Supplement_C_PICO_2

PICO 1: What are the factors (barriers, facilitators, determinants...) that need to be taken into account to avoid a patient to become non-adherent?

Rationale

Knowing the factors that may determine adherence should help the clinician to tailor prescription strategies, to medications, exercise and physical activity or splints in persons they treat for rheumatic and musculoskeletal diseases (RMD).

These factors have been identified in many studies and comprehend various domains. One of more commons classifications is the 5 dimensions of medication adherence framework by the World Health Organization (WHO)[1]:

- patient factors
- condition factors
- therapy factors
- social/economic factors, and
- health care system factors

In fact, the list appears to be very extensive.

Nevertheless, if the professionals involved in the care of persons with RMD had a checklist of factors (or domains) related to non-adherence, they would be in a better position to identify the reasons for not being adherent to a prescription and to tailor the appropriate strategies to reduce the problem.

Methods

We performed an overview of systematic reviews (SR).

Two search strategies were designed, each directed to capture studies including persons with RMD in which factors associated with adherence to medications or to exercise / physical activity, respectively, were examined (Searches available as supplementary file).

The criteria for study selection was: 1) the population should include people with RMD, 2) specifically aimed at studying barriers or facilitators of adherence in medications or exercise / physical activity, and 3) preferred design is systematic review (SR).

The risk of bias of the included studies was examined with the AMSTAR-2 tool.

For the synthesis, each SR is presented individually and, subsequently, a final list of factors by topic (medications / exercise) is displayed. In the list, the factors are aggregated by domains and by whether they can be modified or not.

In addition, we tried to identify factors that may be present at the initiation of adherence or at later moments (persistence).

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[1] Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2

Results

The two searches produced a number of records shown in Table 1.

Table 1. Results of search strategies.

Database	Provider	Hits for medications	Hits for exercise/PA	Date of search
Pubmed		836	531	2018.06.12
Embase	Embase.com	1559	875	2018.06.12
CINAHL	Ebsco Host	210	212	2018.06.12
Cochrane	Wiley	995	739	2018.06.12
Total		3600	2357	2018.06.12
Total after duplicate search in Endnote		2844	1943	
Total to screen after excluding duplicates in Covidence		2835	821	2018.06.09

Of the 2835 records from search on medications + 821 records from exercise, 1146 were duplicates between them (both results were analysed together), and therefore excluded. Of the 2510 scanned by title and abstract, 4 were finally selected to read in detail on exercise and 24 on medications.

Factors related to adherence to medications

Of the 24 articles studied in detail, 14 SR were included, together with a study identified by hand search. The reasons for excluding 10 studies after detailed exam are shown in

Table 5. The included studies are shown with a basic description in and their results in Table 3.

Table 2 and their results in Table 3.

Table 2. Studies included.

Study	Design	No. studies	RoB	Population	Outcome
[1]	SR of observational studies	16	Moderate	Gout on ULT (allopurinol mainly)	Validated measures of adherence (MPR mostly)
[2]	SR of SR	31	High	Long-term conditions (only 1 SR on an RMD, RA)	Not well specified. Adherence
[3]	SR of qualitative studies	5	Moderate	OA	Adherence (experience)
[4]	SR of observational studies with meta-analysis	24[2]	High	RA receiving treatment with csDMARDs or bDMARDs[3]	Validated measures of adherence[4]
[5]	SR of observational studies and RCT	90	Moderate	Any rheumatic disease	Any measure of adherence
[6]	SR of observational studies	11	Low	RA with MTX	Validated measures of adherence (Questionnaires)
[7]	SR of SR	51	High	Chronic therapies in long-term conditions (2 SR in	Any measure of adherence

[2] Only RA studies analysing adherence. The SR also includes studies of dyslipidaemia and studies in which outcome was persistence.
[3] It also compares RA vs dyslipidaemia
[4] 24 studies with RA, 50% using MPR and PDC, and 50% PRO, pharmacy refill data, pill counts, continuous measure of medication gaps, or MEMS.

