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Review Article

Impact of pictograms on medication adherence: A systematic literature review

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ABSTRACT

Objective: The aim of this systematic review was to investigate the potential effect of pictograms on patient adherence to medication therapies.

Method: PubMed, MEDLINE, Embase, CINAHL, and CENTRAL were searched for relevant articles. Experimental studies testing the use of pictograms in patient counselling regarding medication therapy, which quantitatively measured adherence, were included.

Results: Seventeen studies were identified that fulfilled our inclusion criteria. These were heterogeneous with respect to study setting, population size, and the medication regimen tested. All the studies had methodological quality limitations. The pictogram interventions differed with respect to complexity, intervention length, and the measured adherence outcome. Ten studies (58.8 %) reported a statistically significant effect, of the pictogram intervention in question, on patient adherence to medication therapies. Of these, 80 % involved populations at elevated risk for non-adherence.

Conclusion and practice implications: Pictograms used in combination with written and/or oral information can have a positive impact on patient populations that are highly at risk for non-adherence when counselled on the proper use of medicines.

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Contents

1. Introduction

Patient adherence to medication therapies is a primary determinant of treatment success, and medication non-adherence is a common and recognized problem in health care [1–3]. Adherence is defined as “the extent to which a person’s behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed-upon recommendations from a healthcare provider” [1]. However, many patients do not follow treatment recommendations for different (and complex) reasons [1,2]. The World Health Organization (WHO) has defined five “dimensions” that affect adherence: The patient, the therapy, the health system, the condition, and the socioeconomic

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environment [1]. Medication non-adherence may result in adverse health outcomes and increased healthcare spending [1,3].

Medical information supports medication adherence through facilitating the correct use of medicines and improving the level of understanding while simultaneously generating positive attitudes towards treatment [1]. Traditionally, information for patients regarding correct medicine use (in Europe) involves verbal counselling by healthcare personnel (HCP), which is supplemented by written information in the form of a patient information leaflet (PIL) provided by the medicine manufacturer [4]. However, several shortcomings apply to this approach: The PILs have no consent standards, are known for small print and lengthy texts written at an advanced reading level, and contain generalised rather than personalised information [5–7].

Notably, pictures or pictograms that graphically illustrate and/or emphasise instructions for the correct use and storage of medicines can facilitate communication between HCPs and patients. A pictogram can be defined as a picture or symbol that represents a word or phrase. A literature review reported that including pictograms in patient counselling could reduce the frequency of medication dosing errors related to the administration of liquid medications [8]. Moreover, pictograms in combination with spoken and/or written medicinal instructions have been demonstrated to enhance the visual attention, comprehension, and recall of medication instructions provided [8–10]. It has also been reported that patients prefer to have pictograms and written or oral information used in combination. This is especially true for patients with low health literacy, as well as elderly patients [10]. Patient-centric development, as well as testing and validation in distinct patient populations, is of importance to the utility of pictograms used in medication counselling [11–13], hereby called pharmaceutical pictograms.

Previous reviews have emphasised the role of pharmaceutical pictograms on patient comprehension and recall of medication instructions, but these include only a small number of studies that report an effect on patient adherence [8–10]. The aim of this systematic review was to investigate the potential effect of pictograms on patient adherence to medication therapies. Additional objectives of the study were to detect and describe pictogram interventions that positively affect adherence and to evaluate the potential contribution of pictograms to the efficacy of complex interventions.

2. Methods

This is a systematic literature review performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14], where the databases PubMed, MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant studies. An initial search in PubMed was conducted in December 2017 with the following search strategy: (pictogram OR pictograph OR picture OR pictorial OR graphics OR visuals OR icon OR symbol) AND (adherence OR compliance OR concordance), limited to publication dates from 1997/01/01 to 2017/12/31, and English as the publication language. PubMed, MEDLINE, Embase, CINAHL, and CENTRAL were searched in May 2018 using the following search strategy (referred to as the second search strategy): (pictogram OR pictograph OR pictorial OR picture), combined with (AND) the following MeSH Terms: (medication adherence OR patient adherence OR patient compliance). These searches were limited to English language studies published between 1997/01/01 to 2018/05/31. Additional filters were “peer reviewed” or “academic” journals for the MEDLINE and CINAHL searches, respectively.

The Population, Intervention, Comparison, and Outcome (PICO) of the study were: patients on medication (Population), pictogram(s) had to be involved in an experimental study design (Intervention), no specific criteria for the comparison (C), and the studies had to quantitatively measure adherence (Outcome). To be included, the studies also had to report on original data and be published in a peer-reviewed journal.

