

Breast cancer oral anti-cancer medication adherence: a systematic review of psychosocial motivators and barriers

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Abstract

Purpose In the past decade, there has been an increase in the development and use of oral anti-cancer medications (OAMs), especially for breast cancer—the most prevalent cancer in women. However, adherence rates for OAMs are often suboptimal, leading to lower survival rate, increased risk of recurrence, and higher healthcare costs. Our goal was to identify potentially modifiable psychosocial facilitators and barriers that may be targeted to increase OAM adherence for breast cancer patients.

Methods We systematically searched PubMed for studies published in the U.S. by June 15, 2016 that addressed the

following: (1) OAMs for breast cancer; (2) medication adherence; and (3) at least one psychosocial aspect of adherence.

Results Of the 1752 papers screened, 21 articles were included and analyzed. The most commonly reported motivators for adherence are patient-provider relationships ($n = 11$ studied, 82% reported significant association) and positive views and beliefs of medication ($n = 9$ studied, 89% reported significant association). We also identified consistent evidence of the impact of depression and emotions, perception of illness, concern of side effects, self-efficacy in medication management and decision making, knowledge of medication, and social support on OAM adherence.

Conclusions Compared to traditional demographic, system, and clinical-related factors that have been well documented in the literature but are not easily changed, these cognitive, psychological, and interpersonal factors are more amendable via intervention and therefore could generate greater benefit in improving patient compliance and health outcomes. As OAMs shift treatment administration responsibility onto patients, continuous provider communication and education on illness and regimen are the keys to supporting patients' medication behavior.

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Keywords Breast cancer · Medication adherence · Compliance · Psychosocial · Oral medication · Patient-physician relationship

Introduction

In the past decade, there has been an increase in both the availability and use of oral anti-cancer medications (OAMs). Historically, the majority of patients with cancer

received treatment intravenously (IV); OAMs now comprise 25% of oncology medications in the development pipeline [1, 2]. Most patients (>90%) prefer oral medications over IV therapies because of the convenience and sense of autonomy the medications provide [1, 3–5]. There is also evidence that OAMs improve patients' quality of life during long-term adjuvant treatment [6]. Prescribing OAMs shifts the responsibility of following and administering a regimen from providers to patients. Cancer patients have been incorrectly assumed to have “too much to lose” and be highly motivated to abide by providers' instructions [7]. However, like other chronic diseases, adherence rates to OAMs are often suboptimal and require further examination [1, 8–10].

Among women, breast cancer is the most common cancer. With almost 250,000 new cases diagnosed each year, breast cancer is also the second leading cause of cancer-related death [11]. While a large number of OAMs has been developed for breast cancer, studies have also shown that non-adherence to breast cancer OAMs is significantly associated with lower survival rate [12, 13] and higher risk of recurrence [13, 14]. As many breast cancer OAMs are prescribed for up to a decade, long-term adherence becomes more challenging. For the purposes of this paper, discussion of OAMs is limited to pharmaceuticals that treat or prevent cancer (e.g., oral chemotherapy and hormonal therapy) and does not include supportive therapies (e.g., anti-emetics or pain medications).

We conducted a systematic literature review to identify studies addressing psychosocial indicators of oral medication adherence among women with breast cancer. Demographic and treatment/illness-related factors relating to OAM non-adherence have been well-studied, but there is conflicting evidence regarding the magnitude and direction of their associations with adherence [1, 15, 16]. Moreover, because demographic and clinical characteristics are often non-modifiable, investigating their effects may be less advantageous when designing intervention programs. Although less studied, psychosocial factors influence patient medication-taking behavior and are more likely amenable through patient support programs to increase adherence. Psychosocial factors can be categorized as individual or interpersonal [17, 18]. Individual characteristics include perceptual and cognitive factors like belief and knowledge in medication, perception and acceptance of the illness, and quality of life. There are also psychological factors including depression, stress, attitude, feelings of self-efficacy, and fear of side effects. Interpersonal factors include social support, relationships, and interaction with physician/caregiver. We operationalized adherence as initiation, persistence, implementation, and discontinuation [19]. Initiation refers to patients' decision and action to start a medication;

implementation (which most articles denoted generally as adherence) describes taking doses according to prescription instructions; persistence indicates the length of time patients stayed on course with the regimen; and discontinuation refers to stopping therapy before completing the prescribed duration.

Our goal was to identify potentially modifiable psychosocial factors that may be targeted to increase the effectiveness of patient support programs aimed at preventing OAM non-adherence for breast cancer patients. By focusing on patients' perception, psychology, and social connections rather than demographic or clinical factors, this study reveals new insights about some of the unmet psychosocial needs and key factors that may have the greatest potential to be altered through interventions and thus improve patient adherence and health outcomes.