Study	Design	No. studies	RoB	Population	Outcome
				osteoporosis and 1 including RA)	
[8]	SR of qualitative studies	56	Low	1,383 adult patients (1,149 RA, 191 SpA, 43 not specified)	Experiences
[9]	SR of observational studies (+ 1 RCT)	24	Moderate	RA, SpA and PsA	Validated measures of adherence
[10]	SR of observational studies	11	Moderate	SLE	Validated measures of adherence
[11]	SR of observational studies	18	Low	RA or undifferentiated inflammatory arthritis	Validated measures of adherence
[12]	SR of observational studies	24	High	Gout	Validated measures of adherence
[13]	SR of observational studies	31	Low	RA	Validated measures of adherence
[14]	Grounded theory review	27[5]	Moderate	IMIDs (12 RA, 6 IBD, 5 SLE, 1 in UC) and 3 gout	Any definition of adherence
[15]	SR of observational studies	73[6]	Low	IMIDs (RA, AS, PsA and IBD and PS)	Any definition of adherence

Abbreviations: RoB, risk of bias; BMQ, Beliefs about Medicines questionnaire;

Table 3. Studies included: Results – Factors associated with adherence in RMD.

Study	Factors
[1]	Consistent predictors of **non-adherence**: - Younger age - Having a gout flare (before post-index SUA testing) - Having no record of tophaceous gout Consistent predictors of **adherence**: - Hypertension - Previously diagnosed gout (as compared to newly diagnosed gout).

[2]	- Health care system-related:
	  o Health literacy
	  o Lack of medication knowledge
	- Patient-related dimension:
	  o Poor communication on doctor's part
	  o Do not trust doctor
	  o Concern about adverse effects, avoid side effects
	  o Beliefs about medications
	  o View on symptoms - felt good so did not take medication
	  o Alcohol/substance misuse
	  o Forgot
	  o Depression leading to reduced motivation
	- Social and economic dimension
	  o Cost and lack of insurance
	  o Lack of caregiver
	  o Secrecy/stigma
	  o Access to health care and resources
	  o Cultural beliefs
	  o Busy competing priorities
	  o Education level
	- Therapy related dimension

[5] 6 quantitative, 12 qualitative and 9 mixed-method studies
[6] 26 in RMD

Study	Factors
	○ Change to routine ○ Pill burden, drug regime too much
[3]	Four major themes emerged : - severity of symptoms; - perceived effectiveness of medication; - side effects and acceptability; - Knowledge and education.
[4]	Predictors of **non-adherence**: - Combination of csDMARDs - Steroid use - Use of SSZ vs MTX Predictors of **adherence**: - Older age - Female gender - Previous DMARD use - Oral DMARDs - Infliximab vs adalimumab - Satisfactory contact with health provider - Receiving large amounts of healthcare information
[5]	A total of 17 factors (38 sub-factors) were identified: - Patient-/caregiver-related factors: ○ Patient's demographics ▪ age ▪ gender ▪ ethnicity ▪ education level ○ Patient's personality factors ▪ forgetfulness ▪ patient's coping behaviour ▪ personality traits ▪ poor quality of life ○ Disease and treatment perceptions ▪ disease perception and knowledge ▪ belief in the need of medication ○ Caregiver Issues ▪ caregiver's personality ▪ dependence on caregiver - Therapy-related factors ○ Choice of drugs ▪ Dosage form ▪ Drug's properties (taste, colour, smell, size) ▪ Route of administration ○ Side effects of therapy ▪ Side effects experienced ○ Length and complexity of treatment ▪ Long duration ▪ Number of drugs prescribed ▪ Complex dosing regimen ○ Signs and Symptoms ▪ Severity of symptoms ○ Medical treatment plan ▪ Switching current therapy - Condition-related factors ○ Mental Health ▪ Depression ▪ Anxiety and panic disorder ○ Prognosis ▪ Poor prognosis - Health-system-related factors ○ Failure to understand/lack of medical instruction ▪ Lack of patient education