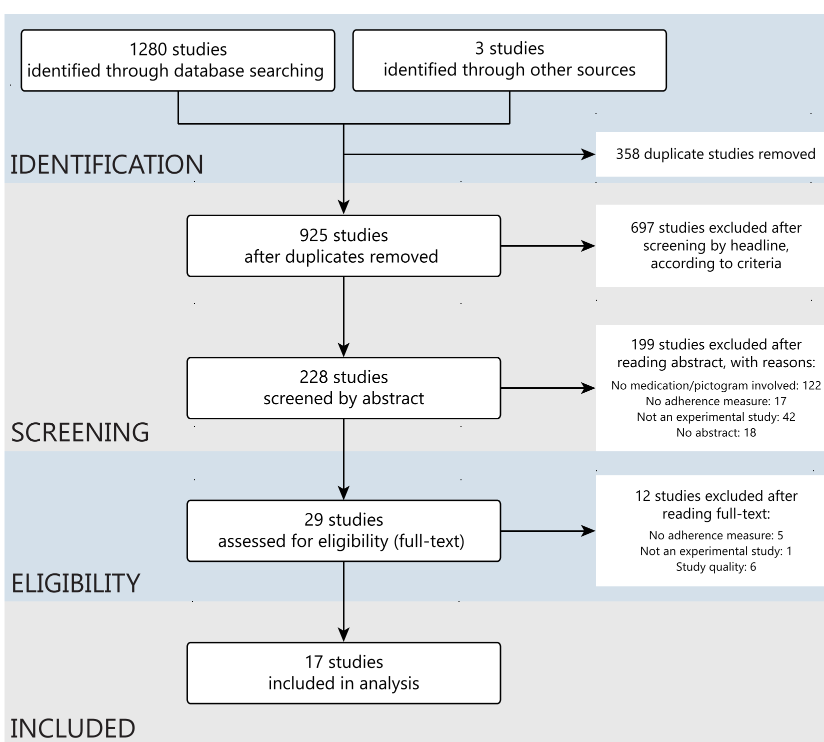

Fig. 1. Study flow diagram.

Table 1
Characteristics and summary of included studies.

Study reference	Study setting, country	Study design [a]	N (loss to follow-up)	Study population [b]	Intervention(s)[c]	Control	Adherence effect measurement [d]	Result
Braich *et al.* 2011 [33]	Clinic, India	RCT, three arms	225 (87)	Low literacy patients on postoperative cataract medications (eye drops)	Education on medication use: I1) Oral information combined with pictograms I2) As for I1, but patients took pictograms home	Oral education on medication use	Eye drop bottle amount measurement at baseline and 28 days after surgery	Both intervention groups had significantly improved adherence at day 28 ($p < 0.001$), as judged by the percentage of eye drops used
Chan and Hassali 2014 [34]	Outpatient pharmacy, Malaysia	RCT, three arms	126 (16)	Patients on antihypertensive and antidiabetic medications	I1) Medication labels using enlarged fonts I2) Medication labels incorporating pictograms	Regular-size text medication labels without pictograms	MMAS-8 at baseline and 4 weeks after intervention	No significant effects on adherence between study groups
Dowse *et al.* 2014 [35]	Clinic, South Africa	RCT	116 (52)	HIV patients new to ARVT	PIL containing text and pictograms	Standard care	HIV Treatment Adherence Self-efficacy Scale (HIV-ASES, 0–10 scale) at baseline and 1, 3, and 6 months after intervention	No significant effects on adherence self-efficacy between study groups
Dowse and Ehlers 2005 [24]	Outpatient clinic, South Africa	RCT	87 (0)	Patients on short-course antibacterial medications	Medication labels incorporating pictograms	Text-only medication labels	Pill count/volumetric measurement and self-reported adherence 3–5 days after intervention, reported as a combined adherence result in %	Significantly ($p < 0.01$) higher adherence in the intervention group (89.6 %) compared to the control group (71.5 %)
Holzheimer *et al.* 1998 [36]	Outpatient, Australia	RCT, four arms	80 (24)	Children (2–5 years of age) on prophylactic anti-asthmatic medications	Interventions used in asthma education of children; I1) Asthma videotape and asthma book including pictograms I2) Asthma videotape and unrelated book I3) Unrelated videotape and asthma book including pictograms	Unrelated videotape and unrelated book	Parent diary starting at 1 month pre-intervention and continuing until 3 months post-intervention	No significant effects between intervention groups and control regarding non-compliance days
Kalichman *et al.* 2013 [29]	Outpatient, USA	RCT, three arms	446 (45 for pill count)	Low health literacy HIV patients on ARVT	I1) Adherence counselling including written information with pictograms, adherence tool of choice I2) Standard adherence counselling including written information with illustrations and comic strips, adherence tool as pill box	General health improvement counselling	HIV RNA viral load at baseline and 9 months after intervention, and monthly pill counts from intervention start for 9 months	Significantly greater undetectable HIV viral loads for patients with marginal literacy in both intervention groups compared to control. Patients with lower health literacy demonstrated no significant effects of interventions.
Kripalani *et al.* 2012 [37]	Primary care clinic, USA	RCT, four arms	420 (20)	Patients with coronary heart disease	I1) Refill reminder postcards I2) Medication schedules including pictograms I3) Combination of I1 and I2	Usual care	Electronic pharmacy refill records reported as CMG for 1 year of follow-up after interventions	No significant effects on adherence between study groups
Mansoor and Dowse 2006 [23]	Primary care clinic, South Africa	RCT, three arms	127 (7)	Low health literacy patients on ARVT	I1) PIL including pictograms I2) PIL without pictograms	Usual care (no PIL)	Pill count and self-reported through questionnaires approximately 14 days after intervention	Significantly ($p < 0.05$) improved adherence both based on pill count and questionnaire, in the I1 group compared to I2 and control
Mohan *et al.* 2014 [38]	Safety net clinic, USA	RCT	208 (8)	Patients on antidiabetic medications	Personalised medication schedule including pictograms (PictureRX^{TM})	Usual care with handwritten list of medication	ARMS (8 items) approximately one week after enrolment	No significant effects on adherence between study groups
Monroe *et al.* 2018 [39]	HIV clinic, USA	RCT	46 (4)	Adult HIV patients on ARVT and antihypertensive and/or antidiabetic medications	Personalised medication schedule including pictograms (PictureRX^{TM})	Usual care with regular discharge medication list	Electronic pharmacy refill records reported as MPR calculated from 180 days pre-intervention and 180 days post-intervention	No significant effects on adherence between study groups
Murray *et al.* 2007 [27]	Ambulatory care practice, USA	RCT	314 (44)	Heart failure patients ≥50 years of age using	Pharmacist multi-level intervention including written medication information and	Usual care	MEMS, MPR by using prescription records and self-reported through questionnaires.	Significant effect on overall adherence (% of prescribed medication taken) between

