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Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: A systematic review

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ABSTRACT

Background and aims: The use of oral anticancer drugs has increased in modern oncology treatment. The move from intravenous treatments towards oral anticancer drugs has increased the patients' own responsibility to take oral anticancer drugs as being prescribed. High rates of non-adherence to oral anticancer drugs have been reported. A systematic literature review was conducted to gain insight into determinants and associated factors of non-adherence and non-persistence in patients taking oral anticancer therapy.

Review methods: PubMed, Cochrane, Web of Science and Cinahl were systematically searched for studies focusing on determinants and associated factors of medication non-adherence and non-persistence to oral anticancer drugs. The methodological quality of the included studies was assessed by two independent reviewers. No studies were excluded based on the quality assessment.

Results: Twenty-five studies were included and systematically reviewed. The quality of the studies was moderate. Associated factors influencing medication non-adherence and non-persistence to oral anticancer drugs are multifactorial and interrelated. Older and younger age, and the influence of therapy related side effects were found to be predominant factors.

Conclusion: Non-adherence and non-persistence to oral anticancer drug therapy are complex phenomena. More qualitative research is needed to facilitate the development of patient tailored complex interventions by exploring patients' needs and underlying processes influencing medication non-adherence and non-persistence to oral anticancer drugs.

Introduction

The use and the number of different oral anticancer drugs (OACD) have increased in modern oncology.[1] Currently, 25% of the cancer chemotherapy in development can be taken orally.[1] Many of the available OACD are primarily cytostatic in nature and most effective when given over long-term periods.[2] OACD such as imatinib, has transformed chronic myeloid leukemia (CML) from a lethal to a chronic disease.[3] The use of OACD improves the quality of life of cancer patients by reducing hospital stay and give them a greater sense of control over their treatment while guaranteeing the treatment efficacy,[4] however also poses important challenges such as managing side effects, the prolonged treatment period and adherence issues.

Several studies show that most patients (range 54–89%) prefer to be on an oral therapy compared to intravenous therapy[5–8]; this mainly because medication can be taken at home and no needle has to be placed.[5,8,9] The shift from intravenous treatments towards OACD therapy increases patients' responsibility to take their OACD rigorously as being prescribed by their physician.[2] Because of the association between adherence and treatment success, concerns about non-adherence to OACD therapy have become an increasingly important issue in oncology.[2,10,12]

Until now, multiple definitions exist[11,13] but there is no universally accepted definition of medication (non-)adherence.[10] For this review, non-adherence has been operationalized based on the definition by Ruddy et al. (2009), who consider a patient to be non-adherent if "doses are missed, extra doses are taken or doses are taken in the wrong quantity or at the wrong time". This definition

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was chosen because of its concreteness. Non-persistence occurs when patients "don't take their medication as long as prescribed".[11] The terms non-persistence and early discontinuation are used interchangeably in the literature.

A literature review by Foulon et al. (2011) reports on OACD therapy non-adherence rates between 0% and 84%. The variation is mainly related to (1) differences in the type of OACD therapy (e.g. side effects, complexity of regimen), (2) differences in the definition of adherence being applied in the primary studies, and (3) differences in the assessment of medication adherence. OACD therapy non-adherence rate in breast cancer patients was found to be as high as 23% over a one year period.[14] Treatment discontinuity was found in 17% of the patients after two years[15]; and even in 31% after five years.[16] Marin et al. (2010) reported that 26.4% of the CML patients was ⩽90% adherent with their prescribed OACD therapy. Similar results have been found in a Belgian setting.[17] One third of the patients with CML appeared to be non-adherent with their treatment; only 14.2% was found to be completely adherent.[17]

Non-adherence and non-persistence significantly reduce the efficacy of OACD therapies.[2] Non-adherent patients with CML, treated with the OACD imanitib, were less likely to achieve complete cytogenetic responses (CCyR), resulting in a reduced success rate.[18–20] In the study by Noens et al. (2009), patients taking 74.0–76.8% of the prescribed dose had a less good response than patients taking 89.9–92.7% of the prescribed dose. In breast cancer patients, lower survival rates were found for patients being <80% adherent to the oral drug tamoxifen.[21] Non-adherence to OACD therapy was also related to higher healthcare costs due to the increased number of doctor visits, longer hospital stays and more frequent hospitalization.[22,23]

Given the magnitude and consequences of non-adherence in patients on an OACD therapy, an exploration of associated factors and underlying processes of medication non-adherence is needed. Factors influencing medication non-adherence and non-persistence are complex due to the multifactorial and interrelated character.[24] Understanding the complexity of non-adherence and non-persistence to OACD is important as it can inform the development of an intervention to enhance adherence and persistence with this type of medication. A literature review is therefore a crucial step in the development of such interventions.[25]

Literature reviews on medication non-adherence or non-persistence with OACD therapy are often not conducted and/or reported in a rigorous systematic way.[2,11,26] To our knowledge, only one systematic review including literature up until 2002 on non-adherence and non-persistence in patients taking OACD, has been conducted.[12] In the latter review different OACD have been considered.

The aim of our review is to provide an updated overview of determinants and associated factors of medication (non-)adherence and (non-)persistence in patients taking different types of OACD.

Methods

Search strategy

Four electronic databases were searched: PubMed, the Cochrane database, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy consisted of MeSH terms and free text words subsequently combined (see Table 1).

All titles and abstracts were screened independently by two reviewers (MV & KL). If the abstract did not provide enough information to decide upon inclusion/exclusion, the full paper was retrieved for further screening. Disagreements about inclusion or exclusion were discussed between the reviewers until consensus was reached. The reference lists of the included articles were reviewed and additional articles were considered if appropriate.