Methods

Search strategy and selection criteria

For this systematic review, we searched PubMed to identify all English-language, U.S.-based publications on OAM adherence published as of June 15, 2016. To obtain relevant studies, we queried using both MeSH terms and free text words related to breast cancer, oral anti-cancer medication, and adherence. The specific search terms are listed in Table 1. We also manually reviewed the reference lists of other OAM adherence review papers [18, 20–22] to identify additional relevant articles.

We included retrospective and observational studies, randomized controlled trials, interventional research, and qualitative studies. Systematic or literature reviews, commentaries, and single case study articles were excluded. Relevant studies needed to have taken place in the U.S. and meet the following three requirements: (1) examine OAMs for breast cancer; (2) assess medication adherence (e.g., initiation, persistence, discontinuation, or medication-taking behavior); and (3) address at least one psychosocial aspect of adherence. “Psychosocial” was defined as factors relating to the psychological and social well-being of the patient, including individual (cognitive, perceptual, psychological state, behavior) and interpersonal (social support, relationships, provider interaction) characteristics. Psychological characteristics attributed as *symptoms* of the treatment were not included, such as depression as a side effect of OAM. Interventions were carefully evaluated to determine if the studies addressed a psychosocial aspect of patient behavior. Articles that looked at financial burden and OAM adherence were only included if they specifically noted the psychosocial implications of cost.

Table 1 Search queries with MeSH and free text words

	OR		OR		OR
MeSH terms	Medication adherence		Antineoplastic drugs		Oral
	Medication compliance		Anti-cancer drugs		Endocrine
	Medication persistence		Antitumor drugs		Tamoxifen
	Patient compliance		Cancer chemotherapy drugs		Aromatase
	Patient adherence		Chemotherapeutic anti-cancer drugs		
	Patient cooperation				
Free text words	Discontinuation	AND	Hormone therapy	AND	AND
	Persistence		Endocrine therapy		Breast
			Oral antiestrogen therapy		
			Adjuvant therapy		
			Chemotherapy		
			Consolidation chemotherapy		
			Induction chemotherapy		
			Maintenance chemotherapy		
			Chemotherapy, adjuvant		
			Immunotherapy		

The authors conducted a multi-step process to extract relevant articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two researchers first screened all titles to exclude irrelevant articles. Two researchers then independently read abstracts to further extract eligible articles. If a title or abstract did not provide enough information to assess eligibility, the abstract or full paper respectively was retrieved. One researcher subsequently screened full papers to further exclude articles not meeting the criteria. After this process, 21 articles remained.

Quality assessment

Due to the nature of medication adherence behavior research, articles were only informally assessed for their quality and impact. A large majority of the studies included were observational studies that primarily utilized surveys or interviews rather than randomized or controlled clinical trials, therefore rendering standard quality assessments that generally focus on risk of biases neither appropriate nor relevant. Minor quality issues common among articles included the use of convenience samples and not explicitly describing the handling of missing data. Overall, the research objectives, methodology design, and data collection procedures were deemed appropriate, and no articles were excluded for quality reasons.

Data extraction and analysis

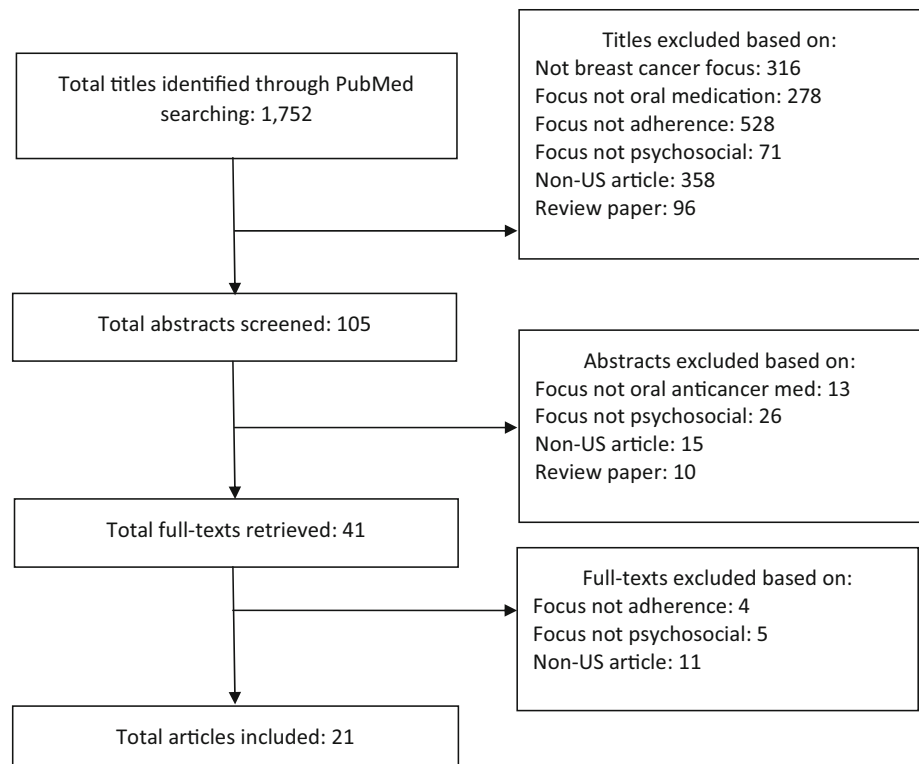
At least two team members independently read each of the final 21 article to extract data and summarize findings into

