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Title Page

Title: Why don't patients take their analgesics? A meta-ethnography assessing the perceptions of medication adherence in patients with osteoarthritis.

Concise Title: Medication adherence in osteoarthritis.

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ABSTRACT

Introduction/objectives: Whilst analgesics and medications have demonstrated efficacy for people with osteoarthritis, their effectiveness is dependent on adherence. This has previously been reported as particularly low in this population. The purpose of this meta-ethnography was to explore possible perceptions for this.

Method: A systematic review of published and unpublished literature was undertaken. All qualitative studies assessing the attitudes or perceptions of people with osteoarthritis towards medication adherence were eligible. Study quality was assessed using the Critical Appraisal Skills Programme Qualitative tool. Analysis was undertaken using a meta-ethnography approach, distilling to a third order construct and developing a line of argument.

Results: From 881 citations, five studies met the eligibility criteria. The meta-ethnography generated a model where medication adherence for people with osteoarthritis is perceived as a balance between the willingness or preference to take medications with the alternative being toleration of symptoms. Motivators to influence this 'balance' may fluctuate and change over time but include: severity of symptoms, education and understanding of osteoarthritis and current medications, or general health which may raise issues for poly-pharmacy as other medications are added or substituted into the patient's formulary.

Conclusions: Medicine adherence in people with osteoarthritis is complex, involving motivators which will fluctuate in impact on individuals at different points along the disease progression. Awareness of each motivator may better inform clinicians as to what education, support or change in prescription practice should be adopted to ensure that medicine adherence is individualised to better promote long-term behaviour change.

Keywords: drug; compliance; systematic review; musculoskeletal; elderly

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INTRODUCTION

Osteoarthritis is a painful and debilitating chronic musculoskeletal disease which most commonly affects older people, impacting on their lifestyles, functional independence and quality of life [1,2]. The most common joints affected by osteoarthritis include the carpometacarpal, knee, hip and spine [3]. It is projected that the number of people with osteoarthritis will increase to nearly 67 million by 2030 in the United States of America alone [4,5]. With an ageing population, this will pose a major social and healthcare burden on already stretched primary and secondary care settings [6].

The NICE guidelines [7] and similar international recommendations have placed medications such as paracetamol, codeine and NSAIDs as frontline treatments for this population [7,8,9]. Whilst these have clearly demonstrated efficacy for people with osteoarthritis, such treatments are only effective whilst people comply with prescriptions [7,10]. Treatment adherence has been acknowledged as a major problem within this population in relation to exercise, weight-management and medication [10,11]. Whilst cited as a problem, little evidence has been undertaken to explore why medication adherence is a particular problem for people with osteoarthritis. With better understanding on the reasons why people do not adhere to their medications, it may be possible to develop strategies to counter these reasons and perceptions. If successful, the efficacy data on medications may be more likely to transfer into clinical outcomes, resulting in greater patient wellbeing, but also capability to self-manage symptoms, reducing burden on healthcare services.

Given this rationale, the purpose of this review was therefore to examine the perceptions of people with osteoarthritis to medications to better understand why people take or do not take medications for symptom control.

MATERIALS AND METHODS

This systematic review was undertaken within the Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [12] statement.

Search Strategy

The primary search was undertaken of the published literature databases: AMED, EMBASE, MEDLINE, PsycINFO, BNI, CINAHL, the Cochrane library on 10th November 2015. The secondary search included the grey literature and trial registries: OpenGrey (System for Information on Grey Literature in Europe), WHO International Clinical Trials Registry Platform, Current Controlled Trials and the United States National Institute of Health Trials Registry). All searches were undertaken from database inception to Week 2 November 2015. An example of the MEDLINE search strategy is presented in **Table 1**. The basis of this was modified for the other search strategies.

All reference lists of included papers and relevant review papers were screened to identify potentially omitted articles. All corresponding authors were contacted by email to determine whether any currently unpublished or previously unidentified papers could be identified for the final review.