Study	Factors
	▪ Lack of patient involvement o Health-care provider communication and patient counselling ▪ Poor communication ▪ Gibberish ▪ Rushing during drug counseling ▪ Failure to explain medical jargon o Trust in physician ▪ Lack of trust ▪ Dissatisfaction with doctor visits o Drug supply at pharmacy ▪ Shortage of drug supply - Socioeconomic-related factors o Cost issues ▪ High treatment cost ▪ Unable to afford medication for long term o Social support ▪ Living alone ▪ Large caregiver burden ▪ Lack of community nursing services to pack the medications
[6]	7 studies investigated 38 factors and their association with adherence to MTX in RA - Demographic factors (n=6): overall weak and conflicting evidence of association with adherence - Psychological factors (n=3): consistently associated with adherence: o High beliefs about the necessity of MTX o Good mental health (negative association) o Non-avoidant coping o Active coping o Self-efficacy with regard to taking medications - Disease-related factors (n=6): conflicting results with disease duration, disease activity and disability - Treatment-related factors (n=5): conflicting results with MTX monotherapy - Patient-reported and clinical outcomes (n=3): association between adherence and treatment response.
[7]	They identified 771 individual factors grouped into 40 clusters mapped to the 5 WHO categories. Most factors were determinants of implementation (initiation of adherence), and only 47—determinants of persistence with medication. (See Table 4)
[8]	6 themes (with subthemes): - Intensifying disease identity (severity of sudden pharmacotherapy, signifying deteriorating health, daunting lifelong therapy) - Distressing uncertainties and consequences (poisoning the body, doubting efficacy, conflicting and confusing advice, prognostic uncertainty with changing treatment regimens) - Powerful social influences (swayed by others' experiences, partnering with physicians, maintaining roles, confidence in comprehensive and ongoing care, valuing peer support) - Privilege and right of access to biologic agents (expensive medications must be better, right to receive a biologic agent, fearing dispossession) - Maintaining control (complete ownership of decision, taking extreme risks, minimizing lifestyle intrusion) - Negotiating treatment expectations (miraculous recovery, mediocre benefit, reaching the end of the line). (See Figure 1)
[9]	The main predictive factors – age, sex, comorbidity, baseline clinical condition, previous or concomitant use of DMARDs, anti-TNF in monotherapy or in combination with MTX – produced diverse, even divergent results across studies.
[10]	Determinants of non-adherence included: - having depression - rural residence - lower education level - polypharmacy
[11]	- There is **no evidence** for any association with adherence:

Study	Factors
	○ sex, ○ being single, ○ being employed, ○ coping style, ○ BMQ concerns scale, ○ SIMS action scale, ○ SIMS adverse effects scale, ○ disease duration, ○ Ritchie score, ○ HAQ score, ○ AIMS2 score, ○ number of side effects, ○ frequency of medication schedule, ○ number of medicines, ○ the use of folic acid, ○ a previous inpatient stay, ○ and level of MTX dose. - There is **strong evidence** for a positive association between a prescription for DMARDs 6 months prior to anti-TNF treatment and adherence to anti-TNF treatment. - Related to anti-TNF treatment there is **limited evidence** ○ for negative associations: ▪ weekly costs of anti-TNF, ▪ having Health Maintenance Organization (HMO) insurance compared to other types of insurance and out-of-pocket costs for anti-TNF ○ for a positive association ▪ 'other' race as compared to Whites. - **Strong evidence** with the belief that the medication for RA is necessary to treat the illness, measured with the 'necessity subscale' of the BMQ - Despite no level of evidence (only 1 low-quality study) **good communication with the healthcare provider** is positively associated with adherence. - Intrapersonal factors: limited evidence for ○ positive association with general cognition ○ negative association for having a busy lifestyle
[12]	Strong evidence for positive association with medication adherence: - older - higher number of comorbidities - diabetes - hypertension Strong evidence for negative association with medication adherence: - African-American and Māori descent Weak or conflicting evidence for negative association: - smoking status, - body mass index, - socio-economic status - perceived health status - understanding illness, Moderate positive association: - lower serum uric acid concentration - higher serum uric acid - zero gout flares - receiving ULT from a specialist instead of a generalist
[13]	Among 100 possible factors potentially effecting adherence, 7 adherence-associated factors were found in at least 2 different studies. - use of infliximab compared with etanercept or MTX - use of MTX compared to SSZ or to etanercept - belief in the necessity of the medications - older age - white race
[14]	- 4 non-modifiable factors: age, gender, ethnicity, disease duration - 11 modifiable risk factors: ○ patients not understanding treatment,

Study	Factors
	○ side effects / adverse events, ○ forgetfulness / inconvenience, ○ dose regimen, ○ forgetting instructions, ○ medication ineffectiveness, ○ presence of a mood disorder, ○ lack of motivation or social support, ○ disease severity, ○ cost, ○ presence of a comorbid condition
[15]	Despite a very large amount of factors tested, only the psychosocial ones seem to be consistently associated (positive or negative): - Treatment concerns - Emotional well-being - Patient-physician relationship - Self-efficacy Practical barriers were also found associated to non-adherence

Abbreviations: RoB, risk of bias; BMQ, Beliefs about Medicines questionnaire;

[7] in their overview of SR covering 19 different disease categories identified 771 individual factor grouped into 40 clusters mapped to the 5 WHO categories. The following is a list of all factors (without the reference) synthesised by the authors as having evidence of an influence (positive or negative) on adherence to medications or inconclusive (neutral). Factors clearly related to non-RMD diseases were deleted from the list.