two tables. Disagreements in article eligibility and data extracted were discussed until agreement was reached. Extracted article details included study design (longitudinal or cross-sectional, data collection method and timeline), study population (total number of patients, recruitment process, demographic characteristics), measure and definition of adherence, results (psychosocial and other relevant factors that influenced adherence), and limitations.

Results

Figure 1 shows the flow diagram for study selection. The initial search yielded 1752 articles. After applying eligibility criteria, we identified 105 relevant studies. After screening of the abstracts, 41 were selected for full-text assessment, of which 21 studies fulfilled the inclusion criteria. Studies were excluded for the following reasons: (1) not focused on breast cancer, (2) not focused on orally administered medication, (3) not focused on adherence, (4) not addressing a psychosocial aspect of patient care, (5) non-U.S. based article, and (6) review paper.

Table 2 describes all included study characteristics and key findings. Three qualitative studies [23–25] used focus groups or interviews and recorded responses in text which provided rich insights pertaining to patient psychology and motivation. Most studies investigated hormonal or endocrine therapy (90%, $n = 19$), while few investigated oral chemotherapy regimens (10%, $n = 2$) [26, 27]. Less than half of the studies (33%, $n = 7$) defined how they measured adequate adherence. Variations in the definition of the key subject made comparisons challenging. For

Fig. 1 Flowchart of study selection

example, one article defined adherence as > 80% of pills taken correctly [28], while another defined non-adherence as ingesting < 90% or > 110% of the prescribed medication [27]. Four studies used objective medication adherence measures such as prescription refill data and MEMS pill bottle caps; however, most (81%, $n = 17$) used patient self-reports or verbal discussion, one of which also included physician's written prescription directives [27].

Among women diagnosed with breast cancer and taking OAMs, a prominent facilitator for adherence was patients' belief in the importance and benefit of therapy—the second most commonly reported factor positively associated with adherence among the 21 included papers [24, 26, 28–32]. Jacob Arriola et al. further found that belief in medication mediated the relationship between adherence and physician communication [29]. Similarly, positive views of the OAM [32–34] and emotions such as happiness and enthusiasm towards the medication [35] were associated with increased adherence. Worry of recurrence was also a motivator for both initiation and persistence [32]. Moreover, a study by Neugut et al. found that patients who completed their adjuvant chemotherapy regimen were more likely to have a new appreciation for life, felt like they were gaining personal strength and seeing new possibilities, and anticipated benefits of the treatment [26].

Although not as consistently measured, greater knowledge of medication [23, 24], access to related information

[24], and health literacy [24, 36] had a significant impact on adherence. One qualitative study of historically underserved breast cancer survivors found that patients with inadequate information about the medication were more likely to be non-adherent [25].

Feelings of self-efficacy and self-control were reported in four studies to be related to adherence [23, 36–38]. The two constructs can refer to patients' confidence in their ability to take a medication correctly as well as patients' perceived ability to choose or alter treatment. One qualitative study noted that patients often weighed the pros and cons of ongoing treatment and felt capable of making a choice—including changing or stopping the regimen [23]. Liu et al. indicated a statistically significant difference of 72 vs 91% in adherence rates between patients with low and high feelings of self-efficacy in patient–physician interactions [39].

Six papers found that negative emotions (e.g., annoyance, reluctance) and attitudes towards medication [35, 37] and concerns about OAMs [29, 32, 34, 38] were associated with non-adherence. It is important to distinguish that the anticipation or awareness of side effects may have different influences on patients' behavior than the actual experience of these adverse symptoms. Kahn et al. reported that experiencing side effects the patient had not been warned about decreased adherence from 85 to 65% [40]. Concerns for later side effects also negatively impacted adherence

Table 2 Study characteristics and factors influencing patient adherence to breast cancer OACMs

