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Adherence enhancing interventions for oral anticancer agents: A systematic review

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ABSTRACT

Background: The use of oral anticancer agents has increased in the last decades. Adherence is a crucial factor for the success of oral anticancer agent therapy. However, many patients are non-adherent.
Objective: The objective was to evaluate the effectiveness of adherence interventions in patients taking oral anticancer agents.
Methods: A systematic literature search was performed in Medline and Embase. Titles and abstracts and in case of potential relevance, full-texts were assessed for eligibility according to the predefined inclusion criteria. The study quality was evaluated. Both process steps were carried out independently by two reviewers. Relevant data on study design, patients, interventions and results were extracted in standardized tables by one reviewer and checked by a second reviewer.
Results: Six controlled studies were included. Only one study was randomized. The study quality was moderate to low. One study showed statistically significant results in favor of the adherence intervention, two studies showed a tendency in favor of the intervention, one study showed an inconsistent result depending on the adherence definition and one study showed almost identical adherence rates in both groups. One study showed a tendency in favor of the control group.
Conclusions: Although most of the interventions are not very effective, it appears that certain adherence enhancing interventions could have a promising effect. One crucial point is the consideration of the baseline adherence when choosing patients to avoid ceiling effects. The evidence is limited due to lack of sufficient studies and partly inconsistent results. Further high quality studies are needed.

Introduction

The use of oral anticancer agents (OACA) has increased in the last decades. It is assumed that one quarter of newly developed anticancer agents could be taken orally [1] and the amount of oral therapy in cancer treatment will probably increase further. Adherence, defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [2]," is lower in patients taking OACA compared to patients taking intravenous chemotherapy [3]. Adherence rates in cancer patients range from less than 20–100%, depending on patient characteristics, therapy and adherence measurement/definition [4,5]. Most patients prefer to take their medication orally [6]. Adherence is one predisposing factor for the success of OACA [7,8], in particular when considering the long period in which OACA have to be taken correctly. Thus, adherence has become an important issue in modern oncology treatment.

However, several factors (patient characteristics, treatment characteristics, disease characteristics, setting) exist, for which an influence on patient adherence in patients taking OACA has been shown [9]. The factors can be roughly divided in the following five dimensions: Social and economic, health care system, health condition, therapy and patient [10].

Social and economic factors are all factors concerning the social an economic status of a person. For example, poverty and income can result in conflicting priority-setting regarding the use of limited resources. The consequence can be that adherence is reduced because the priority for other demands than medications (e.g., food) is perceived higher.

Health care system factors are all factors that relate to the organizational structures of the health care system/services and characteristics of the health care professionals. This includes e.g., the coverage of health insurance, patient-provider relationship or medication distribution.

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Health condition related factors are all factors that affect the patient regarding certain disease. These include the severity of disease, severity of symptoms, prognosis or availability of effective treatments.

Therapy related factors are factors that relate to a certain therapy like the regime complexity or adverse events.

Patient factors are related to the patient attitudes, knowledge, beliefs, perceptions and expectations. For example the health literacy or beliefs about cure [10].

Different types of interventions to enhance patient adherence can be applied that target one or multiple of the five described adherence influencing dimensions. The potential of interventions to enhance adherence is probably raised by simultaneously targeting several of the influencing dimensions. But the effectiveness of an adherence enhancing intervention depends not only on the intervention itself but also on the applicability for a specific patient group.

On the one hand, many adherence interventions exist for chronic conditions for which a statistically significant influence on patient adherence as well as on clinical outcomes was proven. On the other hand, there are many ineffective interventions [11].

To the best of our knowledge only one review investigating interventions to enhance patient adherence for OACA exists [12]. This review was not prepared systematically. Furthermore as adherence is meanwhile an often discussed issue in OACA therapy, it could be expected that the review don't cover all relevant studies on this topic that have been probably published in the last five years.

The objective of this systematic review was to identify and summarize all controlled studies examining the effectiveness of adherence enhancing interventions for adult patients taking OACA.

Methods

Search strategy

A systematic literature search was performed in the databases Medline (via Pubmed) and Embase (via Embase excluding Medline records). The search strategy combined various synonyms, antonyms, acronyms and medical subject headings related to adherence, oncology as well as OACA and was adapted for each database (the full search strategies are available in Appendix I). The search was performed in December 2012. We did not limit the publication date and language in the search strategy.