Table 1 (*Continued*)

Study reference	Study setting, country	Study design [a]	N (loss to follow-up)	Study population [b]	Intervention(s)[c]	Control	Adherence effect measurement [d]	Result
				cardiovascular medications	medication labels that contained pictograms, 9-month active intervention period		Measurements during intervention period (9 months) and 3 months post-intervention	intervention and control group (10.9 % difference, 95 % CI 5.0–16.7 %). The effect dissipated in the post-intervention period. No significant effects on adherence between study groups when measured by self-reporting
Negarandeh *et al.* 2013 [30]	Diabetic clinic, secondary care level, Kurdistan	RCT, three arms	135 (8)	Low health literacy patients with type 2 diabetes	Educational medication interventions consisting of: I1) The teach-back method I2) Pictograms	Usual care	MMAS-8 at baseline and 6 weeks post-intervention	Significantly ($p < 0.001$) higher adherence in the intervention groups (I1 6.73, I2 7.03) compared to the control group (3.63), but not significant between intervention groups
Ngoh and Shepherd 1997 [25]	Outpatient, Cameroon	RCT, three arms	78 (0)	Illiterate patients on antibacterial medications	Educational medication interventions consisting of oral education in addition to: I1) Pictograms and an "advanced organiser" I2) Pictograms	Usual care	Pill count on or after the fourth day of intervention, presented in % (pill count adherence ratio)	Significantly ($p < 0.05$) higher adherence in the intervention groups (I1 = 94.6 % and I2 = 89.6 %) compared to the control group (77.5 %)
Okonkwo *et al.* 2001 [26]	Outpatient, Nigeria	RCT, three arms	632 (180)	Children (0.5–5 years of age) with malaria on chloroquine syrup	Medicine dispensing information given as: I1) PIL including pictograms I2) PIL including pictograms and verbal instructions	Medicine dispensing without information	Volumetric measurement and self-reported by a questionnaire 48 hours after intervention. Results given as combined results and defined adherence as non-compliant, partial compliant, or fully compliant	Significantly ($p < 0.001$) higher proportion of fully compliant children in the intervention groups (I1 51.9 %, I2 73.3 %) compared to the control group (36.5 %)
Shet *et al.* 2014 [32]	Clinic, India	RCT	631 (98)	Adult HIV patients initiating ARVT	Adherence support by a mobile phone intervention once weekly for the study duration. The intervention included: a) interactive voice response calls b) neutral picture (pictogram) messaging services	Usual care	HIV RNA viral load (time to virological failure) and pill counts measured at baseline and at weeks 4, 8, and 12, and then every 12 weeks until week 96	No significant effects on adherence between study groups
Yin*et al.* 2008 [28]	Hospital, USA	RCT	245 (18)	Parents or caregivers of children (30 days to 8 years of age) on liquid medications (daily dose and ≤14 days of therapy)	Medication counselling including medication instruction sheets with plain language, pictograms (HELPix), and teach-back	Usual care	Self-reported adherence by interview at baseline and 3–5 days after medicine dispensing, reported as non-adherence in % (>20 % deviation of the prescribed dose)	Significantly ($p < 0.05$) higher adherence in the intervention group (9.3 % non-adherent) compared to the control group (38 %)
Zerafa *et al.* 2011 [18]	Hospital, Malta	RCT (reported by authors as case-control)	86 (6)	Cardiac surgery patients on medications	Pharmacist intervention consisting of medication counselling with written medication information sheets including pictograms	Usual care	Patient compliance questionnaire 8 weeks after surgery discharge	Significantly ($p < 0.001$) higher compliance in the intervention group (88.2 %) compared to the control group (66.4 %)