Eligibility Criteria

Studies were included if they:

(a) examined patient perceptions of medication and drug adherence or compliance. We assessed compliance for any medication including analgesics, anti-depressives or anti-psychotics for example, but only for people with osteoarthritis.

(b) recruited people with osteoarthritis (irrespective of body region). Diagnosis of osteoarthritis was defined by the American College of Rheumatology (ACR) criteria for diagnosing osteoarthritis [13].

Participants described as having experienced knee pain for more than 25 of the last 30 days, and experienced morning stiffness of less than 30 minutes in duration were also included if a specific documentation of ACR criteria was not provided.

(c) qualitative or survey design studies. We did not place a restriction on the language of paper or date of publication.

Two reviewers (TD, TS) independently reviewed the titles and abstracts from all potentially relevant papers using the pre-defined eligibility criteria. Full texts of all potentially eligible papers were reviewed by the two reviewers before making a final decision on eligibility. Studies that did not satisfy the eligibility criteria were excluded. Any disagreement between the reviewers on paper eligibility was resolved through discussion.

Data Extraction

One reviewer (TD) independently extracted all data onto a pre-defined data extraction table. This was verified by a second reviewer (TS). Data extracted included: the number of participants; age of participants; gender mix of cohort; duration of osteoarthritis; presence of multi-joint osteoarthritis; presence and type of co-morbidities; perceptions, attitudes, experiences, views of people towards medication adherence and compliance. Any disagreements in data extraction between the two reviewers were resolved through discussion.

Outcome Measures

The primary outcome measurement was patient experience of medication adherence and the barriers and facilitators reported by participants.

Quality Assessment

We critically appraised each included paper using the Critical Appraisal Skills Programme (CASP) qualitative appraisal tool [14]. Two additional criteria were incorporated to the CASP assessment which were deemed important for this specific research question. We assessed whether the sampling frame provided variability for: (1) degree of pain; (2) medication adherence/non-adherence. This was felt important given the research question and requirement to gain a representation of the osteoarthritis population on two ‘moderators’ which may have directly influenced perception of medication adherence. One reviewer (TD) independently appraised each paper. This was verified by a second reviewer (TS). If disagreements arose in critical appraisal assessment, this was resolved through discussion between the two reviewers.

Data Synthesis

The qualitative study data were synthesised using a meta-ethnography approach. Through this, following data emersion, emerging themes were identified to examine how concepts juxtaposed or related to one another [15]. Relevant themes were grouped into categories by two reviewers independently (TD, TS). Categories were created on the basis of primary data from the included studies rather than prior knowledge [15]. Constant comparative techniques were then used to compare how emergent categories related to the primary data/original texts. The results were compared between each reviewer and consensus was reached through discussion to identify all agreed primary and secondary-order themes. Analysis of these key categories was then undertaken through the reciprocal translation, refurational analysis and development of lines of argument to gain a third-order construct [15,16].

RESULTS

Search Results

The results of the search strategy are presented in **Figure 1**. A total of 881 citations were identified from the search strategy when duplicates were removed. After full-texts were reviewed, 76 papers were deemed potentially relevant. Following re-assessment, five satisfied the eligibility criteria and were included.

Quality Assessment

The results of the critical appraisal are presented in **Table 2**. As this illustrates, three of the five studies presented with high quality, two presented as low quality. Recurrent limitations across the evidence-base included not explicitly relating the results into clinical practice to facilitate the transferability of the results in four studies [17,18,19,20]. Only two studies clearly explored the relationship between the researcher and participant and considered the impact of these on their findings [17,20]. Both Milder et al [18] and Sale et al [19] documented their data collection processes clearly, but neither clearly documented and presented their data analysis approaches clearly. However, recurrent strengths illustrated in all studies included clarity in the research question and design adopted, a clearly documented recruitment strategy, a clear statement of findings, and recruited people with a varied level of pain and medication adherence levels, to explore a variety of attitudes and perceptions on this topic.