Study selection

To be eligible for this review the studies had to meet all the following inclusion criteria:

1. Patients with malignant neoplasms.
2. Patients taking OACA.
3. Patients $\geqslant$16 years.
4. Interventions including a component to enhance patient adherence (no different dosages or different types of application of the same substance, intake without the presence of a health care professional).
5. Outcome: Adherence (not persistence).
6. Study type: Controlled studies.
7. Publication language: English or German.

Adherence interventions including different dosages and application types were excluded because it implicates different pharmacodynamics and pharmacokinetics and are associated with different adverse events and effectiveness that have an impact on adherence. Titles and abstracts of all hits in electronic databases were screened. The full-texts of potentially eligible articles were obtained and screened. Two independent reviewers assessed the fulfillment of the review inclusion criteria in both steps. Differences between the reviewers were discussed until consensus was reached. We hand-searched the reference lists of all included publications. The authors were contacted in case of any unclear inclusion criteria.

Assessment of methodological study quality

The RCT (randomized controlled trial) and non-RCT (definition non-RCT: investigators had direct control over study conditions but interventions were not randomly assigned, e.g., quasi RCT [13]) were assessed using the nine items of the Cochrane Effective Practice and Organization of Care Group tool [14]. However, the tool is not designed to assess cohort studies. For the methodological quality assessment of cohort studies a tool provided by the National Institute for Health Clinical Excellence (NICE) was applied (evaluation questions for both instruments are available in Appendix II). All questions were rated as fulfilled and not fulfilled (low risk of bias/high risk of bias). The quality assessment was performed independently by two reviewers. Disagreements were resolved in a discussion or by involving a third person. Due to the obvious nature of adherence enhancing interventions blinding of patients and the personnel involved in the adherence intervention is not feasible. All corresponding quality criteria were therefore generally not applied to investigators performing the adherence intervention and participants but referred to personal that measured or assessed the adherence and personnel delivering cancer care.

Data extraction and synthesis

The data were extracted in standardized tables tested beforehand. Information about the study period, region/setting of the study, cancer type, OACA, demographic and clinical inclusion criteria, intervention/s and control, the definition and measurement of adherence, and the study results for adherence at last follow-up were summarized in these tables. Data were extracted by one reviewer and checked by a second for accuracy. Available data on other outcomes were also extracted and are presented additionally. All values in the tables are means unless otherwise indicated. A p-value below 0.05 was regarded as statistically significant.

High study heterogeneity was expected because of the diversity of adherence enhancing interventions and different populations taking OACA. Thus, a quantitative data synthesis using a meta-analysis was not planned a priori.

Results

The literature search resulted in 2309 hits after electronic removal of duplicates. Ninety-five titles and abstracts were rated as potentially relevant for and the full-texts were screened. In this process step 88 publications were rated as irrelevant. Seven publications satisfied all inclusion criteria. Two studies seemed to be based in great part on the same participants [15,16]. The authors were contacted and confirmed the assumption. Thus, six studies (seven publications) were included. A hand-search of references of the included studies revealed no further relevant publications. The selection process is illustrated in the flow-chart (see Fig. 1).

RCT, non-RCT and cohort studies were identified. The overall methodological quality of the studies was moderate to low (results of the quality assessment for RCT, non-RCT see Table 1 and cohort studies Table 2). At least three quality criteria were not met in each