[a] RCT, randomised controlled trial.
[b] ARVT, antiretroviral therapy; HIV, human immunodeficiency virus.
[c] I1, intervention in study arm one; I2, intervention in study arm two; I3, intervention in study arm three; PIL, patient information leaflet.
[d] MMAS-8, 8-item Morisky Medication Adherence Scale; CMG, cumulative medication gap; ARMS, Adherence to Refills and Medications Scale; MPR, medication possession ratio; MEMS, Medication Event Monitoring System.

All search results were exported to EndNote X8.1 software. Results from the initial PubMed search were evaluated separately by the three review authors according to the inclusion criteria. First, the results were screened by reading the article titles and excluding articles that were not relevant according to the inclusion criteria. Next, the study abstracts were evaluated, and non-relevant articles were excluded. Finally, the full-text articles selected by all three authors were collected and assessed for their relevance relative to the inclusion criteria. Any disagreements regarding the eligibility of studies were reconciled at the final step by discussion and consensus.

Results from the second search strategy in PubMed, Embase, CINAHL, MEDLINE, and CENTRAL were initially evaluated by one of the review authors (H.S.) by removing article duplicates and evaluating titles and abstracts as described above. Additionally, the reference lists of the identified studies were hand searched to retrieve additional relevant articles. Finally, the retrieved full-text articles were independently reviewed by two of the three authors according to the inclusion criteria. In cases of uncertain eligibility, all three authors read the article, and consensus on whether or not to include the article was reached by discussion. In total, the reviewers discussed inclusion for nine studies. Study design and the outcome measurement (adherence measure) were reasons for discussion for five and four studies, respectively. A study flow diagram is provided in Fig. 1.

The included studies were independently analysed by two of the authors, and data were extracted to present the key features of the intervention studies and reflect on points of difference that could affect the interpretation of the pictogram intervention. The following variables were extracted: study setting, study design (defined as randomised controlled trial [RCT] or non-randomised study [NRS]), number of study participants, short description of study participants, type of intervention(s) with emphasis on the pictogram contribution, adherence effect measure(s), time of adherence measurement, and adherence outcome.

The RCT studies were assessed by two of the authors for risk of bias using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [15]. RCTs with a high risk of bias in four or more dimensions were excluded. The NRSs were assessed by two of the authors, who described pre- and post-intervention risk of bias according to an abridged version of ROBINS-I—a tool for assessing the risk of bias in non-randomised studies of interventions [16]. NRSs with a critical or serious risk of bias both at pre- and post-intervention were excluded.

The heterogeneity of the studies with respect to patients, pictogram interventions, and adherence outcome measurements precluded a meta-analysis. Consequently, the results of this review are presented narratively.

3. Results

Our database searches identified 1,283 studies, of which 358 were duplicate results. A total of 896 studies were excluded based on their title or abstract, while a further twelve studies were excluded upon full-text review. Seventeen studies were included for analysis in this literature review, ten of which were published in the past 10 years. The studies were initially categorised as either RCT (n = 18) or NRS (n = 5), with pictograms being part of an intervention to increase medication adherence or compliance. The NRSs tested pictograms in a pre-post intervention study design, but were all excluded from the final analysis due to poor study quality. One other study, which was reportedly a case-control study, was included [18] since it tested an intervention with the aim of increasing medication adherence, and was therefore judged by the authors of this review to be an RCT with an experimental study design.