Table 4. Factors affecting adherence, modified from the article by [7]

	Negative effect	Positive effect	Neutral effect
Socio-economic			
Family support	- Lack of family support - Irregular supervision by a family member	- Family financial support - Family support in executing medication	- Family emotional support - Family involvement during hospitalization or follow-up
Family/caregivers factors	- Disorganized biologic families - Family in conflict - Responsibilities in the home such as providing income and caring for children - Low parental educational level - Family beliefs about the nature of the patient's illness - Having several adults involved in pill supervision	- Two-parent families - Family cohesiveness - Higher caregiver education level - Responsibilities in the family	- Knowledge of family members regarding disease - Number of people in the household - Marital status
Social support	- Lack of social support - Less acculturation - Low social functioning - Low social rank of an illness	- Emotional support - Good social adjustment - Including significant others into therapeutic alliance - Supervision of medication administration by others - Patients' support to patients	- Social support
Social stigma of a disease	- Stigma of a disease at workplace, among the family and friends - Fear of disclosure and wanting to avoid taking medications in public places	-	-

	Negative effect	Positive effect	Neutral effect
Costs of drugs and/or treatment	- Cost of drugs (co-payment) - Costs of drugs and treatment)	-	- Having health insurance
Prescription coverage	- Lack of, or inadequate medical/prescription coverage	-	-
Socio-economic status	- Low income - Poverty - Lower socioeconomic status - Financial constraints - Wanting to remain sick to qualify for financial support	-	- Socioeconomic status - Financial support from outside the family
Employment status	- Unemployment - White-collar employment	-	- Employment status
Healthcare team and system-related factors			
Barriers to healthcare	- Barriers to high-quality care - Lack of providers/caregiver availability - Poor access to a health care facility (e.g., long waiting times, queues, lack of privacy, inconvenient appointment times, inconvenient opening hours) - Seeing different language speaking therapist (i.e., Spanish-speaking therapist in US Latinos) - Difficulty in obtaining sick leave for treatment - Having no time to refill prescriptions, or other pharmacy-related problems	- Good access to medication and health service - Good access to a health care facility	- Access to care - Greater distance from the clinic - Current inpatient status - Rural settings (vs. urban) - Type of transportation used
Drug supply	- Poor drug supply - Unavailability of medications (e.g., prescription ran out)	-	-
Prescription by a specialist	-	- Referral/prescription by a specialist	-
Information about drug administration	- Unclear information about proper drug administration - Greater number of prescribing physicians - Conflicting messages between GPs and specialists on medication - Discrepancies between treatment guidelines and common clinical practice (as patients try to ask several specialists) - Use of multiple pharmacies	- Doctor's ability to provide appropriate information as to the drug administration - Being given information about the action of the drugs	-
Healthcare provider-patient communication and relationship	- Poor healthcare provider-patient relationship - Poor patient–physician communication - Lack of trust in doctors and healthcare - Lack of patient satisfaction with their healthcare - Limited caregiver adherence strategies	- Quality, duration and frequency of interaction between the patient and doctor - Offering enough time to the patient, leaving space to talk about problems concerning medication or side effects - Patient involvement in decision making - Encouraging self-management - Doctor responsiveness	-