Author & publication yr [reference #]	Study Design: 1. Longitudinal (L) or cross-sectional (C); Participant N <avg age>; 2. Data collection method & timeline 3. Target/recruited participants	A. Definition & B. Measure of Adherence (or persistence and discontinuation)	Psychosocial factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)	Other factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)
Bender et al. 2014 [43]	1. L; N = 91 <age 56.7> 2. before initiation, at 6, 12, & 18 months 3. BC patients at Univ. cancer institute	A. (Not specified) B. MEMS caps on pill bottles	(-) depression & anxiety (x) belief in medication, social support	(-) poorer physical function, better verbal fluency, exp side effect (x) age, financial hardship
Bhatta et al. 2013 [28]	1. C; N = 381 < age 58> 2. 15 pg self-administered survey 3. white & black patients in Univ cancer registry	A. Adh: > 80% of pills taken correctly. Persistence: complete 5-year therapy B. Author-designed Q (i.e., how often missed adjuvant therapy?)	(+) perception of importance of therapy, higher value of doctor's opinion	(x) income, education, cost, race
Demissie et al. 2001 [42]	1. L; N = 303 < age 67.5> 2. surgical record, phone interview at 5, 21, & 33 months 3. age > 55, 5 Boston area hospitals	A. Discontinuation: not taking tamoxifen at 21 or 33 months B. Interview Q (taking med at present time?)	(+ initiation) ability to communicate w/physician, perceived ability of physician (-) depression	(+ initiation) # of physicians (-) exp side effects, estrogen receptor-negative tumors (x) age, standard primary tumor therapy
Fink et al. 2004 [30]	1. L; N = 497 < age 65–80> 2. medical records, interview at 3, 6, 15, 27, 39, 51, 63 month 3. estrogen receptor + BC, over 65 year, stage I–III in tumor registries in 4 states	A. Non-persistence: stop taking med completely B. Author-designed self-report Q (if prescribed tamoxifen, if still taking?)	(+persistence) beliefs of benefits & risks of med	(+) 4 or more positive lymph nodes (x) age, regimen complexity, exp side effects
Friese et al. 2013 [32]	1. L; N = 743 < age 20-79> 2. phone survey at 9 mon, 4 year 3. Black & Latino focused, 2 metropolitan cancer registries 2005–2007	A. Persistence: taking OACM in the last week at 4-year post-initiation B. Self-report Q (taken med last wk?)	(- persistence) negative view towards therapy	(+) multiple medications, increased age (- initiation) concern of side effects, worry about risk (-) exp side effects (x) race, comorbid conditions, SES

Table 2 continued

Author & publication yr [reference #]	Study Design: 1. Longitudinal (L) or cross-sectional (C); Participant N <avg age>; 2. Data collection method & timeline 3. Target/recruited participants	A. Definition & B. Measure of Adherence (or persistence and discontinuation)	Psychosocial factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)	Other factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)
Hershman et al. 2016 [34]	1. L; N = 523 < age 69> 2. pharmacy record, interview at 6, 12, 18 months and 2, 3, 4 years 3. adult women age 20 + from New York, Detroit, and Northern California with stage I–III BC (BQU/AL)	A. Non-persistence: > 90 day gap following the date of anticipated completion of any ET prescription B. Prescription refill	(+ persistence) positive attitude about ET (OR: 0.51) (- persistence) QOL (OR: 0.98), low treatment satisfaction (OR 0.99), breast cancer concerns, intrusive thoughts (OR: 1.04), avoidant thoughts (OR: 1.03), higher impact of events score (OR 1.02) (x persistence) interpersonal process of care (P–P communication), perceived level of decision-making difficulty	(-) lower income (x) age, race, employment, comorbidities
Jacob Arriola et al. 2014 [29]	1. C; N = 200 < age 58.5> 2. self-report survey and medical chart abstraction 3. BC patients from same health system in a SE city	A. (Not Mentioned) B. MARS (Medical Adherence Report Scale) self-reported survey (ever forget to take your med?)	(+) higher frequency of physician communication, belief in necessity of medication (-) concerns about medication	(x) race, education, marital status
Kahn et al. 2007 [40]	1. L; N = 881 < 26% age < 50, 44% age 50–65, 30% age > 65 y> 2. survey 4 years post-diagnosis, medical record abstraction 3. NICCQ data of BC patients stage I–III from 5 metropolitan areas	A. Discontinuation: no longer taking tamoxifen after 4 years B. Author-designed self-report Q	(+) adequate role in decision-making (81% vs. 73%), better support from doctors (82% vs 69%), provider input on medication (80% vs 56%), patient-centered care in first 12 months (78–82% vs. 52–67%) (-) less social support	(+) younger age, positive hormone status (-) side effects they were not warned about, exp side effects (x) race, edu, insurance, OOP costs, BMI, comorbidity
Kimmick et al. 2015 [38]	1. C; N = 112 < age 63.7> 2. self-reported questionnaire and medical records 3. older post-menopausal breast cancer survivors	A. (Not Mentioned) B. MMAS (Morisky Medication Adherence Scale) + eight author-designed self-report Qs (how often do you skip doses?)	(+) self-efficacy (-) concerns about medication, lower self-efficacy in communicating with physicians	(-) cost, exp side effects
Kirk et al. 2008 [31]	1. C; N = 328 < age 18–80> 2. self-report survey online 3. women BC survivors using Y-ME National Breast Cancer Organization website	A. (Not Mentioned) B. Online self-reported survey (Are you taking your meds as directed?)	(+) knowing it might improve clinical outcome, reminder of importance	(+) better management of side effects (-) exp side effects, cost of medication, forgetfulness (x) race