Characteristics of Included Studies

The characteristics of the included studies are presented in **Table 3**. Of the five included studies, three were semi-structured interviews [18,19,21], two were survey study designs [17,20]. Two studies were undertaken in Australia [17,18], one in Canada [19], one in France [21], whilst Blamey et al's [20] study was undertaken in the UK.

A total of 519 participants were included in the analysis. This included 404 participants from the two survey studies [17,20], and 115 participants who were sampled for the three semi-structured interview

studies [18,19,21]. There were largely equal proportions of males and females represented in each study, with the exception being Alami et al [21] where 73% of the cohort were female, and Blamey et al [20] where 71% were female. Mean age of the cohorts ranged from 55 years [20] to 62 years [17]. All studies recruited independent community dwelling subjects rather than institutional care home residents. Whilst neither Milder et al [18] nor Blamey et al [20] signified the proportionality of the specific joints affected by osteoarthritis, this was documented in three papers. Participants in Laba et al [17] and Alami et al [21] presented with solely knee osteoarthritis whilst Sale et al's [19] cohort presented with hip and/or knee osteoarthritis. The co-morbidities presented in each cohort were documents in three studies [17,18,19]. In these studies, a significant proportion presented with at least one co-morbidity, 93% in Milder et al's [18] case. The most common co-morbidities were hypertension and heart conditions (52%)[17], and diabetes mellitus (over 50%)[19].

Meta-Ethnography

Four themes emerged. These included: severity of symptoms; perceived effectiveness of medication; side effects and acceptability; and knowledge and education.

Severity of symptoms

Three factors were perceived as important moderators to medication adherence for people with osteoarthritis related to severity of pain. The level of pain experienced by the patient was regarded as an important variable to adherence. People who reported greater pain felt more likely to adhere to their prescribed analgesic regime rather than those who experienced less pain [19,20]. Furthermore those who experienced greater pain levels also reported taking their analgesics pre-emptively rather than as-and-when required [19]. The severity but also impact of pain on individual's lifestyles and sleeping patterns were also perceived as important factors in medication adherence [19]. This distinction in symptom severity and frequency was made in patients through those who used analgesics to manage occasional flares in symptoms (non-adherence, self-managing their medications) as opposed to those who experienced recurrent or daily symptoms who were more likely to use symptoms as their guide to administration [19].

Perceived effectiveness of medication

A recurrent factor which impacted on adherence was the patient experience regarding the effectiveness of the medication. Sale et al [19], Milder et al [18] and Laba et al [17] reported that people with osteoarthritis were more adherent to their medications if they felt that the medication would relieve pain sufficiently over and above potential negative side effects. This 'balance' between the pros-and-cons of taking medications was seen as critical in decision-making for this population, and emphasised the need for clarity and education on medications.

The issue of effectiveness was also related to the mode of action. Laba et al [17] reported that people who were prescribed a slow-acting, disease-modifying medications such as glucosamine or cod liver oil were more adherent as opposed to fast-acting, immediate pain relief provided with NSAIDs. This was hypothesised to be related to the side-effects of NSAIDs over disease-modifying drugs, but it remains unclear whether this is the case or whether it can be attributed to a preference to these medication types [17].

Side effects and acceptability

In relation to the balance between 'pros-and-cons' for regularly taking medications, the major disincentive remains side-effects and how taking medications can be effectively implemented within people's lifestyles with least inconvenience or complications. Fear related to side-effects were reported in four studies [17,18,19,21]. Side-effects were defined as either providing minor effects such as constipation or doziness [17,18,19], or more serious, long-term effects such as stomach ulcers or addiction [17,18,19,21]. The principle concern surrounded NSAIDs and long-term usage was gastric complications. However, Alami et al [21] and Sale et al [19] emphasised a fear regarding addiction with this being an overwhelming side-effect influencing individual's medication adherence. This was firstly related to a fear that with continued use, individuals could not 'manage' without analgesics, with a fear of dependency and loss of control without medications [19]. Secondly, Alami et al [21] acknowledged participant's fears that analgesics, morphine in this instance, may 'mask' symptoms and therefore provide a confusion as to being able to detect pain or not, and the paradox

that if they take their medications, they may not be able to acknowledge they are suffering and therefore, for some reason, feel fraudulent in attending routine medical reviews for osteoarthritis. In this way, there may be a suggestion that some people still wished to feel that they are in some suffering to be able to identify themselves as someone with osteoarthritis rather than someone who takes medication to mask symptoms.

