceptualization, resources, writing – review & editing; **Marianna Agnese Masiero:** Conceptualization, writing – review & editing; **Ricardo Pietrobon:** Writing – review & editing; **Gabriella Pravettoni:** Supervision, project administration.

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CONFLICT OF INTEREST STATEMENT

The authors have stated that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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