Selection criteria

Articles were included if they addressed OACD therapy, focused on determinants and associated factors of medication adherence/compliance and/or medication persistence of patients aged 18 and older, and were evaluated as being of strong or moderate methodological quality. Factors considered to evaluate methodological quality for quantitative studies were: the presence of selection bias, allocation bias, confounders, study design, blinding, data collection methods, withdrawals and drop-outs, and the appropriateness of the analysis to the research question.[27] For qualitative studies, methodological quality was evaluated considering clear statement of the aims, the relationship between researcher and participants, ethical issues, rigorousness of the data analysis, clear statements of the findings, value of the study, appropriate methodology, design, recruitment strategy and data collection.[28]

The primary outcomes of the primary studies had to be (non-) adherence and (non-)persistence to OACD therapy to be eligible for inclusion. Only original research articles published between 1990 and April 2012 and written in English, French, German or Dutch were included. Study design was not used as a selection criterion. Studies conducted in developing countries were excluded because of the different context and differences in healthcare delivery systems.

Quality assessment

The methodological quality of each study was independently evaluated by two reviewers (MV & KL) using (1) the Quality Assessment Tool developed by Vyncke et al.[27] for quantitative studies, and (2) the Critical Appraisal Skills Programme (CASP) developed by the Public Health Resource Unit[28], National Health Service, England (2006) for qualitative studies.

The Quality Assessment Tool of Vyncke et al.[27] is based on a tool developed by the Effective Public Health Practice Project[29] and used by Mirza et al.[30] This tool was chosen because of (1) the extensiveness of the assessment of methodological quality and, (2) the usability for quality assessment of different quantitative research designs. The tool considers presence of selection bias and confounders, study design, blinding, data collection methods, withdrawals and drop-outs, appropriateness of the analysis to the research question, and the integrity of the intervention. The item on integrity of the intervention was not applicable for this review. For each item, two reviewers (MV & KL) assigned a rating of strong, moderate or weak based on the evaluation criteria of the quality assessment tool. Discrepancies in the reviewers' evaluations were discussed until consensus was reached.

The CASP includes 10 questions to assess (1) rigorousness, (2) credibility and, (3) relevance of the qualitative study by answering yes/no for each question. The first two questions are general screening questions considering whether the goal of the study is clear, and whether a qualitative methodology is appropriate for the study. When both questions are positively answered, it is worth proceeding to the remaining detailed questions to consider methodological quality.[28]

Data abstraction and synthesis

Two reviewers (MV and KL) independently extracted the data from each article. Findings were summarized using a data extraction sheet (Table 2). This sheet included the following items: author(s) and publication date, research focus, design, the definition of medication non-adherence and non-persistence, measurement, participants (n), factors associated with medication

Table 1
Search strategy with MeSH terms and free text words.

	OR		OR	OR
MeSH terms	Medication adherence Patient compliance		Administration, oral Antineoplastic agents	Neoplasms
	Medication compliance Medication persistence Medication non-adherence Medication non-compliance Patient adherence Patient cooperation Patient non-compliance Patient non-adherence		Oral drug administration Antitumor drugs Antitumor agents Antineoplastic drugs Antineoplastics	Tumor Cancer
Related terms	Concordance Non-persistence Early discontinuation Early discontinuance Treatment discontinuation Treatment discontinuance Treatment interruptions Pill discontinuation Pill discontinuance Abandonment	AND		AND

non-adherence or higher adherence, and factors associated with medication non-persistence or higher persistence. Inconsistencies in data extraction were discussed until consensus was reached.

Results

Selection of articles

The literature search resulted in 3351 articles. Duplicates ($n = 485$) were excluded. Based on the selection criteria, 85 full texts were retrieved and reviewed; resulting in 25 articles for inclusion. No relevant articles were added after reviewing the reference list of the included articles. A flow chart of the search strategy is presented in Fig. 1.

Methodological quality of the included studies

Details on the quality assessment of the included studies are presented in Table 3 for studies with a quantitative approach, and in Table 4 for studies with a qualitative or mixed method approach. In general, the overall methodological quality of the quantitative studies was moderate. None of the studies mentioned the influence of confounders on the results. For all studies, the method for the assessment of medication adherence was clearly indicated. Few studies reported on power calculations ($n = 1$)[17] and on how they handled missing data ($n = 1$)[31] and drop-outs ($n = 2$).[32,33] None of the studies with a qualitative design adequately described the relationship between researcher and participants. However, the methodology, design, and data collection were evaluated as being

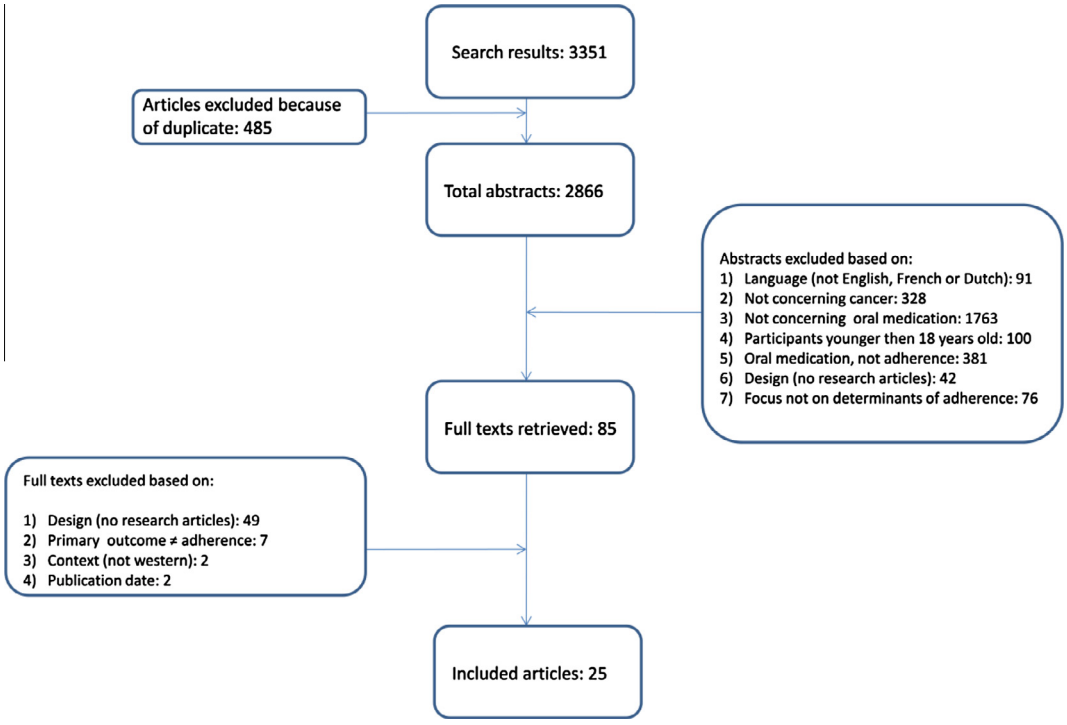

Fig. 1. Results of the search strategy.

