Introduction

The high rates of poor medication adherence are recognized as major worldwide health problem, being associated with adverse health outcomes and higher costs of care. However, there is a high variability, not only in the report of the prevalence and costs associated to nonadherence [1, 2], but also across studies assessing different types of interventions aiming to improve patient's medication adherence [3].

In addition to the consequences of ignoring the different components of the adherence process (i.e., initiation, implementation and discontinuation) [4], a potential cause for this inconsistency may be the methodological issue on the choice of measurements to assess medication adherence in randomized controlled trials [5]. Measurements of medication adherence are important estimates that can provide better evidence on the consequences, determinants, risk factors, and interventions to improve adherence [6]. There are numerous subjective and objective methods available for assessing medication adherence [7-9] being: patient self-reports (e.g. patient interviews or written questionnaires), pill counts (e.g. comparing the number of doses remaining in a container with the number of doses that should remain) and electronic capture of pill bottle opening (Medication Event Monitoring Systems - MEMS) the most used in routine practice [5]. Previous studies assessing the concordance of all these measures have yielded conflicting results and, to date, no universally agreed consensus on the most ideal method to assess medication adherence exists [10, 11].

Another drawback for the selection of the most effective interventions to improve medication adherence is the low number of studies comparing them directly and simultaneously. Most of the clinical trials assessing interventions aiming at enhancing patient's medication adherence usually compare one or two interventions against a standard or usual care[3]. New comparative statistical methods, such as network meta-analyses, can provide a broader overview of the effect of all interventions in one single model, while reducing bias [12]. Also known as indirect meta-analysis or multiple treatment comparisons, this technique was developed as an extension of pairwise meta-analysis and combines both direct (i.e. based on existing comparative studies in the literature) with indirect evidence (i.e. based on common comparators when direct evidence is not available) to obtain pooled effects sizes [13]. However, limited research has been undertaken to statistically determine the comparative effect of non-pharmacological complex interventions to improve medication adherence. To date, few network meta-analysis on this topic have been published, being mostly focused on interventions targeted at patients with viral infections [14-16].

Thus, the objective of this study was to perform a systematic review with network meta-analysis to assess the impact of the different measures of adherence used to compare the effectiveness of complex interventions to enhance patients' adherence to prescribed medications in any medical condition.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analyses (PRISMA NMA) [17] and Cochrane Collaboration recommendations [18]. The protocol is registered on PROSPERO (CRD42018054598).

Search strategy and eligibility criteria

The literature selection was performed in two steps. First, searches in the medical literature for relevant pairwise meta-analyses that compared complex interventions to improve medication adherence in adult patients with any clinical condition were performed. The searches were conducted in PubMed (in October 2017) without any restriction based on publication date or language. The complete search strategy used to identify the meta-analyses is available in supplementary material. Two independent reviewers performed the screening (by title and abstract reading) and full-text appraisal of the meta-analyses identified. Discrepancies were resolved with a third reviewer during consensus meetings.

In a second step, primary studies included in the meta-analyses identified in the first step were extracted. Two independent reviewers performed the screening and full-text appraisal of these primary studies with contributions from the third reviewer in case of disagreements. Finally, studies of interventional design (i.e. randomized or non-randomized trials) that compared any intervention aimed at improving patients' medication adherence versus another intervention or standard care were included. The outcome of interest was medication adherence. Studies evaluating short-period results (follow-up until 3 months) that reported adherence using any the following measures: self-reported measures (i.e. here named as self-report), calculated adherence rates from dispensing data, pill counts or estimates from a healthcare professional records (i.e. here named as pill count), and electronic monitoring of bottle or pill box opening (i.e. generic named as MEMS: medication event monitoring system) were included.

Studies including pediatric population (under 18 years), other type of treatments (over-the-counter medications, depot medications, vaccines), articles not defining the adherence measure or not evaluating medication adherence, studies without a comparison group, and articles where the intervention was given to the health care provider rather than to the patient, were excluded. Unpublished studies, letters to editor, commentaries, books and articles written in non-Roman characters were also excluded.

Data extraction, variable definitions and quality assessment

Using a standard data sheet, data extraction was performed from articles that met the inclusion criteria: study baseline characteristics (authors' names, year of publication, country, sample size, patients' clinical conditions, sex and age, trial follow-up, evaluated interventions), (ii) methodological aspects (e.g. trial design); (iii) measures of adherence (i.e. self-report, pill count, MEMS) and the respective rates of adherent patients for each measure. The outcome of adherence was defined by the proportion of patients in each study arm meeting the trial defined adherence criteria (e.g. proportion of doses taken over a defined time) with various cutoff values (90%, 95%, 99%, 100%).