The included studies were heterogeneous regarding study setting, the number of participants, study population, the choice of interventions and controls, and the adherence effect measurement used (see Table 1). Regarding geographic location, six studies were conducted in the USA, while two were conducted in India, and three in the Republic of South Africa. The remaining six studies were performed in Cameroon, Malaysia, Australia, Kurdistan, Nigeria, and Malta, respectively. Studies were conducted both in primary and secondary healthcare settings. The number of participants in each study (*n* = number of participants at the start of the intervention) varied between 46 [39] and 632 [26], with the median number of participants being 135 [30]. A total of 3,995 patients were included across all studies combined. The study population was diverse in terms of age, clinical disorders, treatment regimens, and the level of health literacy. The most frequently targeted medication therapies were antiretroviral therapy (five studies) and cardiovascular medications alone or in combination with antidiabetic medicines (four studies). The remaining studies targeted antidiabetic medicines (two studies), antibacterial medicines (two studies), anti-asthmatic medicines (one study), chloroquine syrup (one study), cataract medication (one study), and general liquid medications (one study). While pictograms were involved in interventions regarding medication therapy in all included studies, there were substantive differences between the studies regarding the intervention complexity, healthcare personnel involved in the interventions, intervention length, and the adherence outcomes measured. As a result, there was insufficient common ground for quantifying total differences between intervention and control groups or estimating pooled effect sizes for analysis across studies regarding the overall effect on adherence.

Of the included studies, 10 studies (58.8 %) reported a statistically significant effect of pictogram interventions on patient adherence to medication therapies. All studies were performed in hospital, clinic, or outpatient settings. The studies differed with respect to the medication therapies selected, number of medications, as well as whether the treatment was short-term or for chronic use. In some cases, sufficient details regarding the medication therapies were not provided. For example, the study by Mansoor and Dowse involved medicines used in antiretroviral therapy (ARVT) but did not specify which medicines were administered [23]. In contrast, the medication therapies used in studies by Dowse and Ehlers, Ngoh and Shepherd, and Okonkwo *et al.* were well defined (amoxicillin, phenoxymethylpenicillin, and co-trimoxazole; ampicillin, sulfamethoxazole-trimethoprim, metronidazole, and tetracycline; chloroquine syrup, respectively) [24–26]. Some studies described polypharmacy in their study population (e.g., Murray *et al.*, and Zerafa *et al.* [18,27]), whereas others did not provide any information regarding other medicines used [28].

In six of the ten studies demonstrating a significant effect of a pictogram-based intervention, the interventions were complex and involved both pictograms and medication counselling combined with adherence tools or teach-back [18,25,27–30]. In other studies, plain interventions using pictograms in patient medication information and instruction leaflets [23,26], or on labels [24], also proved to be effective in increasing patient adherence.

Various methods were used to measure adherence, including pill count, volumetric measurements, electronic pharmacy refill records, viral load, self-reported adherence scales, self-reported adherence by vignettes or interviews, and the use of medication event monitoring systems (MEMS). Consequently, the adherence definitions and outcome effects were not reported in a consistent manner. For instance, in a study by Dowse and Ehlers, adherence was determined by pill count or volumetric measurement of antibacterial tablets or suspensions, respectively. Additionally, patients in this study reported on adherence using a questionnaire, with a total adherence score being calculated and converted into a percentage [24]. In contrast, Ngoh and Shepherd measured adherence using pill counts only, and results were given as a pill count adherence ratio [25]. Subjective self-reported adherence effect measures were used in 11 of the studies included in this review [18,23,24,26–28,30,34–36,38]. An example is the study by Negarandeh *et al.*, which utilised the "8-item Morisky Medication Adherence Scale" (MARS-8) [30]. This study reported significant effect on adherence using medication educational interventions

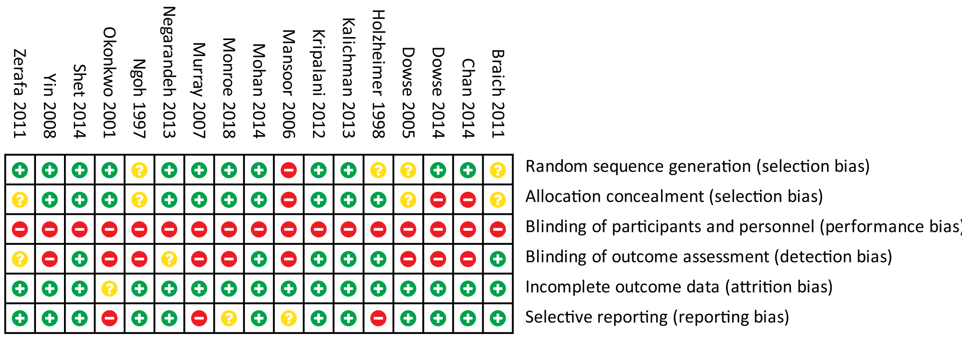

Fig. 2. Risk of bias analysis of the included RCTs. +, low risk of bias; ?, unclear risk of bias; -, high risk of bias.