Table 2
Study characteristics, determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs.

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Lebovits et al. (1990)	Patient non-compliance with self-administered chemotherapy	Prospective cohort study	Taking <90% or taking >110% of oral anticancer drugs	(1) Percentage of drug missed during 26 weeks of treatment, (2) self-report in interview based on direct questioning how many pills have been taken during the preceding week of the interview	Patients with breast cancer (51)	(−) Treatment location (private and clinic settings rather than academic setting), lower income (and lower socioeconomic status)	NA
Demissie et al. (2001)	Predictors of use, side effects, and discontinuation of adjuvant tamoxifen	Prospective cohort study	Discontinuation (not further specified)	Self-report by computer-assisted telephone interviews at second follow-up, asking detailed questions (not specified) about discontinuance of oral anticancer drug	Older women with breast cancer (303)	NA	(−) Side effects (depression, nausea, vision problems, and vaginal bleeding) (+) patients who were estrogen receptor-positive
Partridge et al. (2003)	Non-adherence to adjuvant tamoxifen therapy	Retrospective analysis of data	Taking <80% of the doses of prescribed tamoxifen	Refill data (dosage, quantity dispensed, and number of days supplied) extracted from the paid claims from the New Jersey Medicaid program and the New Jersey Pharmaceutical Assistance to the Aged and Disabled (PAAD) program	Women with primary breast cancer (2378)	(−) ⩽45 years old, ⩾85 years old, nonwhite subjects, longer duration of therapy, patients who had had a mastectomy (rather than breast-conserving surgery) (+) patients who had a consultation with a medical oncologist before initiation of tamoxifen	NA
Fink et al. (2004)	Patient beliefs about risks and benefits of tamoxifen therapy and tamoxifen discontinuance	Prospective cohort study	Discontinuation (not further specified)	Self-report by telephone interviews at 3, 6, 15 and 27 months by asking whether women discontinued tamoxifen	Older women with estrogen receptor-positive breast cancer (597)	NA	(−) Having neutral or negative beliefs about the value of tamoxifen, having positive nodes
Grunfeld et al. (2005)	Adherence beliefs about taking tamoxifen	Cross-sectional	(1) Answering "no" on the self-reported question; (2) lower scores (without a cut-off score) on the Medication Adherence Report Scale (MARS-5)[a] indicating non-adherence	(1) Self-report with a single question: "In the past week, have you taken your tamoxifen everyday?", (2) MARS-5	Women with breast cancer aged 35–65 years old (110)	(−) Lower perceived necessity for tamoxifen and no benefit to be gained from taking tamoxifen, side effects (hot flashes, night sweats, concentration or memory difficulties, sleep problems, emotional problems, weight gain, and loss of libido) (+) the belief that taking tamoxifen would stop the patients from developing breast cancer	NA
Atkins & Fallowfield (2006)	Intentional and non-intentional non-adherence to oral anticancer drugs	Cross-sectional	Anwering 'occasionally', 'sometimes', 'quite often', or 'very often' on 2 questions assessing intentional and non-intentional non-adherence	Self-report on 2 questions: "How often do you forget to take your tablets?" and "How often do you choose not to take your tablets?"	Women with breast cancer (131)	(−) younger age, disliking aspects of medication (side effects, inconvenience, difficulties swallowing tablets)	NA
Lash et al. (2006)	Adherence to tamoxifen over the five-year course	Prospective cohort study	Discontinuation (not further specified) by self-report in interviews	Self report by telephone interviews at 3, 6, 15, 27, 39, 51, and 63 months after surgery (questions not specified)	Older women with breast cancer (462)	NA	(−) Having or developed initial severe side effects (+) more prescription medications at baseline
Barron et al. (2007)	Early discontinuation of tamoxifen	Retrospective analysis of data	Non-persistence: ⩾180 consecutive days of no tamoxifen supply without alternative hormonal therapy during that time	Refill data (number of days supply, quantity and dosage of tamoxifen) extracted from the Irish Health Services Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy database	Women with breast cancer aged 35 years or older (2816)	NA	(−) History of antidepressant use (use in the year preceding the tamoxifen initiation), age (older than 75, between 35 and 44), increased number of prescriptions per month/year before starting tamoxifen

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Table 2 (*continued*)