To better standardize the results obtained with the different adherence measures, two additional measures were calculated: an overall composite measure and an objective composite measure. The overall composite measure represents the rate of adherent patients obtained from any of the measures (self-report, pill count or MEMS) in each study. If more than one measure was reported in the study, a mean among the rates of adherent patients from the different measures was calculated. The objective composite measure considers only the results obtained from objective methods (pill count or MEMS), calculating the mean if both measures were reported in the study.

To improve interpretability, the adherence-enhancing interventions were grouped in the following categories: attitudinal, economic, educational, technical, as defined in Table 1. These categories represent the single components of complex interventions and were created based on previous literature definitions [19-23]. Multicomponent interventions included more than one single category (e.g. attitudinal + economic). Standard care was considered as the usual care defined in the primary study (e.g. regular medication pick-ups including consultations with physician or pharmacist).

The methodological quality of the included studies was assessed by two independent reviewers using the Cochrane Collaboration Risk of Bias Assessment tool (RoB) [18]. The criteria for judgment of some domains of the RoB tool were adapted to this study, giving the complexity of the interventions.

Data analysis

Network meta-analysis is a technique recommended by the International Society for Pharmacoeconomics and Outcome Research to compare the profile among different interventions [13, 24]. To inform the comparative adherence rates among the different measures for all the interventions, a network meta-analysis using Bayesian framework for each measure of adherence (i.e. self-report, pill count, MEMS, overall composite measure, objective composite measure) based on the Markov Chain Monte Carlo simulation method (burn-in of 20 000 iterations and 50 000 iterations for estimation) was performed. Arm level entry data was used. For the inclusion of multiple-arms studies, correlations for in the likelihood between arms were considered. A common heterogeneity parameter was assumed for all comparisons. A conservative analysis of non-informative priors was used [25, 26]. Effect sizes measures were expressed as odds ratio (OR) with a 95% credibility interval (CrI). Both fixed and random-effect models were tested and the one with the lowest deviance information criteria (DIC) was selected. Convergence was attained based on visual inspection of Brooks-Gelman-Rubin plots and potential scale reduction factor - PSRF ($1<PSRF\leq1.05$)[26, 27]. To increase the estimate precision of the relative effect sizes of comparisons and to properly account for correlations between multi-arm trials, ranking probabilities for each measure of adherence were calculated via surface under the cumulative ranking analysis (SUCRA) [28]. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (it always ranks first). To estimate the robustness of the network, inconsistency, defined as the difference between the pooled direct and indirect evidence for a comparison, was assessed using node-splitting analysis (p-values<0.05 reveal significant inconsistencies in the network) [29]. All analyses were performed using software Addis version 1.17.6 (Aggregate Data Drug Information System; http://drugis.org/addis) [30].

To validate the composite measures, additional analyses were performed to evaluate the contribution of each single component of the complex interventions (i.e. attitudinal, economic, educational, technical) on patients' adherence. A score was created to rank single components in each adherence measure according to the results obtained in the rank order. The score was calculated as the mean of the ordinal positions of the interventions comprising each component (Score = Σ positions occupied by the component in the rank order / frequency of the component). For instance, a component included in interventions positioned as first, third and fifth, would score 3 [(1+3+5)/3].

Results

The systematic review process identified 920 records on medication adherence, of which 61 were meta-analyses and had their references (primary studies) extracted (see supplementary material for complete references). From the initial 1119 primary studies included in the 61 meta-analyses, 689 were fully assessed for eligibility, with 168 studies finally included in the qualitative synthesis (see supplemental material for complete references). Of these, 91 studies reported dichotomous results on patients' adherence and subsequently were included in the network meta-analyses (Figure 1).

The 168 included studies were published between 1971 and 2016, with a median in 2006 (IQR 1999-2011). Studies included 42,338 participants. Most of them had a follow-up period of 12 weeks (25.0%), followed by studies with 4-6 weeks (17.9%) and 8-10 weeks (17.9%). The evaluated interventions were: educational (n=63 studies); technical (n=56); attitudinal (n=28); educational + attitudinal (n=23); educational + technical (n=23); educational + attitudinal + technical (n=5); attitudinal + technical (n=2); economic (n=1); economic + technical (n=1); attitudinal + technical + economic (n=1). Standard care was the comparator in 151 studies (89.9%).