The acceptability and inconvenience of specific dose regimes were identified as detrimental effects which impacted on medication adherence. Laba et al [17] and Milder et al [18] reflected findings that daily, more formulaic, 'pill-loading' prescriptions posed greater problems in adherence. Conversely, Alami et al [21] reported greater support and adherence towards topical treatments such as Diclofenac cream being led and administered locally which were perceived as more 'understandable' in mode of action than oral analgesic alternatives.

Only Laba et al [17] reported medication adherence was influenced by out-of-pocket costs in their study from Australia.

Knowledge and Education

Issues surrounding knowledge and education arose around: practical support and education on how to and when to take medications; on the benefits and rationale for taking medications; and the impact of education and knowledge on participant's self-efficacy towards their medication regime.

Recurrently respondents cited limited knowledge and support on practical aspects of their medication regime. By being unclear on factors such as timing, dose and frequency of medications, over what time-scales, respondents reported being disillusioned and limited in motivation to adhere to their recommended regimes [17,18,19]. This was compounded through limited support and follow-up guidance from medical services [21]. Similarly both Sale et al [19] and Alami et al [21] reported the belief that the trivialising of osteoarthritis by healthcare professions, instilled a similar perception of the disease in individuals. This consequently had a negative impact on people's desire to follow an analgesic regime. However, in instances where patients felt involved and incorporated in decision-

making on medication regime, and felt listened to and invested within, medication adherence was reported as greater [21].

Finally, participant's self-efficacy and locus of control over their disease and self-management was reported to pose a significant impact on medication adherence [17,20].

Line of Argument

The line of argument for these four themes created a new interpretation comprising one component with four inter-relating moderators. This is presented in **Figure 2**'s schema. At the core of medication adherence for people with osteoarthritis is the balance between the willingness or preference to take medications with the alternative being toleration of symptoms. This is dependent on multiple factors being: the effectiveness of medication, severity of side-effects, severity of symptoms and effectiveness of the medication. These all inter-relate and the loading or weight of these symptoms may fluctuate at different times for individuals dependent on status of current symptoms, education and understanding of the osteoarthritis and current medications or general health which may raise issues for poly-pharmacy as other medications are added or substituted into the patient's pharmacological requirements.

DISCUSSION

The findings of this meta-ethnography suggest that medication adherence for people with osteoarthritis is multi-factorial, with different ‘moderators’ being more significant at different times. It also suggests that people with osteoarthritis may have specific reasons for poor medication adherence compared to other medication conditions, related to health beliefs and perceptions surrounding osteoarthritis as a disease process. Now identified, these ‘moderators’ to medication adherence may be considered to individually tailor medication adherence to improve behaviour change for specific subgroups of the osteoarthritis population. These findings are largely based on a high quality evidence-base. However, given that three studies did not clearly state the relationship between the participants and researchers [18,19,21], it is not possible to ascertain whether this had an impact on the findings through social desirability bias.

A key finding was the variability in factors perceived by people with osteoarthritis as moderators to adherence. This reflects differing characteristics within responders purposively sampled to gain such variability. Factors such as severity of symptoms, duration since diagnosis, gender and country of origin were all variables which were assessed in this study. This reiterates the requirement not to consider the osteoarthritis population as a homogenous group, i.e. not people with knee osteoarthritis, but people presenting with differing health beliefs, different levels of education and understanding of their condition and medication regimes, with different symptoms, with different expectations of their symptom management and physical requirements. Through this understanding of various strategies must be tailored and individualised to have a meaningful impact on medication adherence. Such a recommendation has been seen within the medication adherence literature in hypertension [22], asthma [23] and depression [24]. However, this understanding is particularly valid in the osteoarthritis population given the acknowledged variability in health beliefs regarding the condition itself, irrespective of beliefs surrounding pharmacological management [25]. Future interventions therefore should consider the individualisation of behaviour change, adopting models such as the social ecological model, to provide a theoretical underpinning for long-term behaviour change promoting medicine adherence.