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Darkow et al. (2007)	Treatment interruptions and non-adherence with imatinib	Retrospective analysis of data	(1) Treatment interruptions: failure to refill imatinib within 30 days from the end of supply of the prior prescription (2) < 50% low MPR[b]; 50–90% intermediate MPR, 90–95% high MPR, > 95% very high MPR	Refill data from an anonymous database including electronic pharmacy records and medical claims	Patients with CML (267)	(−) increased amount of different medication, starting with higher dose imatinib (⩾600 mg), high cancer complexity (difficulty of managing the patient because of e.g. comorbidities), female gender	(−) Female gender, high cancer complexity
Kahn et al. (2007)	Patient centered experiences in breast cancer - predicting long-term adherence to tamoxifen use	Prospective cohort study	Persistence not specified	Patient self-report survey. Question(s) about non-persistence: not specified	Breast cancer patients (881)	NA	(−) Older age (>65), severe side effects, negative and unknown hormone receptor status, no single doctor mainly responsible for follow-up, less participation in decision making than wanted, receiving too much or too less support than needed from caregivers, not previously informed about side effects
Güth et al. (2008)	Non-adherence with adjuvant endocrine therapy	Retrospective analysis of data	Discontinuation (not further specified)	Self-report during follow-up (not further specified)	Postmenopausal patients with invasive breast cancer (325)	NA	(−) Patients who did not have follow-up in an oncologic unit but rather with a general practitioner
Kirk & Hudis (2008)	Barriers in adherence to oral hormonal therapy	Cross-sectional	Taking <100% of oral anticancer drugs	Self-reported internet survey with 30 questions about intake of oral anticancer drugs as directed	Patients with breast cancer (328)	(−) Treatment related side effects, cost of the medication, forgetfulness, constant reminder of cancer diagnosis	NA
Ma et al. (2008)	Non-compliance with adjuvant radiation, chemotherapy, or hormonal therapy	Retrospective analysis of data	Stop or refuse to take tamoxifen within the 1st year of treatment (if not stopped on the advice of a physician)	Data not further specified on discontinuation of tamoxifen – extracted from the breast cancer database of the senior author including data from the registry as well as electronic medical data used in a retrospective chart review	Women with breast cancer (788)	NA	(−) Younger (mean of 54 versus 59 years old), white, larger ductal cancers, treated with mastectomy rather than lumpectomy and radiation, ductal pathology
Marques & Pierin (2008)	Factors affecting cancer patient compliance to oral anti-neoplastic therapy	Cross-sectional	⩽3 Points on Morisky and Green Test[c]	Morisky and Green Test	Cancer patients under anti-neoplastic oral therapy in a private hospital (61)	(−) longer treatment time, type of medication (mercaptopurine, dexamethasone, thalidomide, and hormone therapy drugs), patients who had alternative treatment (massage) (+) patients who previously had radiotherapy	NA
Owusu et al. (2008)	Predictors of tamoxifen discontinuation	Retrospective analysis of data	Discontinuation: ⩾60 days discontinuing tamoxifen during 5 years after initial tamoxifen prescription	Refill data (date of initial tamoxifen prescription and date of discontinuation) extracted from cancer register, administrative, and clinical databases	Older women with estrogen receptor-positive breast cancer (961)	NA	(−) Older age (>75), increasing comorbidities, indeterminate estrogen receptor status, have had breast-conserving surgery without radiotherapy

Kimmick et al. (2009)	Adjuvant hormonal therapy use among insured, low-income women with breast cancer	Retrospective analysis of data	(1) Adherence by MPR ⩽80%, (2) non-persistence as a 90-day gap in prescription fill	Refill data extracted from the North Carolina Central Cancer Registry (CCR) and North Carolina Medicaid Claims administrative database	Insured, low-income women with breast cancer (1491)	(+) Nonmarried status	(+) Nonmarried status, having more comorbidities (Charlson comorbidity index[d] of 3 compared with 0), regional rather than local stage of tumor
Noens et al. (2009)	Prevalence, determinants, and outcomes of non-adherence to imatinib therapy	Prospective observational study	(1) Patient Visual Analog Scale (VAS) rating, (2) ⩾1 positive answers on the Basel Assessment of Adherence Scale (BAAS)[e], (3) pill count: other dose taken than prescribed during 90-day period	BAAS scale, VAS rating the overall adherence, pill counts	Patients with CML (169)	(−) Bothersomeness of symptoms, number of symptoms, number of adverse events, third person perceptions of adherence, higher age[f], longer time since CML diagnosis[f], living alone[f], male sex[f], longer time on imatinib[f], imatinib dose more than or equal to 600 mg/day[f], higher degrees of chronic care received[f], higher (self-)reported functional status and quality of life[f], shorter median duration of treatment follow-up visits (presumably a proxy of vigilance)[f], years of physicians' professional experience[f] (+) knowledge ofdisease and treatment[f], more medications to be takendaily[f], secondary school or higher education[f], self-efficacy in long-term medication behavior[f], physicians' higher number of active patients with CML seen in the past year[f], median duration of the first visit with a patient newly diagnosed with CML[f], (practicing in a university or teaching hospital[f], holding specialization in hematology[f])	NA
Hershman et al. (2010)	Early discontinuation and non-adherence to adjuvant hormonal therapy	Retrospective analysis of data	(1) Non-adherence by MPR <80%, (2) early discontinuation if 180 days elapsed from the prior prescription without a refill	Refill data (date of prescription and date of refill) from the pharmacy information management system from the Kaiser Permanente of Northern California	Early stage breast cancer patients (8769)	(−) African American race, lumpectomy, unknown tumor size, lymph node involvement, comorbidities	NA (−) Younger (<50 years old) or older age (⩾65 years old), lumpectomy (v mastectomy, comorbidities (+) married status, receipt of chemotherapy or radiotherapy, longer prescription refill interval
Partridge et al. (2010)	Adherence and persistence with oral adjuvant chemotherapy	Cross-sectional	MEMS <80%	MEMS	Older women with early-stage breast cancer (161)	(−) Having node-positive disease, received partial mastectomy/ lumpectomy/excisional biopsy	NA
Regnier Denois et al. (2010)	Behavior and representations of patients and oncologists on adherence with oral chemotherapy	Qualitative study design	Occasionally forget intake of oral anticancer drug	Self-report in patient interviews and focus group interviews	Patients with breast cancer (42)	(−) Change in routine (town visits, visiting friends, going on holiday), not understand prescriptions, side effects, changes in timing for taking the treatment in terms of meal times	NA

(*continued on next page*)

Table 2 (*continued*)