	Negative effect	Positive effect	Neutral effect
		- Doctor's ability to demonstrate empathy - Doctor's ability to elicit and respect the patient's concerns - Perceived healthcare provider support	
Follow-up	- Inadequate discharge planning - Fewer outpatient visits - Poor follow-up by providers	- More visits to a nonmedical therapist - Seeing a greater number of physicians	- Clinic attendance
Condition-related factors affecting adherence			
Presence of symptoms	- Asymptomatic nature of the disease or absence of - symptoms	- Increased severity and number of symptom - Disability	- Pain duration - Pain intensity
Disease severity	- Lower affective pain ratings	- Disease severity - Perceptions of disease severity	- Disease severity Worse clinical status - Possible consequences of missed doses
Clinical improvement	- Clinical improvement, disappearance of symptoms, feeling better/cured	-	- Perception of a clinical improvement
Psychiatric condition	- Psychiatric disorders - Negative symptoms/motivational deficits	- Lower rates of narcissistic-histrionic personality disorder (in depression)	-
Certain diagnoses/indications	- Indication (pain medication vs. other medications)	- Rheumatoid arthritis vs. - other types of arthritis	-
Duration of the disease	- Chronic nature of the disease - Longer time since clinic visit	- Longer duration of pain	- Duration of the disease
Therapy-related factors			
Adverse effects	- Adverse effects - Decreased quality of life while taking medications	-	- Adverse effects
Patient friendliness of the regimen	- Complexity of the regimen (e.g., complex/frequent dosing - schedule/number of tablets) - Dosing frequency - Number of prescribed medications (polymedication) - Less medication prescribed (in patients with chronic non-malignant pain) - Doses during day (particularly the middle-of-day or early-morning doses) - Instability of the regimen - Inconvenience associated with administration of some medication (e.g., oral biphosphonates) - Injection formulation - Need to adjust dietary habits for taking medication - Problems with opening containers - Disliking aspects of the medication - Poor taste of medication	- Once-daily dosing (vs. more frequent one) - Once-weekly dosing (vs. once-daily) - Fewer drugs prescribed - Fixed-dose combination pills - Long acting formulation - Unit-of-use packaging - Flexibility/patient choice in treatment - Dosing through injections - Regular medication schedule (vs. irregular dose interval)	- Simplicity of regimen - Regimen complexity - Number of prescribed medications - Once-monthly dosing (vs. once-daily) - Route of medication administration - Use of oral medication (vs. depot ones)

	Negative effect	Positive effect	Neutral effect
	- Big tablet size, problems with swallowing tablets		
Drug effectiveness	- Drug ineffectiveness, objective, or perceived	- Relief of symptoms - Objective drug effectiveness	-
Duration of the treatment	- Longer duration of treatment	- Shorter duration of treatment	- Duration of treatment
Drug type	-	-	-
Well organised treatment	-	- Receiving care in structured settings - Treatment at medical center - Well-structured treatment plan -	- Medication supervision status - Having a case manager - Being aware of monitoring
Patient-related factors			
Age	- Younger age - Older and younger age groups (vs. adults) - Very old age (older than 85 years)	- Younger females (vs. older ones)	- Age
Gender	- Male gender	- Male gender	- Gender
Marital status	- Single or divorced (vs. married)	- Being married - Living with someone (vs. living alone)	- Marital status - Orphan status
Education	- Illiteracy	- Education - High IQ	- Education
Ethnicity	- Latinos (vs. Euro-Americans) - Monolingual Spanish speakers - Non-white women	- Caucasian race - U.S. born	- Ethnicity - Place of birth
Housing	- Unstable housing - Homelessness - Residentially mobile - Being away from home	- Structured environment away from home	- Homelessness - Living arrangements
Cognitive function	- Cognitive impairment, low attention and working memory	-	- Neurocognitive impairment Verbal fluency
Forgetfulness and reminders	- Forgetting - Sleeping through a dose	- Making use of reminders - Using friends and family as reminders - Having a routine in which taking drugs could be easily incorporated	-
Knowledge	- Lack of comprehension of disease and treatment - Misunderstanding of the prescription and treatment instructions, and the consequences of non-adherence - Misconceptions reported from the media, lay press, family or friends, about a medication	- Situational operational knowledge - Understanding the need for strict adherence	-
Health beliefs	- Denial of diagnosis - Unrealistic expectations concerning the medication's benefit/risk ratio - Negative patients' beliefs about the efficacy of treatment	- Belief in the diagnosis - Belief in a particular set of health recommendations - Belief in self-efficacy for taking medication - Self-confidence to maintain health status	-