Overall, the included studies were classified as having unclear risk of bias according to RoB tool. Only 10 studies (5.9%) were not randomized. Around 50% of the trials properly described the random sequence generation, but more than 75% were unclear about the allocation concealment. Eighty-one studies were blinded, being 53% single-blinded. For the domains of detection bias and reporting bias, more than 80% of studies were considered with low risk of bias. However, around 20% were classified as having high risk of bias for the attrition domain, because losses in the study were high and authors did not report the reasons for missing outcome data. Less than 10% of studies were funded by the industry or presented conflict of interest (supplementary material).

Five network meta-analyses, one for each adherence measure, were built. The network diagrams of the possible comparisons of interventions are presented in Figure 2 (see supplementary material for list of studies included). Overall, consistency analyses revealed similar patterns among the results of all the adherence measures. Comparing the rank order and SUCRA analyses of each adherence measure, few differences in the results were observed. The node-splitting technique revealed no substantial differences (p-values>0.05) in the magnitude or direction between the results of the direct and indirect effects identified in the any of the networks (see supplementary material).

The network of self-report measure (Figure 2a) included 46 studies and evaluated 6 different interventions with different combinations of the intervention components, except economic. Statistical differences were observed between educational + technical and standard care with OR of 0.46 (95% CrI 0.21, 0.95); educational and standard care [OR 0.60 (0.37, 0.96)] and standard care and technical [OR 1.65 (1.01, 2.74)], all of them favoring the interventions (for complete consistency analyses see supplemental material). By SUCRA analysis (see Table 2 and complete graphs in supplemental material), the multicomponent intervention educational + attitudinal + technical presented the higher probability of being the best alternative for enhancing patients' adherence (73% of probability), followed by educational + technical (67%). Standard care was considered the worst option (8%).

For the network of the pill count measure (Figure 2b), 30 studies were evaluated reporting data on the following interventions: economic + technical; educational + technical; educational + attitudinal; educational, and technical. The intervention economic + technical was statistically superior to all the other interventions and to standard care [OR 0.10 (0.03, 0.35)]. Educational + technical, educational, and technical were again superior to standard care. For complete consistency analyses see supplemental material. By SUCRA analysis (see Table 2 and complete graphs in supplemental material), the multicomponent economic + technical was ranked as the best alternative (99% of probability), followed by educational + technical (76%). Standard care was again the last option (12%).

The measure MEMS was assessed in 22 studies (Figure 2c). The interventions economic + technical and educational + technical were not evaluated for this measure. Statistical differences were observed between educational + attitudinal and standard care [OR 0.27 (0.13, 0.57)] and standard care and technical [OR 2.25 (1.33, 3.91)], both favoring the interventions (for complete consistency analyses see supplemental material). Attitudinal + technical and economic were considered the best interventions (77% and 75% of probability, respectively), while standard care was ranked last (7%) (Table 2).

The two composite measures (overall composite measure and objective composite measure) presented similar results for the networks (Figure 2d and 2e), consistency analyses and rank orders, evaluating the same 10 interventions and standard care (n=91 and n=50 studies included, respectively). For both measures, the intervention economic + technical was the best option (around 90% of probability in the SUCRA analysis) (Table 2) and presented statistical superiority (see Figure 3) against almost all the other interventions and usual care (OR with 95% CrI varying from 0.09 (0.02, 0.33) to 0.25 (0.05, 0.98)). The multicomponent interventions educational + attitudinal, and educational + technical, and the single components educational and technical were statistically better than standard care for both measures. Standard care was ranked as the worst option with less than 6% of probability for both measures.

The additional analyses of the effect of the single components of complex interventions on patients' adherence using different measures is showed in Table 3 (see supplemental material for complete calculation of the score). Whenever reported, the economic component, always followed by the technical component, presented better results for the score, similarly to the results obtained in the networks of different measures. Educational or attitudinal components were ranked after, and standard care was always considered the worst option.