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Eliasson et al. (2010)	Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed	Mixed method study design	MEMS (Medication Event Monitoring System) ⩽90%	(1) Answering "yes" in a patient interview on the question: "It is common that patients at times miss a few doses, for a whole range of reasons. Thinking just of the past 7 days have you missed any doses?", (2) data from a previous quantitative study measuring adherence by MEMS	Patients with CML (21)	(−) (1) Unintentional non-adherence (forgetting, accidentally taking too much, prescribing error, no imatinib available at pharmacy), (2) intentional non-adherence (attributable to side effects, socializing/dining out/drinking alcohol, traveling, diversion from planned activities, temporary illness (cold), risk of pregnancy, negative emotions and feelings, "no real reason/lack of discipline", bad taste, changed doses), (3) consequences of non-adherence (perceived consequences, conflicting information regarding consequences, "getting away with it", reliance on monitoring and health care providers to detect and relay changes in clinical parameters, do not think missing the odd dose make a difference)	NA
Nekhlyudov et al. (2011)	Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence	Retrospective analysis of data	(1) Adherence by MPR ⩽80%, (2) non-persistence by having a gap between two consecutive prescriptions of at least 60 days	Refill data extracted from claims submitted to Harvard Pilgrim Health Care, a non-profit health plan in Massachusetts	Women with early stage breast cancer (2207)	NA	(−) Elderly women (>70 years old at diagnosis – compared to younger than 50 years old), lower income neighborhood (associated factor only during first year of treatment)
Neugut et al. (2011)	Compliance with adjuvant hormonal therapy	Retrospective analysis of data	(1) Non-adherence: MPR <80%, (2) non-persistence: presciption supply gap ⩾45 days without subsequent refill	Refill data extracted from an anonymous Information Warehouse database of medication prescriptions	Women with early stage breast cancer (8110)	(−) Higher out-of-pocket cost, older age	(−) Prescription not by oncologist (by primary care physician), 10 or more other prescriptions, higher out-of-pocket cost, older than 85 years
Sedjo & Devine (2011)	Predictors of non-adherence to aromatase inhibitors	Retrospective analysis of data	MPR<80%	Refill data extracted from the MarketScan® Commercial Claims and Encounters Databases from Thomson Reuters	Commercially insured women with breast cancer (13593)	(−) Younger age (<45 years old), out-of-pocket costs ⩾$30 per prescription, no mastectomy, higher Charlson Comorbidity Index	NA
Streeter et al. (2011)	Factors affecting abandonment of oral oncolytic prescriptions	Retrospective analysis of data	Abandonment (reversal of an adjudicated pharmacy claim without a subsequent paid claim for oncolytic within the ensuing 90 days)	Refill data extracted from administrative claims from the Wolter Kluwer Dynamic Claims Lifecycle Database (pharmacy utilization data)	Cancer patients (10508)	NA	(−) High cost, increased prescription activity, lower income, type of drug (imatinib, sorafenib, sunitinib, erlotinib, lapatinib compared with capecitabine)

[a] Medication adherence report scale (MARS-5) is a scale with 5 items to assess various non-adherent behaviors including how often patients have deliberately not taken their medicines and forgotten to take them. All questions are answered on a five point Likert-scale, resulting in a range from 5 to 25 point, with higher scores indicating greater adherence.

[b] Medication possession ratio (MPR) is a formula used to determine adherence that is measured from the first to the last prescription, with the denominator being the duration from index to the exhaustion of the last prescription and the numerator being the days supplied over that period from first to last prescription.

[c] Morisky and Green test evaluates attitudes regarding treatment and is made up of four questions.

[d] Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned with a score of 1, 2, 3 or 6 depending on the risk of dying associated with this condition. Then the scores are summed up and given a total score which predicts mortality.

[e] Basel assessment of adherence scale (BAAS) is a 4-question clinical interview guide questioning adherence behavior.

[f] Not independent factors and should be interpreted as part of a canonical model of multiple complementary variables.

appropriate. Consequently, none of the studies were excluded after considering methodological quality.

Study characteristics

An overview of the study characteristics, determinants and factors associated with medication (non-)adherence and (non-) persistence to OACD therapy is presented in Table 2.

Different study designs were used: retrospective study designs ($n = 12$), prospective study designs ($n = 6$), cross-sectional study designs ($n = 5$), a qualitative study design ($n = 1$), and a mixed method design ($n = 1$). Sample size ranged from small studies ($n = 21$) to large studies ($n = 13593$). The majority of the studies ($n = 17$) were conducted in the United States of America. The remaining studies were conducted in Europe ($n = 7$) and Brazil ($n = 1$).

Eleven studies focused on medication (non-)adherence, nine studies on medication (non-)persistence or early discontinuation and five studies on both (non-)adherence and (non-)persistence with OACD. Most of the studies ($n = 20$) focused on patients with breast cancer and often included a secondary characteristic (age, stage of the disease or a combination of both). The other studies focused on (non-)adherence and (non-)persistence in patients with CML ($n = 3$), and in patients with different types of cancer ($n = 2$).

Definition and assessment of medication (non-)adherence and (non-) persistence

A wide variation was found regarding the criteria for defining medication (non-)adherence and (non-)persistence and methods for assessment.

Criteria used for defining medication non-adherence were taking less (<80%,[34,35] <90%,[3,31] <100%[32]) or more of the prescribed dose (>110%[31]), lower scores on the Medication Adherence Report Scale (MARS-5),[36] having a Medication Possession Ratio (MPR) $\leqslant$80%,[14,37–40] having $\leqslant$3 points on the Morisky and Green Test,[41] or having $\geqslant$1 positive answer on the Basel Assessment of Adherence Scale.[17] The definition of medication non-persistence included different cut-off rates in number of days with a discontinued intake of OACD ($\geqslant$30,[23] $\geqslant$45,[40] $\geqslant$60 days[39,42] and $\geqslant$180 days[37,43]).

The methods used to assess medication adherence and persistence in patients taking OACD were pharmacy refill data extracted from pharmacy records and medical claims ($n = 11$)[14,23,32,34,38–40,42–45], self report ($n = 10$)[4,15,16,32,33,36,41,46–48] or a combination of both ($n = 2$).[17,31] Only two studies used a Medication Event Monitoring System (MEMS)[3,35], an electronic monitoring system to compile the dosing histories, including one study using a combination of MEMS and self report. No objective methods such as biological markers were used in the included studies.