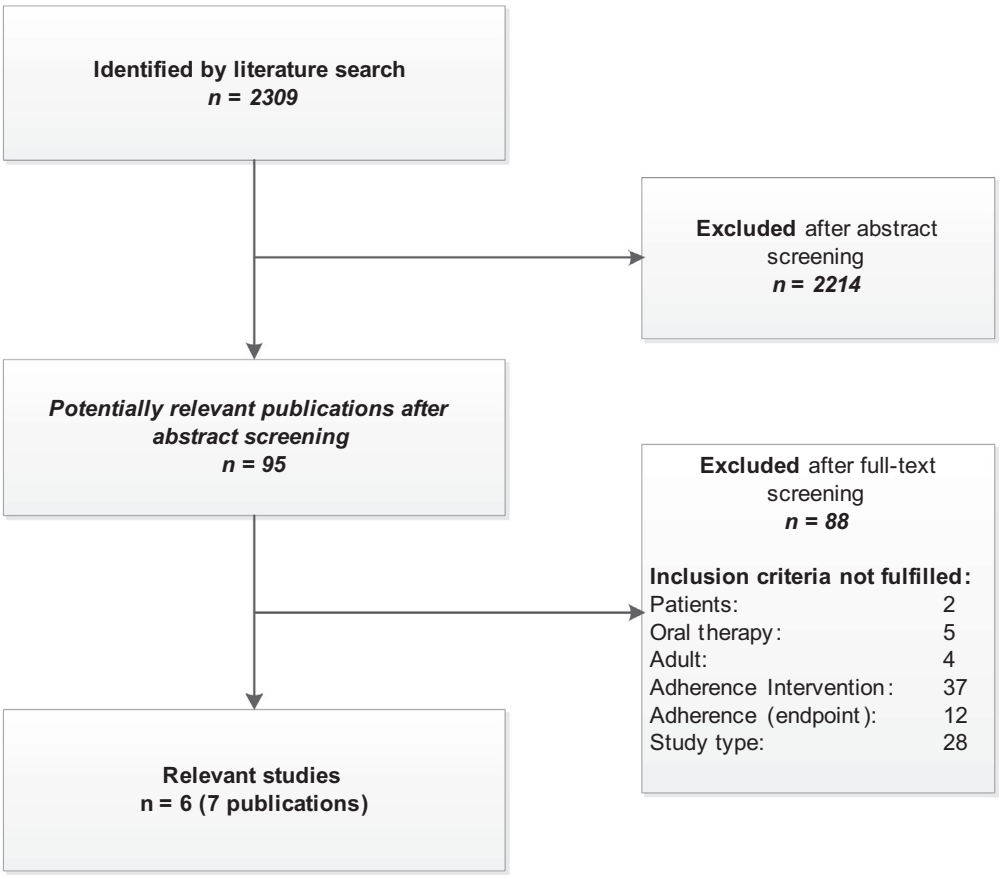

Fig. 1. Flow diagram of study selection.

Table 1
Methodological quality of included RCTs and non-RCTs.

Study	Generation of allocation sequence	Allocation concealment	Baseline outcome measurements	Baseline characteristics	Incomplete outcome data	Knowledge of the allocated interventions	Protection against contaminatio	Selective reporting	Other sources of bias
Levine, Richardson 1987	–	–	–	+	+	–	–	+	+
Macintosh 2007	+	–	–	+	+	–	O	+	+
Moon 2012	–	–	–	+	–	–	–	–	+
Simons 2011	–	–	–	+	+	–	+	+	+

+ Fulfilled.
– Not fulfilled.
O not applicable.

study. In the study with the poorest methodological quality violated only two out of nine criteria [17].

A description of the included studies is illustrated in Table 3 (additional detailed description of patient characteristics and interventions are available in Appendix III). Results are presented in Table 4.

Except for the studies by Moon et al. [17] (South Korea) and Simons et al. [18] (Germany) all studies were performed in the USA.

Khandelwal et al. [19] analyzed in a register-based cohort study an oral chemotherapy cycle management program in 754 patients taking Sorafenib, Sunitinib and/or Erlotinib. The results for doses taken measured with prescription refill showed a tendency in favor of the intervention (44.8 vs. 41.5). There was no statistically significant difference in hospital admissions.

Levine et al. [15] and Richardson et al. [16] compared in a non-RCT three groups (education, education plus pill shaping, education plus pill shaping plus home restructuring) *versus* no adherence intervention in 62 respectively 52 newly diagnosed patients taking prednisone. Results showed a tendency in favor for each intervention arm compared to the control group for all adherence definitions (drug level prednisone and prednisolone within individuals profile range). Statistical significance was only reached for the adherence measure prednisolone within individuals profile range in Levine et al. [15]. Adherence was statically significant higher in each intervention group compared to the control group and in the intervention group consisting of education plus pill shaping plus home restructuring compared to both other intervention groups.

Macintosh et al. [20] compared capecitabine pre-filled per patient's prescription into daily pill boxes to conventional capecitabine

Table 2
Methodological quality of included cohort studies.