Discussion

This is the first systematic review with network meta-analysis to synthetize evidence on the impact of different measures of adherence used to assess the effectiveness of complex interventions to enhance patient's medication adherence during short periods of follow-up. Network meta-analysis are increasingly used statistical tools to provide information on the relative merits of interventions that have never been directly compared, and to increase the precision of effect estimates by combining both direct with indirect evidence [12, 13]. This technique is already widely employed to compare the effectiveness of pharmacological interventions [31], and is also being used for diagnostic test accuracy and surgical interventions evaluations [32-35]. However, the assessment of non-pharmacological complex interventions through a network of comparisons is still unusual [36-38], and few studies using this technique in the field of medication adherence have been published [14-16].

Complex interventions are usually described as those that contain several interacting components, being usually unclear which of the components provide the greater effect. Thus, the report and evaluation of these interventions may be challenging, also because their effectiveness and the replicability rely on how the intervention was designed (e.g. choice and total number of core components) and provided [39, 40]. This results in an excessive number of different interventions available, which may limit the ability to perform pairwise meta-analysis and increases the heterogeneity among trials[41-43]. In this case, the use of network meta-analysis proved to be a reliable and valuable method for the comparative assessment of complex interventions such as those design to improve patient's medication adherence. In this study, five robust networks involving a maximum of 91 studies and comparing 10 different complex interventions (including both single and multicomponent interventions) and standard care were built.

Another parameter that is usually related to a considerable increase in the heterogeneity among studies, is the use of a range of different measures to assess medication adherence [5]. Subjective measurements such self-report and healthcare professional assessments require the health care provider's or patient's evaluation of their medication-taking behavior [44]. The most common drawback in this case is that patients tend to underreport medication nonadherence to avoid disapproval from their healthcare providers. Nonetheless, the low cost, simplicity and real-time feedback of these methods have contributed to their widespread use [45, 46]. Objective measures, including pill counts, electronic monitoring, secondary database analysis and biochemical measures, are thought to represent an improvement over subjective measures [6, 47]. A review of studies comparing MEMS with other methods reported that adherence was overestimated by 17% using self-report measures and by 8% using pill count [11]. However, other studies showed a moderate to high correlation of these measures [48-51] and some researchers also stated that multi-subjective-measure approach may have higher sensitivity over employing a single objective measure [6, 50].

Overall, small differences among adherence rates from subjective and objective measures were found, with similar patterns between the measures in the consistency analyses. Moreover, a deeper analysis of the primary studies reporting more than one measure, revealed that adherence rates were similar among different measures [52-54]. Thus, it is possible that multiple adherence methods can be used effectively to reflect the impact of a given intervention. However, for this to occur, measures and their assessment methods must be fully described and should include standardized operational definitions of medication adherence. This would facilitate comparisons between studies and settings [55]. The methodological and reporting quality of the studies included in this systematic review was moderate. As highlighted by the methodological quality assessment, some domains were mostly of unclear risk of bias, and due to incomplete outcome data, some studies were considered as having high risk of bias.

An alternative solution to address the challenge of analyzing different measures for patients' adherence when data is heterogeneous may be the combination of measures [50]. Some authors have previously recommended the development of a composite measure for the establishment of a broader and more detailed picture of medication adherence [5]. In this systematic review with network meta-analysis, an overall composite measure (accounting for both objective and subjective measures) and an objective composite measure (accounting for pill count and MEMS measures) were created. The results obtained for these two composite measures were similar and reflected the results of each single measure. Moreover, the composite measures allowed the comparison of more interventions in one single model, which enabled other statistical differences to be obtained.

Overall, for all the measures of adherence, results showed that some interventions (educational + technical; educational; technical) performed significantly better than standard care. The intervention economic + technical was the only one considered superior to all the other interventions and standard care. The score results also revealed compelling evidence that economic and technical components of interventions performed better than educational or attitudinal alone for improving patients' adherence in a short-term period of follow-up. Standard care was always ranked as last option. These findings are at odds with those in some previous reports and meta-analyses that highlight the contribution of technical or financial components in complex interventions [14, 15, 20, 56]. However, this study differs to other reviews [3, 57] that indicate no significant difference among interventions. This could be partly explained by the broader analytical approach used in this study, the number of included trials, the design of a composite measure, the categorization of the adherence-enhancing interventions used, and the short follow-up period considered for analyses. It is known that medication non-adherence is affected by multiple determinants, including treatment duration, and the core components of the interventions [1, 58]. Further studies assessing their long-term effect on adherence rates should be conducted, using network meta-analysis to better define the profile of these complex interventions.