	Negative effect	Positive effect	Neutral effect
	- Negative attitude toward or subjective response to medication - Thinking that the treatment could make the patients ill - Having doubts, or not being able to accept disease - Unresolved concerns about time between taking the drug and its effect - Being suspicious of treatment/medical establishment - "Being tired" of taking medications - Feeling that treatment is a reminder of disease - Perceived excessive medication use - Feeling persecuted or poisoned - Lack of interest in treatment - Wanting to be free of medications or preferring a natural approach - Wanting to be in control - Prioritizing work over taking treatment	- Fewer concerns about drugs, belief that medication is safe - Lower belief in natural products and home remedies - Beliefs of control over one's health - Feeling of empowerment - Perceived benefits of adherence - Desire to avoid burdening family members - More motivation - Belief that they are vulnerable or susceptible to the disease or its consequences - Worrying about the disease - Perceived necessity of treatment - Regarding drugs as vital (as opposed to important) - Felt less burdened by taking the medication - Fear of experiencing relapses and future disability	
Psychological profile	- Personality: low conscientiousness, high cynical hostility - Pessimistic ways of coping - Withdrawal coping style, or self-destructive escape coping style - Poor insight - Lack of self-worth - Oppositional behaviours - Laziness/lack of care - Being too distracted or busy	- Optimistic ways of coping - Hope - Insight - Higher self-efficacy - Higher levels of life satisfaction - Internal locus of control - Self-esteem - Lower levels of psychologic distress - Personal control of the disease and therapy - Higher level of self-care agency score - Living for someone, especially, children - Rewarding oneself after injections	- Coping style - Emotional over involvement - Warmth - More insight - Criticism - Less busy lifestyle - Problems with role functioning
Comorbidities and patient history	- Having other concurrent illnesses affecting adherence - Non-adherence in the past - Previous treatment failure - Concurrent diseases or illnesses, including malnutrition - Psychiatric illness, e.g., anxiety/depression - Recent hospitalization - Long hospital stay - Both eye blindness - Impaired motor functioning	- Less chronic co-morbidities - More severe comorbid conditions - Witnessing the consequences of not following medical advice in relatives with other diseases	- Number of medical conditions - Adherence to other parts of an inpatient treatment program - Presence of mood symptoms (or diagnosis of schizoaffective or bipolar disorder) - Anxiety

	Negative effect	Positive effect	Neutral effect
			- Total number of therapists in lifetime - Number of medications prescribed for another condition
Alcohol or substance abuse	- Substance abuse - Injection drugs use (vs. non-injection ones) - Younger age of first marijuana use - Alcohol abuse - Smoking	- Medication taking priority over substance use - Drinking less, or non-drinking	- Injective drug using
Patient-related barriers to compliance	- Transportation difficulties	-	-

Figure 1. Graphic included in the study by [8] on factors related to adherence to DMARD in RA.

Factors related to adherence to exercise

Only 4 SR were identified as fulfilling the criteria and were included [16-19].

[16] is a scoping review with systematic searches of low risk of bias that includes 23 studies (n=4633) of hip or knee OA.

It synthesizes the results into domains:

Domain	Barriers	Facilitators
Knowledge	- Lack of disease knowledge/education - Unclear as to type and intensity of exercise - Being given vague or no advice - Lack of specific instructions - Unclear as to benefits of exercise	- Having undertaken education class about OA - Accurate disease knowledge - Educational booklet about hip and knee OA - Doctor or physical therapist demonstrating exercises
Skills	-	- Higher level of physical fitness - More experience with exercise task
Social/Professional Identity	- Self-perception of being “inactive” - Poor self-image	- Feeling of contributing to the study which will benefit others long term - Positive self-image
Beliefs about Capabilities	- Beliefs about limitations due to disability - Knee pain limiting perceived ability to exercise - Excess weight leading to perceived inability to exercise - Beliefs about severity of symptoms - Stiffness and fatigue limiting perceived ability to exercise - Other joint pain - Hypertension - Higher number of co-morbidities - Fatalism regarding knee OA	- Low level of self-reported physical limitations - Perception of being physically active - Belief that you are taking control of own disability - Lower body mass index - Few or no comorbidities - Joint stiffness
Optimism	- Negative attitude to exercise	- Positive exercise attitude - Positive health attitude
Beliefs about Consequences	- Beliefs about disease - Beliefs about wear and tear - Beliefs about worsening symptoms - Unrealistic expectations of exercise - Belief that exercise has limited effectiveness - Concern over exercise (causing) pain - Fear of jarring knee - Fear of flare-ups - Fear of damaging knee further	- Perceived benefits of exercising - Belief that exercise is good for health - Positive outcome expectations - Pain limiting land-based activities, causing to try pool exercise
Reinforcement	- Lack of improvement with exercises - Being advised not to “overdo” exercise - No professional encouragement	- Previous positive personal experience of exercise - Easing of symptoms with exercise - Improved pain after initial exercise experience - Being offered incentives to exercise - Higher pain levels motivating participant to return to exercise - Receiving medical advice to exercise - Re-appearance of pain when not exercising - Doctors encouragement - Exercise helping to maintain general mobility - Telephone reinforcement - Pain relief as a result of doing aqua-based exercise