Determinants and associated factors of medication (non-)adherence and (non-)persistence to OACD

This review shows that (non-)adherence and (non-)persistence to OACD therapy are influenced by different factors (see Table 2). A distinction is made between factors influencing medication (non-) adherence and factors influencing medication (non-)persistence. Determinants and associated factors of (1) (non-)adherence and (non-)persistence and (2) higher adherence and higher persistence will be structured according to the five categories suggested by the

Table 3
Summary of the quality assessment of the included quantitative studies (23).

	Selection bias	Allocation bias	Confounders	Data collection methods	Withdrawals and drop-outs	Analysis					
						Q1[a]	Q2[b]	Q3[c]	Q4[d]	Q5[e]	Q6[f]
Lebovits et al.[31]	Moderate	Moderate	Weak	Strong	Weak	N[g]	P[h]	Y[i]	Y	Y	Y
Demissie et al.[47]	Moderate	Moderate	Weak	NA[j]	Weak	N	Y	Y	Y	NR[k]	Y
Partridge et al.[34]	Moderate	Moderate	Weak	NA	Moderate	N	Y	N	Y	NR	Y
Fink et al.[15]	Weak	Moderate	Weak	NA	Weak	N	Y	Y	Y	NR	Y
Grunfeld et al.[36]	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Atkins & Fallowfield[48]	Moderate	Moderate	Weak	NA	Weak	N	Y	Y	Y	NR	Y
Lash et al.[16]	Moderate	Moderate	Weak	Strong	Weak	N	P	Y	Y	NR	Y
Barron et al.[43]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Darkow et al.[23]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kahn et al.[46]	Moderate	Moderate	Weak	Moderate	Weak	N	Y	Y	Y	NR	Y
Güth et al.[33]	Weak	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kirk & Hudis[32]	Moderate	Moderate	Weak	Moderate	Moderate	N	Y	Y	Y	NR	Y
Ma et al.[44]	Moderate	Moderate	Weak	NA	Moderate	N	P	Y	Y	NR	Y
Marques & Pierin[41]	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Owusu et al.[42]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kimmick et al.[38]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Noens et al.[17]	Moderate	Moderate	Weak	Strong	Strong	Y	Y	Y	Y	NR	Y
Hershman et al.[37]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Partridge et al.[35]	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Nekhlyudov et al.[39]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Neugut et al.[40]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Sedjo & Devine[14]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Streeter et al.[45]	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y

[a] Sample size or power calculation.
[b] Characteristics of study participants extensively described.
[c] Main results of statistical analysis unambiguously described.
[d] Statistical methods appropriate.
[e] Missing data handled in an appropriate way.
[f] Result section report on all outcome measures mentioned in method-section.
[g] No.
[h] Partially.
[i] Yes.
[j] Not applicable.
[k] Not reported.

Table 4
Summary of the quality assessment of the mixed method study and qualitative study (2).

	Clear statement of the aims	Appropriate methodology	Appropriate design	Appropriate recruitment strategy	Appropriate data collection	Consideration relationship between researcher and participants	Consideration ethical issues	Rigorousness data analysis	Clear statement of findings	Valuability of the study
Eliasson et al.[3a]	+	+	+	-	+	–	+	+	+	+
Regnier Denois et al.[4]	+	+	+	+	+	–	+	–	+	+

+ = Yes, – = No.
[a] Mixed method study.

World Health Organization (WHO, 2003) framework of factors influencing medication adherence.

Patient- related factors

Several patient-related factors were found to be associated with medication non-adherence in patients taking OACD. They can be divided into intentional non-adherence and unintentional non-adherence. Lower perceived necessity by the patient for taking the drug ($n = 1$),[36] perception of no benefit to be gained from taking the drug ($n = 1$),[36] concerns about symptoms ($n = 1$),[17] the opinion that missing a dose makes no difference ($n = 1$),[3] and lower perceived quality of life ($n = 1$),[3] were found as intentional patient-related factors associated with medication non-adherence in patients on an OACD therapy. Forgetting ($n = 2$)[3,32] and accidentally taking too much of the prescribed drug ($n = 1$)[3] were found to be the most common patient-related factors being associated with unintentional medication non-adherence. Self-efficacy ($n = 1$)[17] and the belief that medication intake as being prescribed would help to cure from cancer ($n = 1$)[36] were reported as important patient-related factors associated with higher adherence to OACD therapy. Having neutral or negative beliefs about the value of the drug ($n = 1$)[15] was found to be a patient-related factor associated with non-persistence.

Therapy-related factors

Treatment related side effects are the most frequently reported therapy-related factors associated with non-adherence to OACD therapy ($n = 5$).[3,4,32,36,48] The study by Grunfeld et al. (2005) reported that 46% of the non-adherent breast cancer patients mentioned side effects as primary reasons for non-adherence to tamoxifen. The main side effects reported were hot flashes (32%), night sweats (24%), concentration or memory difficulties (22%), sleep problems (16%), emotional problems (anxiety, panic, depression; 15%), weight gain (15%), and loss of libido (12%). Treatment related side effects were also reported as the primary reason (70%) for medication non-adherence in the study by Kirk and Hudis (2008). OACD side effects were not associated with a specific type of drug in this study. Atkins and Fallowfield (2006) found also a significant association ($p = 0.001$) between disliked aspects (e.g. side effects, difficulties swallowing tablets and inconvenience) of oral anti-tumoral medication in breast cancer patients (e.g. side effects) and non-adherence. Treatment related side effects were also reported as underlying factors for non-adherence in the two qualitative studies.[3,4] One of these two studies focused on CML patients[3] and the other study focused on different types of cancer (metastatic breast, metastatic colon, and adjuvant colon).[4]

Other therapy-related factors of medication non-adherence included longer duration of therapy ($n = 3$),[17,34,41] having a mastectomy rather than breast-conserving treatment ($n = 2$),[34,35] starting with a higher dose of OACD ($n = 2$),[17,23] changed doses ($n = 1$),[3] type of drug (mercaptopurine, dexamethasone, thalidomide, and hormone therapy drugs) ($n = 1$),[41] having a lumpectomy ($n = 1$),[37] and variation in timing for medication intake (e.g. before or after meals) ($n = 1$).[4]

Side effects ($n = 3$),[16,46,47] increased number of prescriptions ($n = 3$),[40,43,45] having a mastectomy rather than breast-conserving surgery (lumpectomy) and radiation ($n = 1$)[44] and the type of drug (imatinib, sorafinib, sunitinib, erlotinib, lapatinib versus capecitabine) ($n = 1$)[45] were associated with non-persistence in patients taking OACD. Having a lumpectomy rather than having a mastectomy ($n = 1$)[37] was found to be associated with higher non-persistence in one study.