The individualisation of medication adherence may also be related at a pathological level. It is acknowledged that not all people with osteoarthritis have the same pathological mechanism. Two broad groups have been hypothesised as the inflammatory-type and the mechanical non-inflammatory type osteoarthritis [26]. It is suggested that medications such as NSAIDs may be most effective for inflammatory-type patients, particularly in providing immediate pain relief. However, this meta-ethnography repeatedly acknowledged a particular challenges with NSAID adherence, attributed to higher perceived side-effects. Given that the ‘balance’ as represented in **Figure 2** related to perceived benefit over risk, it may be suggested that consideration of side-effects over lower efficacy for the mechanical subgroup may dissuade physicians prescribing NSAID for this specific subgroup of the osteoarthritis population as this would have a potential impact on adherence. However identifying the specific phenotypes to determine this subgroup is still developing and therefore, until this is a widely acknowledged practice, such sub-grouping is not feasible.

As suggested, medication adherence may differ across the osteoarthritis population. There is an understanding that osteoarthritis may be ‘just ageing’ rather than ‘medicalising’ the condition [25]. The realisation that osteoarthritis is not currently curative, and that medications for symptom management are long-term can have a negative impact, particularly on the fear of additional and longer-term usage. Addressing this health belief, not only in the individual, but also by supporting and educating patient’s family members or carers may be important as they have an integral part in medication adherence, particularly in those with greater physical and cognitive care needs.

Secondly, compared to medications for other conditions, such as hypertension, Sale et al [19] reported respondents were more comfortable modifying analgesic regimes. This may be attributed to their perception of osteoarthritis as a less life-threatening condition. This issues may require further consideration when counselling patients on both the pathophysiology of osteoarthritis and how medications can alter this through a therapeutic-ladder. Such an analogy may have a significant impact on this moderator in medication adherence for people with osteoarthritis.

A significant limitation posed by the current evidence-base related to sampling bias. As demonstrated in **Table 3**, the populations largely recruited younger/middle aged participants, with the oldest mean age being 62 years [17]. Accordingly, this paper provides valuable insights into medication adherence in younger patients and those newly-diagnosed with osteoarthritis. However, it is not possible to make comment on medication adherence challenges in older people. This is important for a number of reasons. Firstly, with an ageing population expected to present with a greater prevalence of osteoarthritis, medication management in this population should be considered as it will pose an increasing burden on health and social care [5]. Secondly, this population present with unique medical complications which could impact on their capacity to adhere to medication regimes. These are largely around cognitive impairment with declining cognitive function and short-term memory, in addition to multiple co-morbidities such as cardiac, respiratory and gastrointestinal pathologies. Notably the five included studies poorly reported the presence of comorbidities. Accordingly it was not possible to evaluate what affect this may have made on medication adherence. Nonetheless, such comorbidities could theoretically preclude certain medications from being prescribed or alter the mode of delivery, in addition to presenting with further barriers through the increased risk of drug interactions with poly-pharmacy. Based on these reasons, further investigation should be a research priority to identify the specific medical adherence challenges faced by older people and those with a variety of comorbidities. Furthermore research is warranted to seek the views of this group of patient's families and carers in domestic dwellings or care institutions as these may also provide valuable perspectives of wider mechanisms which may impact on medication adherence.