Domain	Barriers	Facilitators
		- Feeling better and able to do more after exercise - Improved mobility after class - Improved confidence/keeping the mind active
Intentions	- Lack of motivation - Laziness - Belief that (already) sufficiently active	- Loyalty to physical therapist - Intention to commence or continue exercise - Determination - Strong motivation - Having initiative - Making efforts to lose weight
Goals	- Short-term goal setting only - Lack of goal setting	- Long-term goals as well as short-term goals - Goal setting
Memory, Attention, and Decision Processes	- Forgetfulness - Too tired - Poor sleep - Lack of participant input to intervention content - Habit of leading an inactive lifestyle	- Good quality sleep - Active involvement by participants in content of intervention - Previous exercise adherence/compliance behaviour - Being more physically active - Exercise adherence in treatment sessions - Ability to adapt lifestyle to symptoms
Environmental context and resources	- Use of a walking aid - Bad weather conditions - Gym-based exercise - Having to go down hills or stairs during walking program - Rigid program - Lack of access to facilities - Concerns about safety - Other commitments - Conflict with routines - Lack of time - Classes not easily available - Transport difficulties - Cost of exercising - Unable to find suitable exercise - Cold changing room temperature - Pool temperature too hot or too cold - Difficult to find parking at the pool - Poorly organized instructor	- Online program - Printed instructions for exercises - Shoes with shock absorption - Easy access to facilities - Pedometer use - Gym-based exercises - Being outdoors while exercising - Ability to accommodate in everyday life - Good weather conditions - No financial trouble - Easily accessible exercise classes - Ease of transportation - Finding suitable exercise - Doctor gave gym referral - Exercise as part of an organized event - Supervision one on one - Physical therapists care - Booster sessions - Physical therapist guidance of exercise program - Well-organized instructor - Pool close to home
Social Influence	- Family commitments - Increased social strain - Exercising alone - Low social support - Lack of family support to exercise - No training partner - Life events	- Low social strain - Living alone - Beliefs of others about the benefits of exercise - Good social support - Socializing - Team commitment and support - Family support to exercise - Training partners - Peer support and interaction during class - Social interaction following class
Emotion	- Anxiety - Lack of enjoyment in exercise - Boredom with exercise	- Improved depression with exercise experience - Enjoyment of exercise
Behavioural regulation	-	- Performing exercise at own pace in own time - Prioritizing exercise

Domain	Barriers	Facilitators
		- Integrating exercise into daily tasks - Ongoing monitoring of exercise - Other responsibilities that encourage exercise (e.g., walking with dog)

[17] is a Cochrane mixed methods review of low risk of bias including trials of OA or self-reported chronic hip or knee (or both) pain (defined as more than six months' duration) in which people's opinions and experiences of exercise-based programmes (e.g. their views, understanding, experiences and beliefs about the utility of exercise in the management of chronic pain/OA) were expressed.

Twelve studies (with 6 to 29 participants) met inclusion criteria for qualitative synthesis. Their methodological rigour and quality was generally good. From the patients' perspectives, ways to improve the delivery of exercise interventions included:

- Provide better information and advice about the safety and value of exercise;
- Provide exercise tailored to individual's preferences, abilities and needs;
- Challenge inappropriate health beliefs and provide better support.

[18] is a systematic review including 10 qualitative studies on barriers and facilitators of physical activity for patients with hip or knee OA of low risk of bias.

Interestingly, they try to separate evidence between adherence to physical activity (n=3) and to exercise (n=7), and between uptake and maintenance, although they fail to get enough studies to explore it.

Facilitators of PA are:

- Aiming at symptom relief and mobility,
- positive exercise experiences and beliefs,
- knowledge,
- a 'keep going' attitude,
- adjusting and prioritising PA,
- having healthcare professionals' and social support

Barriers of Physical activity are:

- Pain and physical limitations;
- non-positive PA experiences,
- beliefs and information;
- OA-related distress;
- a resigned attitude;
- lack of motivation,
- lack of behavioural regulation,

Table 3 Barriers and facilitators: themes, subthemes and number of supporting references

Domain	Major themes	Barriers	No of studies	No of references	Facilitators	No of studies	No of references
Physical health		Physical barriers and limitations (pain and other symptoms; perceived functional limitations)	9	94	PA for mobility, symptom relief and health (PA to maintain mobility; PA for symptom relief; PA for health)	9	34
Intrapersonal/ psychological factors	Experience and beliefs about PA and OA	PA as non-effective, harmful or of doubtful effectiveness	6	36	Exercise as beneficial	7	60
		OA beliefs	5	17	Knowledge about exercise	3	8
	Behavioural regulation and attitude	Resigned to OA	5	10	Keep going despite OA	7	18
		Lack of motivation	6	14	Adjustments, prioritisation and personal effort (adjusting PAs; prioritising PA; personal responsibility and effort in being physically active)	9	41
		Lacking behavioural regulation	4	23			
	Emotions	OA-related distress	6	23	Enjoyment	4	22
Social environment	Health professionals	Lack of advice and encouragement from health professionals	5	22	Support from health professionals	8	50
	Social support	Social comparison as demotivating	5	15	Social support facilitating PA	7	43
		Lack of social support	4	8			

OA, osteoarthritis; PA, physical activity.