Study	Treatment groups unrelated to potential confounding factors	Balanced comparison groups	Groups comparable at baseline	Same care apart from the intervention	Participants blinded	Administers blinded	Followed up for an equal length	Comparable for treatment completion	Comparable with respect to the availability of outcome data	Appropriate length of follow-up	Precise definition of outcome	Valid and reliable method was used to determine the outcome	Investigators blinded to exposure to the intervention	Investigators blinded to confounding/ prognostic factors
Khandelwal 2012	+	+	+	+	O	–	+	+	+	+	+	+	–	–
Tschida 2012	+	+	+	+	O	–	+	+	+	+	+	+	–	–

+ Fulfilled.
– Not fulfilled.
O Not applicable.

pill bottles for one treatment cycle in a cross-over-RCT (24 patients in phase one and 18 in phase two). Doses taken measured with pill count were lower in the intervention group. This difference did not reach statistical significance.

Moon et al. [17] evaluated a counseling service provided by a trained nurse for chronic myeloid leukemia patients taking imatinib in a non-randomized design. The measurement of adherence was not reported in this study. Rates for doses taken were high (>96% in both groups) and almost identical ($p = 0.958$).

Simons et al. [18] analyzed 48 patients starting chemotherapy with breast or colon cancer taking capecitabine in a non-RCT. The patients in the pharmaceutical care group showed a tendency of higher adherence levels measured with the Medication Event Monitoring System for each of the seven adherence definitions (doses taken, days with correct intake, patients with $\geqslant$80% intake, patients with $\geqslant$90% intake, days with $\geqslant$80% intake, days with $\geqslant$90% intake, irregular intake intervals [>14 h or <10 h]) in the intervention group. Statistical significance was only reached for days with correct intake ($p = 0.029$) and irregular intake intervals ($p \leqslant 0.05$). For the irregular intake the relative risk was about the half as in intervention group.

Tschida et al. [21] performed a register based cohort study including patients with an intake of $\geqslant$80% of OACA. The doses taken measured with prescription refill were 65.7% in the group receiving a pharmacy program and 58.0% in the group receiving no intervention to enhance adherence ($p < 0.001$). There were no statistically significant differences in the number of cancer related emergency department visits, cancer related hospitalizations and cancer related length of hospital stay.

Discussion

This is the first review that systematically analyzes the effectiveness of adherence enhancing interventions in cancer care. Six studies were included. One study showed statistically significant results in favor of the adherence intervention [21]. Three studies showed the tendency in favor of the intervention groups [13,14,18,19]. Whereas in two studies results were inconsistent regarding statistical significance depending on the adherence definition [15,16,18]. But is should be considered that sample size in both of this studies was low. One study showed almost identical rates in both groups [17]. One study showed the tendency but no statistically significant differences in favor of the control group [20]. Two studies analyzed admissions [19,21]. The results for this outcome were not statistically significantly different. A high quality systematic review comes to similar results for other indications [11]. However, the methodological study quality was partly very low and all studies revealed methodological flaws. Furthermore, the considerable heterogeneity between the identified studies especially regarding sample size, year of study conduct and different tumor types should be considered in the interpretation of results. Regardless of the nature of adherence interventions, where blinding is generally more difficult or impossible, also the lacking blinding should be kept in mind as a potential source of bias.

Contamination is a well-known problem in educational interventions [22]. The problem is also prominent for adherence enhancing interventions containing educational components. Two of the not statistically significant studies are primarily composed of education components [17,19].

The comparability of the study results is limited because the content of the adherence enhancing interventions is very heterogeneous. Furthermore, there are differences in patient characteristics for which an influence on adherence has been proven [9]. The comparability of the studies is further limited due to different adherence definitions and measurements.

Table 3
Study design/method and patient characteristics.