consisting of pictograms [30]. Such a questionnaire defines adherence according to the specific scale used, rather than an adherence percentage. Zerafa *et al.* used a novel self-made questionnaire named “Assessing Patient Compliance” that reported each patient’s mean percentage compliance as calculated by the total number of correct and incorrect answers [18]. The study found a significant effect on patient compliance upon comparing a pharmacist intervention of medication counselling and written medication information sheets (including pictograms) to standard care [18]. Mixed methods were used in six of the studies [23,24,26,27,29,32], of which five studies reported a significant pictogram intervention effect [23,24,26,27,29]. When using mixed methods, adherence outcomes were either reported separately ([23,29] or in combination [24,26,27].

Among the ten studies reporting significant effects of pictogram-based interventions, heterogeneity was observed in the choice of patient group. Examples of patient groups include HIV patients on antiretroviral therapy (ARVT), patients on antibacterial medications, cardiac and diabetic patients, and children on medication (see Table 1). Patient groups known to experience challenges with adherence, such as patient populations with low (health) literacy [23–25,29,30,33] and children and/or their caregivers [26,28], were involved in eight of the ten studies (80 %).

All included RCTs were assessed according to the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials [15]. This involved a thorough analysis of the risk of bias across seven dimensions: 1) Random sequence generation (selection bias); 2) Allocation concealment (selection bias); 3) Blinding of participants and personnel (performance bias); 4) Blinding of outcome assessment (detection bias); 5) Incomplete outcome data (attrition bias); 6) Selective reporting (reporting bias); and 7) Other bias. The individual results of this analysis are provided in Fig. 2. Fig. 3 presents the cumulated results as stacked bars, presenting the relative frequencies of studies deemed to have a low, unknown, or high risk of bias in each of the seven dimensions.

Our results demonstrate that, without exception, all of the RCTs identified and included in this review had a high risk of bias in at least one dimension. Notably, they all had a high risk of performance bias, reflecting insufficient blinding of participants and/or personnel. In three of the studies [27,29,36], researchers were blinded to compensate for difficulties in the blinding of participants and care providers to the use of pictogram-based interventions. However, while we consider this an improvement over no blinding at all, the fact that participant allocation is known to the participants themselves, as well as the care providers, must be considered to result in a high risk of performance bias.

The second greatest contributor to study bias in this review was the insufficient blinding of outcome assessments, leading to a high risk of detection bias in 10 of **17** studies. Considerable risk of bias was also identified in the dimensions of selective reporting

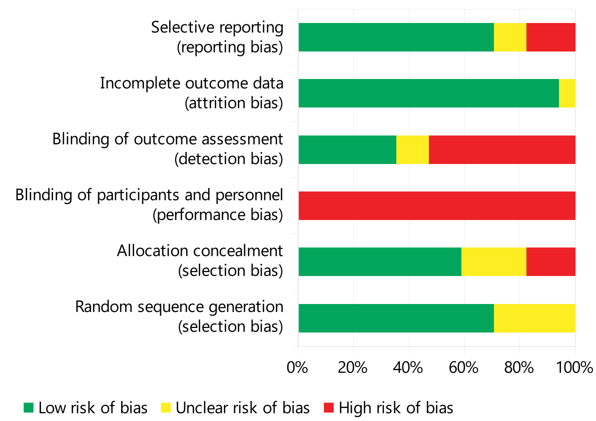

Fig. 3. Cumulative risk of bias observed in the included RCTs.

(4 studies with high risk of bias) and allocation concealment (3 studies with high risk of bias). A high risk of attrition bias was only observed in one study [22]. The majority of studies had a low risk of bias regarding random sequence generation, while six studies had an uncertain level of risk in this dimension.

Five studies were excluded from the review following a full-text reading, since they did not quantitatively measure adherence [40–44], while one study was only a study protocol [45]. Additionally, six studies were excluded because of poor study quality. One RCT study was excluded due to high risk of bias in four or more dimensions [22]. Five of the excluded studies were non-randomised studies [17,19–21,31]. A critical risk of pre-intervention bias was observed in all five studies. In the study by Gazmararian *et al.*, the intervention and control groups were located at different study sites [31]. Moreover, studies by Hawkins *et al.* and Martin *et al.* used convenience sampling of study participants [20,21], while the study by Vetter *et al.* used time-sequential sampling [17]. Notably, the study by Rodrigues *et al.* lacked information to judge the risk of bias in study participant selection [19]. All five studies were observed to have a critical or serious risk of post-intervention bias as well as bias in the measurement of outcomes [17,19–21,31], while Gazmararian *et al.* and Rodrigues *et al.* also had bias in the selection of reported results [19,31]. Two of the studies were pilot studies with a small number of participants [20,21].