Having a higher number of medication prescriptions at baseline was found to be associated with higher persistence in one study.[16] Women needing to take more medications during follow-up were more likely to discontinue the OACD therapy. Longer intervals between two prescriptions ($n = 1$),[37] more medications to be taken daily ($n = 1$),[16] and patients who had radiotherapy before ($n = 1$)[37] were factors associated with higher medication persistence in patients on an OACD therapy.

Disease-related factors

Co-morbidities ($n = 2$),[14,37] unknown tumor size ($n = 1$),[37] and having a node-positive disease ($n = 1$)[35] were associated with medication non-adherence in patients on an OACD therapy. However, co-morbidities were also found to be associated with higher persistence in one study. [38]

Disease-related factors associated with non-persistence to OACD were similar to those associated with non-adherence. However, other factors associated with medication non-persistence were history of antidepressant use ($n = 1$),[43] ductal pathology ($n = 1$)[44] and negative and unknown hormone receptor status ($n = 1$).[46]

Healthcare system factors

Shorter duration of treatment follow-up visits ($n = 1$),[17] prescribing errors ($n = 1$),[3] and conflicting information regarding consequences ($n = 1$)[3] were associated with non-adherence in patients on an OACD therapy. Different doctors responsible for follow-up ($n = 1$),[46] and follow-up by a primary physician rather than an oncologist ($n = 2$)[33,40] were associated with medication non-persistence in patients taking OACD. Not previously being informed about side effects ($n = 1$)[46] less patient participation in decision making than wanted ($n = 1$),[46] and receiving too much or too less support than needed ($n = 1$)[46] were also factors associated with medication non-persistence in these patients.

Enhanced knowledge of the disease and treatment ($n = 1$),[17] having consulted an oncologist in the year before beginning tamoxifen therapy ($n = 1$),[34] longer duration of the first visit with a patient newly diagnosed with CML ($n = 1$)[17], and physicians'

higher number of CML patients seen in the past year ($n = 1$)[17] were associated with higher medication adherence in patients taking OACD.

Social and economic factors

Younger age ($n = 3$),[14,34,48] older age ($n = 3$),[17,34,40] and higher out-of-pocket costs ($n = 3$)[14,32,40] were associated with non-adherence in patients taking OACD. Younger age was defined as $\leqslant 45$,[14,34] older age as $\geqslant 85$,[34] and higher out-of-pocket costs as $\geqslant \$30$.[14] A higher educational level ($n = 1$)[17] was associated with higher adherence in patients taking OACD. Older age ($n = 6$)[37,39,40,42,43,46] was also found to be associated with lower persistence of the OACD treatment. Higher out-of-pocket costs ($n = 2$),[40,45] younger age ($n = 2$),[37,44] lower income ($n = 2$),[39,45] and female gender ($n = 1$)[23] were also influencing medication non-persistence. Married status was found to be associated with higher persistence ($n = 1$).[37]

Discussion

The aim of this review was to determine factors associated with medication (non-)adherence and (non-)persistence in patients taking OACD. This review suggests that (non-)adherence and (non-)persistence in this patient group is multi-factorial, complex and influenced by patient-related, therapy-related, disease-related, healthcare system and social-economic factors. However, generalizations require caution as the included studies used different definitions, methods for assessing medication adherence, and cut-off rates for defining medication adherence.

Methodological quality of the included studies

In general, methodological quality of the included studies was moderate. No studies were excluded after considering methodological quality. The most common methodological limitations were the absence of clear data on withdrawals or drop-out, the absence of a power calculation, and not taking into account possible confounders in the analysis. Further, the self-report questionnaires used in the included studies to assess medication non-adherence were often self-constructed and not always tested for validity and reliability. Only in a few studies, validated self-report questionnaires were used.[17,36,41] Future studies need to address these issues, as they can influence the validity of the study findings.

Study characteristics

Twelve studies used a retrospective study design. This design has several limitations: (1) it often only includes data that are necessary for administrative statistical purposes,[33] (2) it is often limited to specific patient populations and thus findings from these studies may have limited generalizability, and (3) it cannot report on unintentional non-adherence. Causal relationships between non-adherence or non-persistence and determinants of medication non-adherence can also not be detected by using a retrospective design.

In studies with a cross-sectional ($n = 5$) or prospective study design ($n = 6$), the risk of a sample bias has to be considered due to the voluntary character of study participation.[49] Prospective study designs are more appropriate to study determinants of medication non-adherence or non-persistence in patients taking OACD than cross-sectional designs due to the longitudinal character.[17] One study used a qualitative approach and one study a mixed method approach. It seems that qualitative study designs are scarce in our review and in adherence research. This is remarkably as qualitative study designs possess the ability to apprehend an overall view of underlying factors and processes associated with medication non-adherence or non-persistence in order to explain these phenomena.[50] Qualitative research is essential and more appropriate to explore the influence of interpersonal relation aspects in medication adherence and persistence with OACD. These aspects have been identified as important factors influencing medication adherence in other pathologies, but are underexplored in the included studies.[51–53]

Definition and assessment of medication (non-)adherence and (non-)persistence

To date there is no universally accepted definition of medication adherence nor an appropriate method to optimally assess medication adherence and persistence.[54] To define medication non-adherence and non-persistence, different cut-off rates were used. Based on the extracted data from databases, the number of days covered by filled prescriptions or the MPR were often calculated with a cut-off $\leqslant 80\%$ to define non-adherence. This cut-off rate is frequently cited in the literature as achievable or acceptable.[55–57] For MEMS, a cut-off for non-adherence was set on $\leqslant 80\%$ in oral adjuvant chemotherapy in breast cancer patients[35] and $\leqslant 90\%$ in CML patients taking imatinib.[3] The rate of $\leqslant 90\%$ is identified as the most important factor for an adequate molecular response with imatinib.[20] In defining medication non-persistence, several different cut-offs in number of days without subsequent refill of pills were used.[40,42,43,45] There is a need to further explore clinically significant cut-off rates when measuring (non-)adherence to increase comparability in research.