Study	Study type	Number of patients (IG/CG)	Study period	Region/setting	Cancer type*	Therapy	Inclusion/ exclusion criteria	Intervention	Control
Khandelwal 2012	(matched) cohort study	377/377	6 Months	USA/at home	Liver Kidney Gastrointestinal stromal Non-small cell lungpancreatic	Sorafenib, Sunitinib, Erlotinib (typically 5–7 cycles of 28–30 days)	Inclusion: No prescription of study drugs during the prior 6 months	Oral chemotherapy cycle management program by a oncology nurse or pharmacist	No intervention
Levine 1987	Non-RCT	15 (IG1)/ 15(IG2)/ 15 (IG3)/ 17 (CG)	6 Months	USA/medical center	Multiple myeloma Acute leukemia Chronic leukemia Indolent lymphoma Aggressive lymphoma Hodgkin's disease	Prednisone	Inclusion: ⩾ 18 age Newly diagnosed	IG1: Education and home restructuring IG2: Education and pill shaping IG3: Education, pill shaping, and home restructuring	No intervention
Richardson 1987	Non-RCT	12 (IG1)/ 13 (IG2)/ 14 (IG3)/ 13 (CG)	6 Months	USA/medical center	Multiple myeloma Acute leukemia Chronic leukemia Indolent lymphoma High-grade lymphoma Hodgkin's disease	Prednisone	Inclusion: ⩾ 18 age Newly diagnosed	IG1: Education and home restructuring IG2: Education and shaping IG3: Education, shaping, and home restructuring	No intervention
Macintosh 2007	Crossover-RCT	14/10 (phase I) 7/11 (phase II)	42 Days	Canada/ Ambulatory gastrointestinal or breast cancer clinics, chemotherapy day care unit, outpatient pharmacy	Solid tumors	Capecitabine (21-day cycle of capecitabine consists of twice daily dosing for 14 days, followed by 7 days of rest)	Inclusion: ⩾ 18 age Two consecutive cycles of capecitabine Exclusion: Taking other oral anticancer medications	Capecitabine pre-filled per patient's prescription into daily pill boxes for the treatment cycle	Conventional pill bottles for one treatment cycle
Moon 2012	Non-RCT	56/58	3 Years	South Korea/NR	Chronic myeloid leukemia	Imatinib	NR	Counseling service by a trained nurse	No intervention
Simons 2011	Non-RCT	24/24	IG (range): 9 to 138 Days CG (range): Days 13 to 128 Days	Germany/ hospitals	Colorectal Breast	Capecitabine as a single agent or in combination with other agents (2 weeks of twice daily drugintake followed by 7 days of break)	Inclusion: Started a chemotherapy ⩾ 18 age	Pharmaceutical care intervention	No intervention
Tschida 2012	(matched) cohort study	464/464	1 Year	USA / NA	Colon Breast Kidney Other urinary organs Brain Multiple myeloma and immunoproliferative neoplasms Myeloid leukemia Lung	NA	Inclusion: Intake ⩾ 80%	Pharmacy program	No intervention

NA: Not applicable.
* Only stated for ⩾5% of study population.

Most of the included studies use the doses taken as the definition of adherence [17,19–21]. The timing of intake is only considered in one study [20]. To reach a substantial therapy effect patients have to reach a certain adherence level in terms of doses taken and intake timing. The overall mean allows no conclusion on how many patients might benefit from the intervention. Taking this into account, the proportion of patients reaching a specified adherence level should be chosen as the definition of adherence instead of the mean of the whole study population. Additionally, the intake timing should be examined because it allows a more precise assessment of adherence (e.g., missed doses compensated by double dosing would be detected). The lower bounds of needed adher-

Table 4
Adherence measurement, definition and study results.

Study	Adherence measurement	Adherence definition	Mean adherence rate (IG_n/CG (p))
Khandelwal 2012	Prescription refill	Doses taken	44.8/41.5 (0.402)
Levine 1987	Drug levels in serum (prednisone)	Drug levels in serum within individuals profile range	38.0/32.7/37.8/26.8 ($p > 0.01$ for each comparison)
	Drug levels in serum (prednisolone)	Drug levels in serum within individuals profile range	41.7/49.1/59.5/21.9 ($p < 0.01$ for each IG vs. CG; $p < 0.01$ for IG_1 and IG_2 versus IG_3)
Richardson 1987	Drug levels in serum (prednisone)	Drug levels in serum within individuals profile range	33.8/36.1/35.8/31.2 ($p > 0.05$ for each comparison)
	Drug levels in serum (prednisolone)	Drug levels in serum within individuals profile range	38.8/49.0/56.6/24.8 ($p > 0.05$ for each comparison)
Macintosh 2007	Pill count	Doses taken	81/86 (NS)
Moon 2012	NR	Doses taken	96.5/96.6 (0.958)
Simons 2011	Medication event monitoring system	Doses taken	97.9/90.5 (0.069)
		Days with correct intake (not specified)	96.8/87.2 (0.029)
		Patients with ⩾80% intake	100/79 (NR)
		Patients with ⩾90% intake	92/75 (NR)
		Days with ⩾80% intake	100/75 (NR)
		Days with ⩾90% intake	92/72 (NR)
		Irregular intake intervals (>14h or <10h)	RR = 0.51 (<0.05)
Tschida 2012	Prescription refill	Doses taken	65.7/58.0 (<0.001)

NR: not reported; NS: not significant; RR: relative risk.

ence to reach optimal therapy outcomes have to be clinically ascertained because the level of required adherence depends on the therapy and patient characteristics. This fact concerns also the time frame in which OACA has to be taken. Future research should determine the level of adherence needed to reach a substantial clinical effect for different OACA to allow a clinical relevant quantification of patients which are non-adherent and to quantify the clinical relevant benefit of adherence enhancing interventions.