Table 2 continued

Author & publication yr [reference #]	Study Design: 1. Longitudinal (L) or cross-sectional (C); Participant N <avg age>; 2. Data collection method & timeline 3. Target/recruited participants	A. Definition & B. Measure of Adherence (or persistence and discontinuation)	Psychosocial factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)	Other factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)
Lash, et al. 2006 [33]	1. L; N = 462 < 58% age 70–79> 2. medical forms, treatment recs from physicians, interview at 3, 6, 15, 27, 39, 51, 63 months 3. older women, from RI, MI, NC, CA identified by review of hospital pathology reports and tumor registries	A. Non-adherence: completely stop taking medication B. Yes/no question; Are you still taking tamoxifen?	(+) positive views of Tamoxifen	(+) multiple prescriptions (-) exp side effects
Lebovitz et al. 1990 [27]	1. L; N = 51 < age 53> 2. separate interviews w/patient and oncologist at day 1, week 2, 4, 13 and 26 3. oncologists & BC patients at Mt. Sinai Hospital	A. Noncompliance: ingesting 90% or less or 110% + of medication B. Both patient self-report and physician's written prescription directives to assess (1) dosage, based on % missed during 26 weeks of treatment; and (2) behavioral, % of behavioral events or prescribing occasions on which a criterion level of drug was not taken.	(-) higher depressive symptoms and disturbances (x) compliance not related to any of the three measures of physician non-adherence	(-) taking both OACM drugs, treated in private community or clinical setting versus the academic setting (60-62% vs. 20%), worse exp symptoms, lower SES (x) age
Liu, et al. 2013 [39]	1. L; N = 303 < age 51> 2. baseline interview 6 m after diagnosis + 18 months interview assess PP relation + 36 months self-report adh surveys, medical record 3. low-income women and un-/under-insured in CA > 18 yo and part of treatment program	A. (Not Mentioned) B. Self-reported survey	(+) patient-centered comm (59 vs. 94% adh), patients' self-efficacy in patient-physician interactions (72 vs. 91% adh) (x) discuss w/physician why need HT	(+) at least one comorbidity, less-acculturated Latina (than white) (-) exp side-effect; no insurance (56 vs. 91% adh) (x) age, edu, marital, tumor stage, treatment received for BC
Llarena et al. 2016 [41]	1. C; N = 515, < age < 45> 2. chart review w/oncologists, prescription refill data, telephone 3. younger, pre-menopausal patient at Northwestern Memorial Hospital	A. Non-initiation: not initiating within 4 months of prescription. Non-persistence: discontinued for at least 4 months prior to full 5 year of treatment B. Prescription refill data	(-) desire for future fertility (OR = 5.04), (-) being a current smoker (-) initiation) fear of side effects	(+) accepting chemotherapy/radiation, higher cancer stage (-) being a current smoker (x) race, age, alcohol use, insurance status