The findings of this study have methodological and clinical implications. The main strength of this work is the assessment of large networks of evidence for different measures of adherence, which allowed for a broad evaluation of the effectiveness of different complex interventions. The use of robust statistical methods to compare the effect of complex interventions on different outcomes in future studies is strongly recommended. The use of a composite measure seems reasonable to account for any adherence measure but should be further investigated in long-term analyses. Whenever possible, outcome measures and definition of complex interventions for adherence research should be standardized during the conduction and report of studies to improve their methodological quality, comparability, and consequently the formulation of recommendations.

This study has some limitations. To assist interpretability, the adherence-enhancing interventions were grouped into four main categories based on previous literature, but a different approach of categorization might alter some results. The existing evidence limited some of the analyses. Very few trials were available for some of the interventions assessed and not all the possible combinations of core components could be evaluated for all the measures of adherence. Only studies performing short-term assessments of patients' adherence were included in order to maintain a homogenous period of evaluation. Other results may be obtained for different follow-up periods.

Conclusions

Using the network meta-analysis technique, it was possible to compare different measures of adherence for several complex interventions obtaining robust networks with consistent results. Different measures of adherence produced similar results, and the use of composite measures revealed as reliable alternatives to establish a broader and more detailed picture of medication adherence. The comparative effectiveness of the interventions' components should be investigated in long-term studies.

References

1. Sabaté E. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003.
2. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ open.* 2018;8:e016982.
3. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews.* 2014:CD000011.
4. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology.* 2012;73:691-705.
5. Jeffery RA, Navarro T, Wilczynski NL, et al. Adherence measurement and patient recruitment methods are poor in intervention trials to improve patient adherence. *Journal of clinical epidemiology.* 2014;67:1076-1082.
6. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international.* 2015;2015:217047.
7. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical therapeutics.* 1999;21:1074-1090; discussion 1073.
8. Vitolins MZ, Rand CS, Rapp SR, Ribisl PM, Sevick MA. Measuring adherence to behavioral and medical interventions. *Controlled clinical trials.* 2000;21:188S-194S.
9. Arnet I, Kooij MJ, Messerli M, Hersberger KE, Heerdink ER, Bouvy M. Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters. *The Annals of pharmacotherapy.* 2016;50:360-368.
10. Monnette A, Zhang Y, Shao H, Shi L. Concordance of Adherence Measurement Using Self-Reported Adherence Questionnaires and Medication Monitoring Devices: An Updated Review. *PharmacoEconomics.* 2018;36:17-27.
11. El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *British journal of clinical pharmacology.* 2016;82:268-279.
12. Bhatnagar N, Lakshmi PV, Jeyashree K. Multiple treatment and indirect treatment comparisons: An overview of network meta-analysis. *Perspectives in clinical research.* 2014;5:154-158.
13. Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. *Pharmacy practice.* 2017;15:943.
14. Kanters S, Park JJ, Chan K, et al. Use of peers to improve adherence to antiretroviral therapy: a global network meta-analysis. *Journal of the International AIDS Society.* 2016;19:21141.
15. Kanters S, Park JJ, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *The lancet. HIV.* 2017;4:e31-e40.
16. Mills EJ, Lester R, Thorlund K, et al. Interventions to promote adherence to antiretroviral therapy in Africa: a network meta-analysis. *The lancet. HIV.* 2014;1:e104-111.
17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of internal medicine.* 2015;162:777-784.
18. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*: Cochrane; 2011.

19. Sapkota S, Brien JA, Greenfield JR, Aslani P. A Systematic Review of Interventions Addressing Adherence to Anti-Diabetic Medications in Patients with Type 2 Diabetes--Components of Interventions. *PloS one.* 2015;10:e0128581.

20. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews.* 2008:CD000011.

21. Takiya LN, Peterson AM, Finley RS. Meta-analysis of interventions for medication adherence to antihypertensives. *The Annals of pharmacotherapy.* 2004;38:1617-1624.

22. Demonceau J, Ruppar T, Kristanto P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs.* 2013;73:545-562.

23. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Medical care.* 1998;36:1138-1161.

24. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2011;14:429-437.

25. Rucker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. *Research synthesis methods.* 2017;8:392-403.

26. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in medicine.* 2010;29:932-944.

27. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research synthesis methods.* 2012;3:98-110.

28. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Systematic reviews.* 2017;6:79.

29. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Research synthesis methods.* 2016;7:80-93.

30. van Valkenhoef G, Tervonenc T, Zwinkels T, Brock Bd, Hillege H. ADDIS: A decision support system for evidence-based medicine. *Decision Support Systems.* 2013;55:459-475.

31. Zarin W, Veroniki AA, Nincic V, et al. Characteristics and knowledge synthesis approach for 456 network meta-analyses: a scoping review. *BMC medicine.* 2017;15:3.

32. Ge L, Pan B, Song F, et al. Comparing the diagnostic accuracy of five common tumour biomarkers and CA19-9 for pancreatic cancer: a protocol for a network meta-analysis of diagnostic test accuracy. *BMJ open.* 2017;7:e018175.

33. Ma X, Lian Q, Chu H, Ibrahim JG, Chen Y. A Bayesian hierarchical model for network meta-analysis of multiple diagnostic tests. *Biostatistics.* 2018;19:87-102.

34. Song P, Wen Y, Huang C, et al. The efficacy and safety comparison of surgical treatments for stress urinary incontinence: A network meta-analysis. *Neurourology and urodynamics.* 2018.

35. Feng F, Xu Q, Yan F, et al. Comparison of 7 Surgical Interventions for Lumbar Disc Herniation: A Network Meta-analysis. *Pain physician.* 2017;20:E863-E871.

36. Freeman SC, Scott NW, Powell R, Johnston M, Sutton AJ, Cooper NJ. Component network meta-analysis identifies the most effective components of psychological preparation for adults undergoing surgery under general anaesthesia. *Journal of clinical epidemiology.* 2018.

37. Mosseri J, Trinquart L, Nizard R, Ravaud P. Meta-Analysis of a Complex Network of Non-Pharmacological Interventions: The Example of Femoral Neck Fracture. *PloS one.* 2016;11:e0146336.

38. Pompoli A, Furukawa TA, Efthimiou O, Imai H, Tajika A, Salanti G. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. *Psychological medicine.* 2018:1-9.

39. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *International journal of nursing studies.* 2013;50:587-592.

40. Candy B, Vickerstaff V, Jones L, King M. Description of complex interventions: analysis of changes in reporting in randomised trials since 2002. *Trials.* 2018;19:110.

41. Szymczynska P, Walsh S, Greenberg L, Priebe S. Attrition in trials evaluating complex interventions for schizophrenia: Systematic review and meta-analysis. *Journal of psychiatric research.* 2017;90:67-77.

42. Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *The Cochrane database of systematic reviews.* 2004:CD004804.

43. Graham L, Wright J, Walwyn R, et al. Measurement of adherence in a randomised controlled trial of a complex intervention: supported self-management for adults with learning disability and type 2 diabetes. *BMC medical research methodology.* 2016;16:132.

44. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. *Journal of the American Pharmacists Association : JAPhA.* 2011;51:90-94.

45. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *Journal of clinical hypertension.* 2008;10:348-354.

46. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. *British journal of clinical pharmacology.* 2014;77:427-445.

47. van Onzenoort HA, Verberk WJ, Kessels AG, et al. Assessing medication adherence simultaneously by electronic monitoring and pill count in patients with mild-to-moderate hypertension. *American journal of hypertension.* 2010;23:149-154.

48. Shi L, Liu J, Koleva Y, Fonseca V, Kalsekar A, Pawaskar M. Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices. *PharmacoEconomics.* 2010;28:1097-1107.

49. Williams AB, Amico KR, Bova C, Womack JA. A proposal for quality standards for measuring medication adherence in research. *AIDS and behavior.* 2013;17:284-297.

50. Mudhune V, Gvetadze R, Girde S, et al. Correlation of Adherence by Pill Count, Self-report, MEMS and Plasma Drug Levels to Treatment Response Among Women Receiving ARV Therapy for PMTCT in Kenya. *AIDS and behavior.* 2018;22:918-928.

51. Atkinson TM, Rodriguez VM, Gordon M, et al. The Association Between Patient-Reported and Objective Oral Anticancer Medication Adherence Measures: A Systematic Review. *Oncology nursing forum.* 2016;43:576-582.

52. Elkjaer M, Shuhaibar M, Burisch J, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. *Gut.* 2010;59:1652-1661.

53. Holzemer WL, Bakken S, Portillo CJ, et al. Testing a nurse-tailored HIV medication adherence intervention. *Nurs Res.* 2006;55:189-197.