None of the studies examines clinical (e.g., tumor growth) or patient relevant outcomes (e.g., mortality, quality of life). An evaluation of the actual patient benefit of the adherence-enhancing interventions is therefore difficult because the needed adherence to reach therapy success is not known yet.

Additionally, the results of this systematic review have to be interpreted with caution because of the instruments used in the included studies to measure adherence. The measurement of adherence is performed with various instruments. Apart from blood concentration levels all types of applied adherence measurement instruments imply the tendency to overestimate adherence. In particular for self-reporting instruments a higher estimation of intake rather than the true adherence rate has been shown [23]. Pill-counts and prescription refill data do not allow for an assessment of timing adherence [12]. But a more detailed and precise assessment is usually associated with additional effort and is often not feasible in clinical practice. Only Simons et al. use electronic monitoring which considered as the gold standard [18]. But also electronic monitoring can lead to incorrect measures because the amount taken out of the drug package (for example openings without taking medication) is not noticed when using this measurement method. Levin et al. measured blood level concentrations [15]. Even the measurement of blood level concentrations can be inaccurate because they are mostly based on metabolic products that might vary strongly between patients [23]. Furthermore, all but Simons et al. exclusively examinie dose adherence [18]. The influence of the interventions on timing adherence is therefore unknown to the greatest extent.

Effective adherence enhancing interventions should include patients at high risk for non-adherence or for which non-adherence is proven or evident. Only such patients can benefit from an intervention. Furthermore, the unnecessary inclusion of adherent patients would be avoided. This assumption is reinforced by the fact that the two included studies with the highest (>96%) overall adherence show no statistically significant effect of the intervention [17,19]. Unfortunately, the baseline adherence is neither described nor adjusted for in the included studies and the extent of the ceiling effect therefore not assessable.

The identification of non-adherent patients with a validated measurement tool is imaginable and constitutes a possibility to identify patients with a low baseline adherence. However, in practice this is difficult, because patients must be observed before starting an adherence intervention. Moreover, only patients still taking OACA would be eligible. Another possibility would be to identify patients at high risk for non-adherence on the basis of risk factors, in particular for patients starting OACA [24]. A detailed assessment of risk factors before the adherence intervention starts can also support tailoring to the patient needs meaning to target the adherence dimensions that are identified as barriers and, thus, raising the probability of the success of the intervention. Furthermore, costs and inconvenience for patients arising because of including patients who are still adherent and therefore are unnecessarily included in an adherence enhancing intervention could be avoided. Such screening tools were developed for other indications [25]. But to our knowledge no screening tools exists for OACA, yet. Adherence enhancing interventions should be multifactorial and multidisciplinary meaning they should target all of the adherence influencing dimensions that potentially contribute to or were identified as factors for non-adherence.

Pharmaceutical companies should gather and present data on adherence for newly developed OACA to interpret the effectiveness results in light of adherence. This is especially important, because many OACA have side effects and complex intake regimes for which and negative effect on adherence has been shown [9,10].

The presented systematic review is not without limitations. Firstly, an intensive search for grey literature was not performed. Thus publication bias cannot be excluded. Secondly, missing relevant literature published in other languages could not be excluded because we included only English and German literature [26]. Thirdly, we did not evaluate the quality of registry data. The extent of this source of bias is therefore unknown.

Conclusion

Drawing a clear conclusion is difficult because of the low level of evidence/study design and low methodological study quality.

However, it seems that adherence enhancing interventions could have an effect, if the baseline adherence is considered when choosing eligible patients to avoid ceiling effects. Especially educational and counseling interventions seem promising. A reason could probably be that educational and counseling interventions mostly target several of the adherence influencing dimensions. More high quality RCT on tailored multifactorial interventions with an adequate sample size, including non-adherent patients or patients at risk for non-adherence examining clinical or patient relevant endpoints are needed to prove the actual benefit of adherence enhancing interventions in patients taking OECA.

Conflict of interest

This work was funded by Janssen-Cilag Germany. There is no other conflict of interest.

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Authorship

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

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2013.07.004.

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