Table 2 continued

Author & publication yr [reference #]	Study Design: 1. Longitudinal (L) or cross-sectional (C); Participant N <avg age>; 2. Data collection method & timeline 3. Target/recruited participants	A. Definition & B. Measure of Adherence (or persistence and discontinuation)	Psychosocial factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)	Other factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)
Manning et al. 2011 [37]	1. L; N = 165 2. mail-in surveys at 3 and 13-months 3. women BC patients at nine radiation clinics in Missouri	A. (Not Mentioned) B. 4-item author-designed self-report Qs (Some people forget to take their meds - how often does this happen to you?)	(+) feelings of self-control (-) depression, negative attitudes and perceptions of control (x) injunctive norms	
Neugut et al. 2016 [26]	1. L; N = 445, < age 54.5> 2. phone interview three times within 3 months of diagnosis, 4–6 weeks later, and 12–24 weeks post-diagnosis + electronic pharmacy records 3. adult women age 20 + from New York, Detroit, and Northern California with stage I-III BC (BQUAL)	A. Early discontinuation: receipt of < 80% of the number of chemotherapy cycles for the regimen initiated, > 56 days between two chemotherapy claims B. Pharmacy & infusion record	(+) psychological symptoms marginally significant (+ completion) having a new appreciation for life, gaining personal strength, seeing new possibilities, anticipating benefits of chemotherapy (-) high score on Memorial Symptom Assessment scale (OR: 1.92) (x) p-p communication, decision making	(+) higher education, ER/PR negative (-) more cycle required (x) race, exp side effects, physical symptoms, income, marital status, comorbidity
Rust et al. 2015 [36]	1. L; N = 48 < age 54.4> 2. baseline survey, intervention, interview 4–6 months later 3. African-Americans at community-based organization for minority women w/BC or through the ACS	A. (Not mentioned) B. ARMS (Adherence to Refills and Medication) 12-item scale self-report (How often do you plan ahead and refill your meds before they run out?)	(+) health literacy, patient self-efficacy (x) intervention	
Rust, et al. 2011 [24]	1. C; N = 24 < 29.2% age 46–60, 37.5% age > 60 33.3% unknown> 2. two 12-person 1-hour focus groups + demographic questionnaire 3. underserved African-Americans women recruited from a breast cancer organization	A. Adherence or compliance: the extent to which patients take medication regimens prescribed by health providers B. Verbal discussion during focus groups	(+) patient communication, PP relationship, perception of benefit in medication, knowledge of medications, access to informative resources	(+) age > 65 years old (-) fear of side effects, comorbid conditions, cost

Table 2 continued

Author & publication yr [reference #]	Study Design: 1. Longitudinal (L) or cross-sectional (C); Participant N <avg age>; 2. Data collection method & timeline 3. Target/recruited participants	A. Definition & B. Measure of Adherence (or persistence and discontinuation)	Psychosocial factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)	Other factors associated with higher adherence (+), non-adherence (-), or shown no significance (x)
van Londen et al. 2014 [23]	1. C; N = 14 < age 58.8> 2. Four focus groups 3. Women BC patients at University of Pittsburgh Medical Center	A. (Not Mentioned) B. Verbal discussion during focus groups	(+) discussing with provider about side effects, full knowledge of medication (-) lack of trust in provider, lack of support, lack of trust to talk with physician	(-) exp severe side effects, difficulty coping with symptoms, frustration with managing symptoms
Walker et al. 2016 [35]	1. C; N = 86, < age 39> 2. online questionnaire and follow up supplemental survey 3. young women from Helping Ourselves, Helping Others: The Young Women's Breast Cancer Study	A. Non-adherence – failure to take the medication as prescribed MMAS score of > 6 B. Altered MMAS (Do you decide to miss a dose of your current ET?)	(+) positive emotions towards ET including happiness and enthusiasm (-) negative emotions towards ET like annoyance and reluctance	(-) lack of financial comfortability (x) number of exp symptoms (9.6 vs. 8 in adherence and non-adherent groups)
Wells, et al. 2016 [25]	1. C; N = 25 < age 59.5> 2. 1v1 interview, + written demographic survey 3. historically or medically underserved BC survivors from a cancer center in an urban area of SE U.S.	A. (Not Mentioned) B. Verbal discussion during focus groups	(+) having a routine, (-) depression, inadequate info by physicians, looking at books/online for information	(+) taking multiple medications, reduced costs, easy access (-) side effects

Table 3 Summary of psychosocial factors relating to breast cancer OAM adherence (in the order of reporting frequency)

Author & year	Physician comm/trust or patient-provider relationship	Belief of med	Depression/anxiety/ stress/psychological factors	Positive attitude/outlook	Concern about medication or side effect	Feelings of self-efficacy or self-control	Knowledge of med or health literacy	Perceived difficulty or role in decision making	Social support
Bender et al. (2014)		x	-						
Bhatta et al. (2013)	+	+							
Demissie et al. (2001)	+		-						
Fink et al. (2004)		+		+	-				
Friese et al. (2013)		+	+ worry of recurrence		-				
Hershman et al. (2016)	x			+	(OR = 0.51)	- (OR = 1.04)			x
Jacob Arriola et al. (2014)	+	+			-				
Kahn et al. (2007)	+ (78–82% vs. 52–69%)							+ adequate role (81% vs. 73%)	+
Kinnick et al. (2015)	+				-	+			
Kirk et al. (2008)		+							
Lash et al. (2006)				+					
Lebovitz et al. (1990)			-						
Liu et al. (2013)	+ (94% vs 59%)	+				+ (72% vs 91%)			
Llarena et al. (2016)					-				
Manning, et al. (2011)			-	+		+			
Neugut et al. (2016)	x	+	-	+		+		x	
Rust et al. (2015)									
Rust et al. (2011)	+	+				+	+		
van Londen et al. (2014)	+						+		+
Walker et al. (2016)				+			+		
Wells et al. (2016)	+		-				+		