Whilst the findings of this meta-ethnography have allowed a comparison on the beliefs and experiences of medication adherence for people with osteoarthritis across four different countries, there appeared limited variation in these between participants from Australia [17,18], Canada [19], France [21] and the UK [20]. This may be attributed to a 'real' limited variability in beliefs between people from these countries. Alternatively specific differences in cultural background, health psychology, pain perception and self-management may not have been specifically explored which

may truly exist. Further study to compare differences across these countries for these factors would clarify this. Furthermore, differences in perceptions across other cultures, particularly in Asia and Africa, may be beneficial to ascertain how different health systems and populations' cultural backgrounds may provide different insights to those previously reported for medication adherence.

CONCLUSIONS

Medication adherence is a complex problem for people with osteoarthritis, with a number of different 'moderators' which impact on adherence at different times. Adherence is perceived as a balance between willingness or preference to take medications as considered beneficial and effective, with the alternative being toleration of symptoms in the face of negatively perceived factors such as severity of side-effects, severity of symptoms, acceptability of dosing regimes, and overall health beliefs around osteoarthritis. Further study remains to explore whether this adherence such as cognitive impairment, and other medical co-morbidities which could impact on adherence in alternative ways than previously understood.

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Conflicts of Interest: None declared by any author.

FIGURE AND TABLE LEGENDS

Figure 1: PRISMA Flow-Chart depicting the search strategy results

Figure 2: Schema of the line of argument generated from the four themes.

Table 1: MEDLINE search strategy

Table 2: Critical Appraisal – CASP Qualitative Critical Appraisal Tool (modified)

Table 3: Included Study Characteristics Table

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Figure 1: PRISMA Flow-Chart depicting the search strategy results