54. Lee M, Kemp JA, Canning A, Egan C, Tataronis G, Farraye FA. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. *Archives of internal medicine.* 1999;159:2312-2316.

55. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *International journal of clinical pharmacy.* 2014;36:55-69.

56. Levy AE, Huang C, Huang A, Michael Ho P. Recent Approaches to Improve Medication Adherence in Patients with Coronary Heart Disease: Progress Towards a Learning Healthcare System. *Current atherosclerosis reports.* 2018;20:5.

57. Costa E, Giardini A, Savin M, et al. Interventional tools to improve medication adherence: review of literature. *Patient preference and adherence.* 2015;9:1303-1314.

58. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. *Frontiers in pharmacology.* 2013;4:91.

Tables

Table 1. Categories of interventions for improving medication adherence	
Component	**Definition**
Attitudinal	Interventions aiming to modify behavioral intention (theory of planned behavior) based on modifying patient's attitudes or subjective norm, delivered in any form (e.g. written, oral, in group, by telephone).
Economic	Interventions that produce awards (or penalties) associated to a better (or worst) medication adherence.
Educational	Every intervention where a professional provided any type of knowledge (e.g. medication information, disease state information, importance of adherence information), in any form (e.g. written, oral, in group, by telephone), to a patient with the aim of modifying patient's beliefs, attitudes or skills that facilitate adherence.
Technical	Interventions providing any gadget, instrument, or system that facilitate the medication intake, through reminders, regime simplifications, follow-ups, direction observation therapy, self-monitoring, cue-dose training, feedback.

Table 2. SUCRA results for different measures of medication adherence

	Measures				
Interventions	SELF REPORT	PILL COUNT	MEMS	OVERALL COMPOSITE	OBJECTIVE COMPOSITE
ECO + TEC	--	99%	--	92%	91%
ECO	--	--	75%	76%	75%
ATT + TEC	--	--	77%	75%	75%
ATT + TEC + ECO	--	--	69%	68%	65%
EDU + TEC	67%	76%	--	53%	58%
ATT	64%	--	41%	45%	44%
EDU + ATT	34%	12%	65%	43%	51%
TEC	52%	46%	45%	40%	36%
EDU	54%	53%	45%	29%	30%
EDU + ATT + TEC	73%	--	20%	25%	17%
SOC	8%	12%	7%	3%	5%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; ECO: economic; EDU: educational; TEC: technical; SOC: standard of care

Table 3. Impact of single components of interventions on the measures of adherence

SELF REPORT		PILL COUNT		MEMS		OVERALL COMPOSITE		OBJECTIVE COMPOSITE	
Economic	--	Economic	1.00	Economic	2.50	Economic	2.33	Economic	2.33
Technical	2.67	Technical	2.33	Technical	4.25	Technical	5.17	Technical	5.17
Educational	3.25	Educational	3.33	Attitudinal	4.60	Attitudinal	6.00	Attitudinal	6.00
Attitudinal	3.33	Attitudinal	5.00	Educational	6.00	Educational	7.75	Educational	7.50
St care	7.00	St care	6.00	St care	9.00	St care	11.0	St care	11.0

Score was calculated based on the rank order (position and frequency of the components). Lower values represent higher impact of the component on the interventions for improve adherence.
St care: Standar care

Figures captions and legends

Figure 1. Complete flowchart of the systematic review process

Figure 2. Network diagrams of different measures of adherence for complex interventions

(a) Self-report; (b) Pill count; (c) MEMS; (d) Overall composite measure; (e) Objective composite measure. Directly comparable interventions are linked with a line, the number of trials for each comparison are shown in each line. ATT: attitudinal; ECO: economic; EDU: educational; TEC: technical; SOC: standard of care

Figure 3. Consistency results of multiple treatment comparison analyses for patients' medication adherence using overall composite measure and objective composite measure

Interventions are reported alphabetically. Comparisons between interventions should be read from left to right. The estimate (OR with 95% CrI) for each comparison is in the cell in common between the row-defining intervention and the column-defining intervention. For all comparisons, values of OR lower than 1 favors the row-defining intervention. Values of OR higher than 1 favors the column-defining intervention. Significant results are in bold and underlined. ATT: attitudinal; ECO: economic; EDU: educational; TEC: technical; SOC: standard of care