4. Discussion and conclusion

4.1. Discussion

In this review, we have assessed studies designed to evaluate the effect of pictogram-based interventions on patient adherence to medications. From a sizeable and diverse evidence base, various uses of pictograms and different measures of adherence were investigated. Heterogeneity in the design and conduct of the included studies precluded any meta-analysis of observed pictogram effects. However, of the 17 studies included, 10 studies (58.8 %) reported a statistically significant effect of pictogram-containing interventions on patient adherence to medication therapies.

The pictograms utilised in the studies varied, though the majority of study interventions utilised pictograms in combination with verbal medication counselling or text-based instructions of medication therapy. A review by Katz *et al.* concluded that pictograms used to complement textual or oral information were more effective at improving patients' understanding of correct use of medicines than pictograms alone [10]. The current review points to a possible effect of pictograms in combination with oral or text-based medication information or counselling when it comes to improving patient adherence.

The absence of significant effects on patient adherence was common among many of the reviewed studies. We primarily attribute this to insufficient sample sizes. Measuring adherence has proven difficult in many cases, and there is a need for standardisation of reproducible adherence measures. Among the studies included in this review, self-reported adherence by questionnaire or interview was the most consistently successful measure for identifying differences in adherence. However, other methodological aspects may have also contributed to the lack of significant results in many of the studies. Notably, we have found sufficient evidence in our review to sustain the assumption that pictogram-based interventions may indeed serve to improve patients' adherence to medication therapies (see Table 1).

The complexity of interventions limits our ability to interpret the exact contribution of the pictograms on medication adherence. For instance, the study by Kalichman *et al.* utilised pictograms in combination with adherence counselling and adherence tools to enhance antiretroviral therapy [29]. While the study reported statistically significant effect on adherence, it could not determine the exact contribution of pictograms on the observed outcome. In the RCT study by Negarandeh *et al.*, an intervention consisting of diabetes medication education by a nurse combined with teach-back or pictograms (in two separate intervention groups), was tested against standard care [30]. Significant differences in medication adherence were observed between the intervention groups and the control group, though no significant differences were observed between the two intervention groups [30]. In contrast, the RCT by Mansoor *et al.* tested PILs with or without pictograms in two different intervention groups compared to standard care. In this case, adherence to ARVT improved significantly when patients received PILs with pictograms when compared to the other two groups [23]. To test the true effect of pictograms, study designs must allow for comparison of two interventions where the use of pictograms constitutes the only difference.

Patient-related factors may contribute to medication adherence, since age, literacy, and cognitive function have all been identified as negatively impacting adherence [1,2]. In eight of the ten studies with significant intervention effects, patient populations constituted individuals with low health literacy or low age. Dowse and Ehlers tested medicine labels incorporating pictograms on Xhosa African patients using antibacterial medications and observed an effect of literacy on adherence when results were pooled for intervention and control groups [24]. Furthermore, the study by Kalichman *et al.* described an adherence counselling intervention including pictograms, in which an effect was found among the marginal literacy HIV patients on ARTV, but with conflicting results among lower literacy patients [29]. In the studies by Mansoor *et al.*, Negarandeh *et al.*, and Ngoh and Shepherd, the role of literacy in affecting medication adherence was not tested, yet the study populations were selected with literacy as one of the selection criteria [23,25,30]. These results indicate that pharmaceutical pictograms are particularly beneficial to patient populations challenged by low levels of health literacy.

Another factor known to influence adherence is the nature of the therapy [1,10]. The studies in this review were highly diverse regarding therapy type and were described with varying levels of detail. For instance, in the RCT by Negarandeh *et al.*, adherence among type 2 diabetic patients was measured, though no details were provided regarding the prescribed therapies of the study participants [30]. Similarly, a number of the reviewed studies failed to describe the participants' medication therapies in sufficient detail [18,23,28,29]. However, all of these studies described a significant effect of pictogram-based interventions on medication adherence. Therapeutic aspects known to affect adherence include frequency of dosing, complexity of treatment, adverse effects of treatment, the patient's beliefs and attitudes regarding the treatment, and medication effectiveness [1,2]. It is not known to what extent these factors have influenced the results of the studies included in this review.