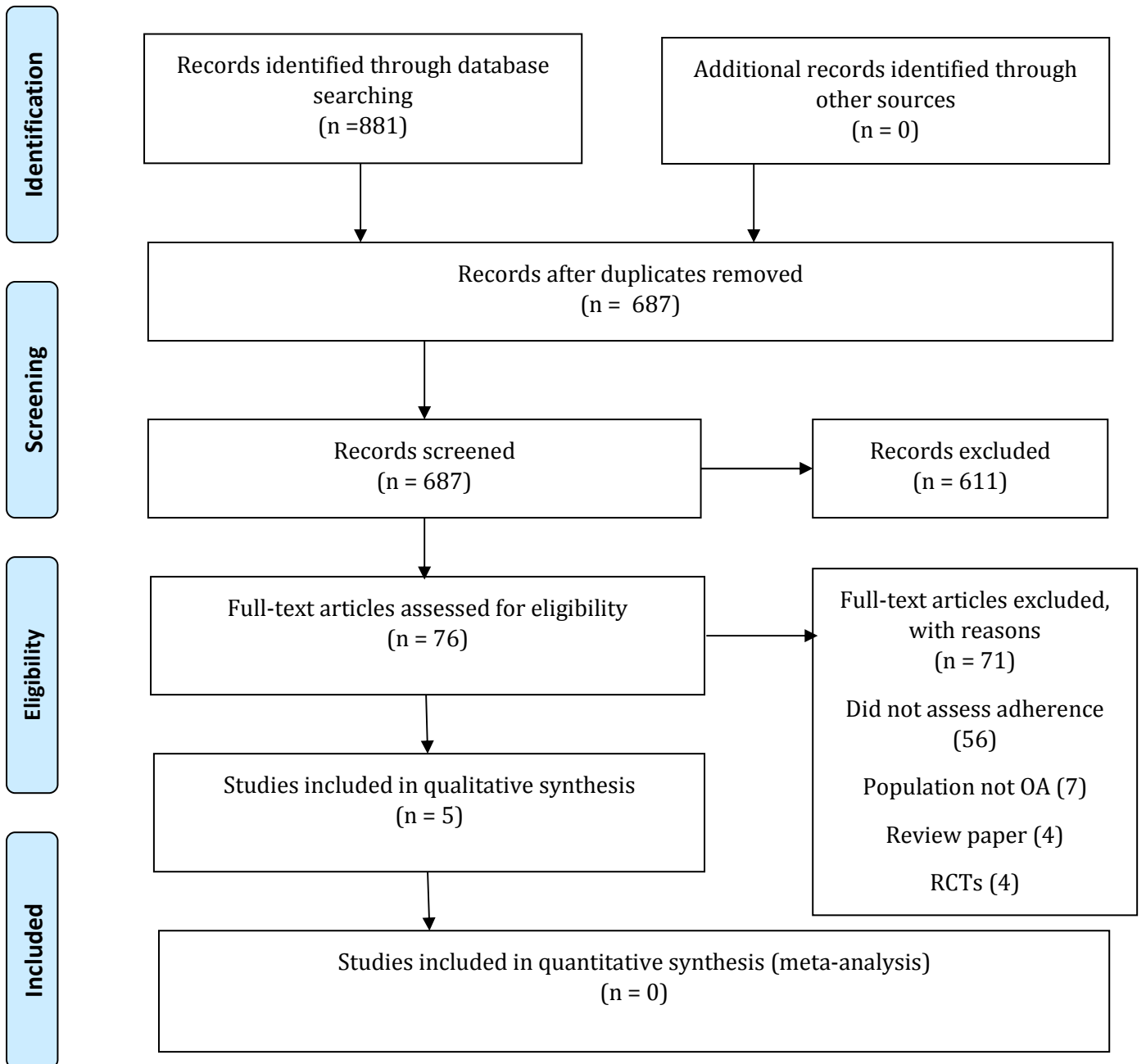


Figure 2: Schema of the line of argument generated from the four themes.