^a The cell symbols indicate factors being reported as associated with higher adherence (+), non-adherence (-), or shown no significance (x). Magnitude of effects is shown when available from the included articles. While some articles discussed the importance or the relation of a broader range of variables, those not explicitly assessed and reported were not recorded here. The following variables were each indicated by only one study as associating with medication non-adherence: avoidant thoughts, desire for future fertility, low treatment satisfaction, and low quality of life

[24] and initiation [32, 41]. Distinctive for this patient population, Llarena et al. observed that desire for future fertility and thus fear of losing fertility as a side effect of treatment had an odds ratio of 5.04 for non-adherence [41].

Difficulty coping with symptoms and frustration in managing the OAM related conditions are disincentives to adherence [23]. Low quality of life [26, 34] and low treatment satisfaction [34] were also negatively correlated with adherence. Several studies showed evidence of depression and disturbances significantly relating to non-adherence [25–27, 37, 42, 43]. A study by Hershman et al. found that intrusive avoidant thoughts about a distressing event and cancer-specific emotional distress decreased the likelihood to adhere [34].

On interpersonal relationships, only two articles addressed social engagement, both finding that a lack of social support was an indicator of non-adherence [23, 40]. Conversely, relationship or communication between provider and patient surpassed other psychosocial factors as the most commonly studied and reported predictor of patient adherence with consistent research evidence. Positive perceptions of the patient–physician relationship [24], communication [24], trust [23], and support [40] were associated with better adherence. The frequency of physician communication also had a significant impact [29]. Two studies specifically looked into patient-centered communication, finding it positively associated with adherence [39, 40]; Liu et al. reported a large difference in adherence rates of 59 vs 94% for patients with the lowest versus highest scores on the Consumer Assessment of Healthcare Providers and Systems (CAHPS) communication scale [39]. In addition, high value of the doctor’s opinion [28], feeling like they had self-efficacy and an adequate role in decision making with the physician [38–40], discussing side effects with the physician [23], and physician input on medication use [40] were all associated with better adherence. In one study, patients with higher perceived efficacy in patient–physician interactions (PEPPI) had a 91% adherence rate while those with lower perceived efficacy had a 72% adherence rate [39]. Interaction with physicians also plays a role in patients’ decisions to start a treatment. Demissie et al. indicated number of physicians, ability to communicate with physician, and perceived capability of physicians were significantly associated with medication initiation [42]. In concurrence, Wells et al. revealed non-adherence was associated with a feeling of inadequate information provided from physicians [25]. Only two studies found that patient–provider communication did not impact persistence [26, 34]. Table 3 presents a concise list tabulating the psychosocial factors each article studied, along with impact magnitude where available.

Discussion

This systematic review emphasizes breast cancer patients’ psychosocial factors relating to OAM adherence. The included articles represent a diverse group of individuals (e.g., race, income, age, insurance status). A myriad of variables related to patients’ cognitive, perceptual, social, and psychological states concerning illness and medication were reported as having significant associations with adherence. Through analyzing and rank order of the findings (in Table 3), the review presents consistent evidence for the impact of psychosocial factors and the need for further attention to these factors in research and clinical care. The study results reveal patient–physician relationship (nine out of the 11 that assessed this reported significant associations) and positive views and beliefs of medication (eight out of nine that assessed this reported significant associations) as the top two best-supported facilitators for compliant patient behavior. We have also identified congruent findings on the influence of depression/emotions, perception of illness, concern of side effects, self-efficacy in medication management and decision making, knowledge of medication, and social support (roughly in the order of study frequencies). These factors are modifiable, making them potential targets for improving adherence more effectively compared to demographic or system-related factors that tend to be static or not in patients’ control. Especially because OAMs place greater responsibility for adherence on patients, identifying and closer examining changeable patient factors rather than unalterable ones provides key insights as to how providers and policy-makers can better address the prevalent issue of OAM non-adherence among breast cancer patients. Of particular importance is the involvement of physicians in connecting and maintaining a relationship with patients, as such positive interaction could also contribute to patients’ knowledge and perception about the prescription, illness, and potential side effects and thus multiply the likelihood of increased adherence.

One limitation in comparing the effects of various indicators of OAM adherence is the lack of common standards in the definition, measurement, and reporting of adherence among the articles. To date, there is no gold standard in measuring method or uniform threshold used to describe adequate adherence. For example, some studies consider adherence as correctly taking medication more than 80% [28], 90% [27], or 95% [44, 45] of the time, while others categorize *any* incorrectly taken or missed dose in the past week or months as non-adherence [46–48]. Among the most popular measure, self-report, author-designed surveys and validated scales vary in length and content across studies. These discrepancies may contribute

to the wide range of non-adherence rates reported in the literature. Further, of the 21 papers reviewed, only a few studies presented the numerical difference in adherence rates between subgroups or the impact level of various factors, making it difficult to analyze or comprehend the relative magnitudes of each factor.