Several different measures of adherence were observed in the reviewed studies. A gold standard adherence measure should be user friendly, highly reliable, flexible, practical, cheap, and easy to perform. Unfortunately, no single method exists, and a mixed method approach is therefore recommended [46]. In this review, six out of 17 studies used a mixed method approach to measure adherence [23,24,26,27,29,32], and five of these studies reported a significant adherence effect [23,24,26,27,29]. Evidently, when using several methods of measurement for the same outcome effect, the analysis and interpretation of results becomes more complex. Therefore, it is important to choose complementary rather than potentially conflicting measures; for example, a combination of a subjective and an objective measurement, with suitability for the study setting, study participants, and any other practical considerations. Many studies in this review (n = 11) utilised subjective self-reported adherence effect measures (e.g., questionnaires) to assess pictogram effect. We recommend using consistent and validated questionnaires, in the interest of enabling statistical comparisons across studies. Self-reported adherence scales can measure medication-taking behaviour, and can also identify adherence barriers and/or patient beliefs associated with adherence [47]. When measuring adherence in any intervention study, selecting the most suitable questionnaire remains important.

The studies included in this review were generally of poor quality. One challenge with pictogram-based interventions is that study participants, in general, cannot be blinded. Still, only three studies described researchers being blinded to participant allocation [27,29,36], while only six studies reported using measures to blind the outcome assessment [29,32,33,36–38]. Furthermore, five studies did not describe the method used to create a random allocation sequence [23–25,33,36], and seven studies had a high risk of selection bias due to insufficient allocation concealment [18,23–25,33–35]. Unfortunately, the observed challenges with study quality complicated our assessment of the reported results and prohibited statistically sound cross-study comparisons.

While some previous reviews have investigated the effect of pictograms on patient adherence to medications, they covered a very limited evidence base. The review by Katz *et al.* concluded that pictograms enhance patients' understanding of medication-taking behaviour, yet included only two studies that assessed adherence [10]. Furthermore, Chan *et al.* reviewed the effects of pictograms when assisting caregivers in liquid medication administration and suggested that pictograms might reduce dosing errors, enhance the comprehension and recall of medication instructions, and improve adherence [8]. However, this review included only five studies, and only one study that measured adherence as an outcome [8]. Barros *et al.* aimed to evaluate the use of pictograms in a healthcare setting to assess their potential effect on patient understanding and medical instruction compliance [9]. They concluded that pictograms can serve as communication tools to enhance visual attention, comprehension, recall, and adherence of provided instructions, though they did not analyse the effects on adherence in detail [9]. Additionally, the review by Nicolson *et al.* concluded that there is some evidence that written information can improve patients' knowledge regarding medicines when compared to no written information; however, due to the poor quality of included studies, the review lacked robust conclusions [48]. Finally, a review of reviews by Ryan *et al.*, that assessed the effects of interventions that targeted healthcare consumers to ensure safe and effective use of medicines, found limitations in the methodological quality of included studies, both at the review and study level [49].

4.2. Implications

The present review documents a possible effect of pictograms on patients' adherence to medications, especially when combined with written and/or oral medication information and utilised on patient populations at high risk of non-adherence. However, the heterogeneity in study design and quality, as well as in the interventions and outcomes measured, prevented us from conclusively asserting that pictograms are effective in improving adherence.

We find it critical that studies examining the effects of pictograms have a high-quality study design adhering to best practises of intervention studies, and use consistent and validated outcome measures of adherence. As such, there remains a need for more high-quality studies, as well as a set of standardised tools and protocols—ideally open source—that are tailored to adherence studies. Moreover, studies assessing the value of pharmaceutical pictograms would benefit from establishing best practices in the design and use of the pictograms themselves.

4.3. Limitations

The present review includes studies from 1997 until 2018; hence, studies up to 20 years old were included [25,36]. Studies performed before the Consolidated Standards of Reporting Trials (CONSORT) statement of 2010 [50], which defines best practice in reporting RCTs, may be of poorer quality. Recent developments in the healthcare sector, and in the ways patients receive and access information, may also have rendered the older studies less relevant. Among the studies included in this review, ten of 17 studies were conducted in 2010 or later. The level of patient adherence majorly impacts health and healthcare expenditure and, hence, adherence served as a natural outcome measure for this review. For the patients themselves, however, the consequences of non-adherence may be difficult to grasp. From the perspective of healthcare personnel, using pharmaceutical pictograms may serve to improve the quality of the information provided to patients, yet evaluating the impact of pictograms on patient adherence may still prove difficult due to their indirect relationship. Other study endpoints could reveal a more direct relationship between the use of pictograms and clinical outcome, though for the time being, we consider adherence to be the gold standard.

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Declaration of Competing Interest

H.S. and L.A.B.S. have none to declare. E.A.T. is one of two co-founders of the company Depict AS and has developed a digital pictogram-based tool for the provision of patient information regarding the correct use of medicines.

CRediT authorship contribution statement

Hege Sletvold: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Project administration, Funding acquisition. **Lise Annie Bjørnli Sagmo:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - review & editing. **Eirik A. Torheim:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Funding acquisition.

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