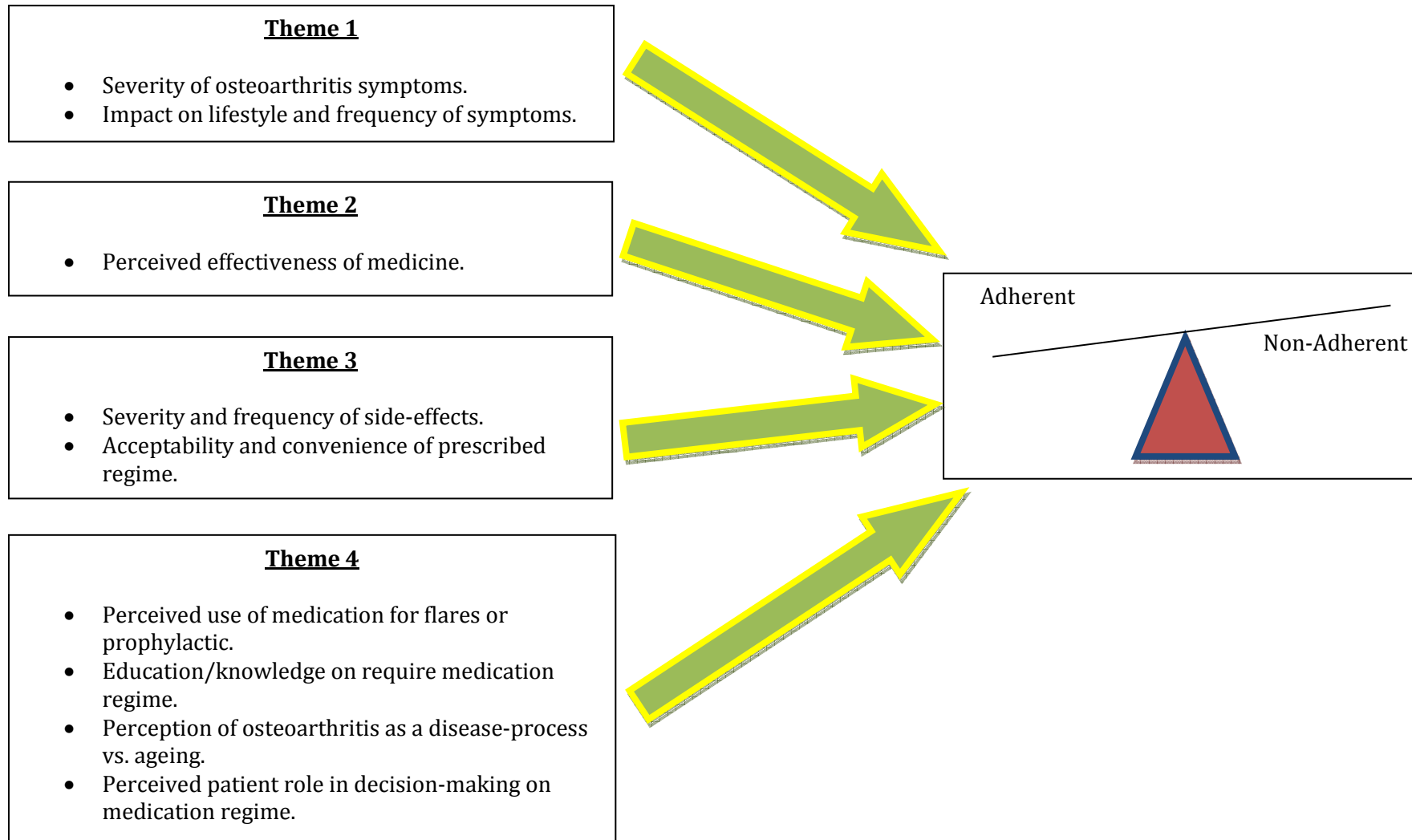


Table 1: MEDLINE search strategy

1. Medication
2. Drug
3. Analgesics
4. Pharmacological
5. OR/1-4
6. Adherence
7. Compliance
8. Concordance
9. OR/6-8
10. Musculoskeletal pain
11. Joint pain
12. Osteoarthritis
13. Arthritis
14. Arthropath\$
15. OR/10-14
16. AND/5,9,15

Table 2: Critical Appraisal – CASP Qualitative Critical Appraisal Tool (modified)

Criterion	Alami et al [21]	Blamey et al [20]	Laba et al [17]	Milder et al [18]	Sale et al [19]
Was there a clear statement of the aims of the research?	✓	✓	✓	✓	✓
Is a qualitative methodology appropriate?	✓	✓	✓	✓	✓
Was the research design appropriate to address the aims of the research?	✓	✓	✓	✓	✓
Was the recruitment strategy appropriate to the aims of the research?	✓	✓	✓	✓	✓
Were the data collected in a way that addressed the research issue?	✓	✓	✓	x	x
Has the relationship between researcher and participants been adequately considered?	x	✓	✓	x	x
Have ethical issues been taken into consideration?	✓	✓	x	✓	✓
Was the data analysis sufficiently rigorous?	✓	✓	✓	x	x
Is there a clear statement of findings?	✓	✓	✓	✓	✓
Is the research valuable to clinical practice?	✓	x	x	x	x
Sample stratification by degree of pain	✓	✓	✓	✓	✓
Medication adherence stratified by pain	✓	✓	✓	✓	✓
Overall Methodological Quality	H	H	H	L	L

H – High Risk of Bias; L – Low Risk of Bias; U - Unclear

Table 3: Included Study Characteristics Table

Study	Study Design	Study country of origin	Sample Size	Gender (m/f %)	Age in years (mean or range or both)	Place of residence (Community vs. care home)	OA Joint Affected	Co-morbidities
Alami et al [21]	Semi-structured interviews	France	81	27/73	>44	Community	Knee	N/S
Blamey et al [20]	Survey	UK	216	29/71	55 (SD 14.8)	Community	N/S	N/S
Laba et al [17]	Survey	Australia	188	48/52	62 (SD 8.5)	Community	Knee	Hypertension/Heart (52%); Ulcer/Stomach (7.5%)
Milder et al [18]	Semi-structured interviews	Australia	15	47/53	>64	Community	N/S	All co-morbidities 93%
Sale et al [19]	Semi-structured interviews	Canada	19	47/53	<66 (67-82)	Community	Hip and Knee	>50% diabetes

F - females; M - males; N/S - Not stated; OA - osteoarthritis; SD - standard deviation; UK - United Kingdom