Non-adherence is a prevalent and complex, multidimensional phenomenon. More clarity in adherence research reporting and further examination of interactive effects of factors is needed. A large majority of the papers ($n = 17$, 81%) simply indicated whether a variable was positively or negatively associated with adherence. Authors generally focused their discussion to statistically significant results, potentially overlooking clinically relevant findings. Often mediating or moderating effects that may help explain inconsistent results were not fully explored. For example, some papers reported no association between race, income, or education and adherence, while others showed less-acculturated minorities [39], non-white/black [26], and patients of lower socioeconomic status [27, 34] were more prone to non-adherence and discontinuation. However, the analyses did not evaluate whether behavior difference was indeed due to race/culture/education or rather a lack of comprehension of the medication procedure and handling, low trust in physicians, and/or different perception of medication or interpretation of instruction. A fuller picture of psychosocial disincentives to adherence would allow patient support programs to better target the sources of prescription-deviating behavior.

In addition, research indicated that factors influencing patient behavior could vary at different stages of treatment due to changes in symptoms, attitudes, finance, or other surrounding elements [19]. Ten studies discussed persistence or initiation specifically. Only two studies [32, 41] examined all three stages of adherence—initiation, persistence, and discontinuation, indicating the difficulty of capturing the complete drug dosing history, even with longitudinal studies. Identifying non-initiators using traditional, pharmacy-based data sources may be challenging. There is gap in our understanding of potential psychosocial differences between those who do and do not start OAM treatment as prescribed. The divide between cross-sectional and longitudinal studies included was roughly equal, but there was no obvious differing focuses or results. The interpretation of the impact of adherence is complicated without temporal order. Study design with a more anticipatory orientation that includes ongoing monitoring of the relevant factors and lasts a whole treatment cycle could provide more actionable insights into patient behavior and allow timely intervention to avoid non-adherence or premature termination of medication. Furthermore, only one article combined multiple measurements by recording both physicians' view of patient adherence and patient self-

reported adherence. Future research should consider additional measures to address the potential bias of overestimation from self-report and derive a more accurate state of adherence [7, 49–51].

Medication adherence entails both behavioral and attitudinal facets [52], but psychometric-oriented or self-perceived measures have not been well developed. Reviews have shown that the effectiveness of patient adherence support programs varies and likely declines over time [53–55]. Only one study [38] distinguished between intentional and unintentional non-adherence. More research on the triggers behind patients' deliberate alteration of medication intake could shed light on why some intervention programs were not successful. For instance, self-efficacy may be interpreted as the ability to understand or communicate with physicians or as the capability to make changes to the regimen as they see fit, leading to higher propensity of self-diagnoses or experimenting with medication.

This study had several limitations. We only included articles originating in the United States and indexed in PubMed. Our findings may not represent psychosocial factors related to breast cancer OAM adherence from other countries or cultures. We identified relatively few qualitative research articles; however, the three qualitative articles included [23–25] provided rich insights about patient psychology and rationale beyond numbers. These qualitative papers primarily examined emotions and feelings towards OAMs and perceptions of physician and social support. Focus group participants in two studies articulated trust and communication with providers as encouragement to taking medication properly and diligently. Patients' desire or expectation of a dependable relationship with providers, especially for serious illnesses like cancer, may not always be met. Providers' consistent involvement in crucial conversations about adherence is important because these patient-provider discussions could help reveal which psychosocial facilitators would be most effectively addressed in interventional approaches to improve adherence.

Conclusion

As OAMs place greater responsibility on patients and their caregivers than facility-based treatment do, providers should focus on building patient-centered and sustainable relationships, clarifying and reiterating the importance, usage, and potential side effects of the medication throughout the treatment duration to ensure adequate adherence. Moreover, incorporating measures and improvement of treatment adherence in healthcare quality assessments could be considered in system reform and payment incentives to encourage care provider team's involvement, including investing time, in the effort to help patients achieve better

adherence and health outcomes. On the other hand, adjusting insurance payment structure to ensure parity between OAMs and IV medications could be an important step in reducing patients' out-of-pocket cost and easing financial distress of patients preferring in-home and self-managed treatments [56]. With the continued transition to OAMs for cancer treatment and need for patient engagement, additional research and adherence-promoting interventions such as symptom/treatment education and ongoing communications are critical to instill patient confidence towards the medication, physician, and patient-self.

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Compliance with ethical standards

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

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