Existing methods to assess medication adherence and persistence include objective methods such as the measurement of metabolites of the medication in body fluids, and subjective methods such as counting tablets, self report and MEMS. In this review, only subjective methods were used, mainly self-report questionnaires or self report in patient interviews.[3,15–17,31–33,36,41,46–48] However, patient self reported medication adherence or persistence is often overestimated because of psychological reasons (fear to be considered unreliable and willingness to please healthcare providers),[54] and because patients may not be fully aware of their lapses in doses.[54] In measuring adherence, a Hawthorne effect must be taken into account[11] as patients might be aware that their adherence or persistence is being studied. MEMS was used in two studies.[3,35] This method has previously showed to be more accurate than self report or pill counts,[58] but measuring adherence by using MEMS is expensive and not always feasible in daily practice.[59] A combination of MEMS and self-report questionnaires is found to be most accurate in measuring medication adherence.[59] The combination of these methods was only used in one study.[3] Other data were obtained from retrospective databases such as pharmacy or insurance records with refill data.[14,23,33,34,37–40,42–45] None of the included studies defined non-adherence as doses being taken at the wrong time. Despite, this might be a critical factor in treatment effectiveness.[11] Future research should also focus on this type of non-adherence and take into account the specific margin of the OACD whereas in between the OACD needs to be taken without losing efficacy of the treatment.

Determinants and associated factors of medication (non-)adherence and (non-)persistence to OACD

Treatment related side effects are predominant factors associated with non-adherence and non-persistence in patients on an OACD therapy. Being inadequately informed about side effects in advance is found to be a factor associated with increased medication non-persistence,[46] while a better knowledge of the disease

and therapy is associated with a higher adherence.[17,60,61] The study by Kirk and Hudis (2008) showed that understanding the clinical importance of OACD is helpful for 90% of the patients to adhere to their therapy. The majority of the patients in the study of Kirk and Hudis (2008) also indicated an appropriate management of treatment-related side effects as an important factor influencing medication adherence. These findings support the need for patient tailored educational support[62–64] and management of symptoms during follow-up.[65]

Both younger and older age were major factors associated with non-adherence and non-persistence in patients taking OACD. This association was primarily found in breast cancer patients. Several studies indicate that younger women do not adjust to breast cancer as well as older women, affecting their medication adherence.[66,67] The study by Compas et al. (1999) suggests that younger women with breast cancer are more affective distressed and tend to cope with stressors in a less adaptive way.[68] However, the reasons for non-adherence and non-persistence in this group of patients remain unclear. A factor that may increase non-adherence and non-persistence in younger women with breast cancer is that younger women are more likely to undergo early menopause caused by breast cancer treatment,[69] which may affect women's child wish. Older patients are often more influenced by polypharmacy for comorbidities and chronic conditions, physical challenges, psychosocial issues (e.g. decreased social support), and increasing incidence of memory problems.[70,71] These factors can also impede medication adherence and persistence.

Implications for practice

The findings from this review provide insight into the complexity of determinants associated with (non-)adherence to OACD in cancer patients. An important finding from the review is that patients taking OACD differ widely (e.g. age, disease entity, co-morbidities, and severity of side effects) underlining the need for different and tailored approaches in support, depending on their preferences, age, therapeutic regimen, disease entity, and severity of side effects. Clinicians should help patients to understand that early recognition of treatment related side effects can be of great benefit to them.[63] Further, patients should be well informed about the long-term benefits of the treatment and how treatment related side effects could be managed in daily life. This education should be tailored and based on patient preferences instead of being uniformly organized.[73] This tailored approach should be performed in a context of reciprocity between the physician and the patient, so patients' expectations and individual beliefs could be discussed and patients could become active actors of their therapy.

Limitations

Some limitations of this review need to be considered. Generalizations require caution as the data obtained from the studies are difficult to compare due to their specific focus (different types of drugs, disease entities, and design), and the different cut-off rates and methods for assessing non-adherence and non-persistence. Only two studies used MEMS to assess non-adherence, so the results should be interpreted with caution. Performing a meta-analysis to generalize results and compare subgroups of cancer patients taking OACD was not possible due to the heterogeneity of the studies.

Most of the studies focus on breast-cancer patients (80%) so the conclusions from this study are mainly relevant for this group. Data on other types of cancer are scarce, for example research in patients taking oral tyrosine kinase inhibitors is limited to the three included studies with CML patients. Therefore, further research should pay more attention to other types of cancer.

In studies using a retrospective design based on pharmaceutical or commercial databases ($n = 8$), and in articles written by authors supported by pharmaceutical grants ($n = 6$), a potential conflict of interest needs to be considered.[72]

Conclusion

This systematic review gives an updated overview of the literature on associated factors and determinants of medication (non-) adherence and (non-)persistence in patients on an OACD therapy. Older and younger age, and the influence of therapy related side effects are predominant factors associated with medication adherence and persistence to OACD therapy. However, influencing factors to medication adherence and persistence to OACD therapy are multifactorial and interrelated. Caution is needed in the interpretation and with the generalizability of the results as the studies differ widely in study focus, definitions and measurements of medication adherence and persistence. Qualitative research could facilitate the development of patient tailored complex interventions by exploring patients' needs and underlying processes influencing medication adherence and persistence to OACD.

Statement of Authorship

All authors have made substantial contributions and approved the conceptions, drafting, and final version of the manuscript.

Conflict of interest

There is no conflict of interest.

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