- lack of professional support
- negative social comparison with coexercisers

[19] is a SR of 10 studies looking at correlates of physical activity (PA). They include mainly cross-sectional studies, not qualitative or longitudinal studies, and thus the SR is considered of moderate to high risk of bias. They group their results into 4 categories:

Categories	Factors	Association with level of PA
Sociodemographic	age	inconclusive
	gender	inconclusive
	race/ethnicity	inconclusive
	education	inconclusive
	employment & income	inconclusive
	marital and living status	inconclusive
	smoking	inconclusive
Physical	RA duration	inconclusive
	body mass index	inconclusive
	comorbidities	inconclusive
	disease activity	inconclusive
	disease severity	inconclusive
	aerobic fitness	inconclusive
	strength and muscle function	inconclusive
	range of motion	inconclusive
	balance	inconclusive
	functional status	inconclusive
	pain	inconclusive
	fatigue	negatively associated
	body composition	inconclusive
Psychological	exercise beliefs and expectations	inconclusive
	motivation	positively associated
	self-efficacy	positively associated
	depression	inconclusive
	life worries	inconclusive
	regulation style (coerced)	negatively associated
	health perception	positively associated
	sense of belonging	positively associated
Social	social support	inconclusive
Environmental	None	-
Other	Previous PA levels	positively associated
	Medications	inconclusive

Messages / synthesis

- Medication non-adherence is affected by multiple determinants, belonging to several different fields.
- Many of these factors are not modifiable, and none of them is a sole predictor of adherence.
- Some factors change with time and can appear at times either to be a cause, or a consequence, of patient non-adherence.
- Non-adherence should not be perceived as patients' fault only. Social factors (such as social support, economic factors, etc.), healthcare-related factors (e.g., barriers to healthcare, and quality of provider-patient communication), condition characteristics, as well as therapy-related factors (such as patient friendliness of the therapy) play an important role in defining adherence.
- Consequently, multifaceted interventions may be the most effective answer toward unsatisfactory adherence, and its consequences.
- Bearing in mind the number of identified determinants and their inconsistent effect on adherence, prediction of non-adherence of individual patients is difficult if not impossible. In particular, the inconsistent effect of demographic variables on patient adherence explains partly why healthcare providers are ineffective in predicting adherence in their patients. In fact, their prediction rate is no better than a coin toss. Neither age, gender, marital status, nor education proved to fully explain the variance in patient adherence across conditions and settings.
- Self-efficacy is a major factor in most studies, both in medication and exercise.
- Barriers are individual
- In exercise, positive experiences while exercising (improvement in pain, physical and psychosocial functioning) do not change beliefs about the causation and prognosis of disease, but concerns about possible dangers of exercise decrease, and patients appreciate how exercise can reduce symptoms (treatment beliefs) and increase exercise self-efficacy.

Table 5. Excluded studies of medication adherence and reasons for exclusion.

Study	Reason for exclusion
MEDICATIONS	
[20]	The results of the SR are not available, except in the form of recommendations.
[21]	This is actually a meta-analysis of the effect of beliefs in necessity relative to concerns, as measured by the necessity–concerns differential and the correlation with medication adherence on a population level. It does not really provide a list of factors or information that can be used.
[22]	The factors studied are actually components of interventions.
[23]	It does not provide factors related to adherence.
[24]	Like the study by Foot et al., this is actually a meta-analysis of the effect of beliefs in necessity and concerns and the association (in terms of odds ratios) with medication adherence across long-term diseases. It does not really provide a list of factors or information that can be used different than perception of need and concerns, which are already state of the art.
[25]	It does not provide information specifically to understand the effect of route of administration on non-adherence
[26]	It uses a systematic approach to the search of related studies, but it is not really a SR.
[27]	It reviews interventions, not really factors and has already been included in another PICO.
[28]	It is not really a SR. It reviews everything in RA in relation to adherence. Difficult to assess risks of bias.
[29]	It is not really a SR. It reviews studies related to a single factor, prospective memory, but it is not possible to assess risks of bias.

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