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A Scoping Review of Interventions to De-implement Potentially Harmful Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Healthcare Settings

ABSTRACT

Objectives: Potentially harmful nonsteroidal anti-inflammatory drugs (NSAIDs) utilization persists at undesirable rates throughout the world. The purpose of this paper is to review the literature on interventions to de-implement potentially harmful NSAIDs in healthcare settings and to suggest directions for future research.

Design: Scoping review

Data Sources: PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar (2000-2022).

Study Selection: Studies reporting on the effectiveness of interventions to systematically reduce potentially harmful NSAID utilization in healthcare settings.

Data Extraction: Using Covidence systematic review software, we extracted study and intervention characteristics, including the effectiveness of interventions in reducing NSAID utilization.

Results: From 7,818 articles initially identified, 68 were included in the review. Most studies took place in European countries (45.6%) or the U.S. (35.3%), with randomized controlled trial as the most common design (55.9%). The majority of studies (76.2%) reported a reduction in the utilization of potentially harmful NSAIDs. Interventions were largely clinician-facing (76.2%) and delivered in primary care (60.2%). Academic detailing, clinical decision support or electronic medical record interventions, performance reports, and pharmacist review were frequent approaches employed. NSAID use was most commonly classified as potentially harmful based on patients' age (55.8%) or history of gastrointestinal disorders (47.1%) or kidney disease (38.2%). Only 7.4% of interventions focused on over-the-counter NSAIDs in addition to prescription. Few studies (5.9%) evaluated pain or quality of life following NSAIDs discontinuation.

Conclusion: Many varied interventions are effective in de-implementing potentially harmful NSAIDs in healthcare settings. Efforts to adapt, scale, and disseminate these interventions are needed. In addition, future interventions should address over-the-counter NSAIDs, which are broadly available and widely used. Evaluating unintended consequences of interventions, including patient-focused outcomes, is another important priority.

Key words: deprescribe, medication overuse, safety, low-value care

- **What is already known on this topic** – *NSAIDs are overutilized by high-risk patients at persistent rates. Interventions to reduce potentially harmful NSAIDs prescribing and over-the-counter (OTC) NSAIDs use are needed.*

- **What this study adds** – *More than 50 studies published internationally from 2000 to 2022 (three quarters of those reviewed) reported on interventions effective in de-implementing potentially harmful NSAIDs. We extracted and summarized characteristics of studies and of interventions to identify research gaps and priorities for future research.*

- **How this study might affect research, practice or policy** – *In light of the large number of effective interventions on record, implementation and dissemination efforts should be the priority of future work.*

BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation through inhibition of cyclooxygenase (COX-1 and -2) enzymes, thereby limiting the production of inflammatory prostaglandins.[1] Representing 5 to 10% of global medication utilization, NSAIDs are commonly used to treat arthritis and musculoskeletal pain, injuries, headache, and other sources of acute and chronic pain.[2] There are six classes of NSAIDs: salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, anthranilic acid derivatives, and selective COX-2 inhibitors.[3] NSAIDs are available in prescription and over-the-counter (OTC) strengths, a variety of different formulations, and oral (most common), intravenous, injectable, and topical forms. The use of NSAIDs has risen globally throughout the last twenty years,[4–8] in part due to increasing rates of chronic and persistent pain and an increasing aging population.

In addition to anti-inflammatory and analgesic properties, NSAIDs have numerous other physiologic effects, which differ by NSAIDs class. For example, NSAIDs can reduce the integrity of the gastrointestinal mucosal barrier and limit submucosal blood flow, increasing risk of ulceration, hemorrhage, or perforation, particularly among vulnerable individuals; COX-2 selective NSAIDs are associated with lower gastrointestinal risk.[1,9] Taking NSAIDs can reduce renal blood flow, alter fluid-electrolyte balance, and increase risk of acute kidney injury.[10] Risk for and worsening of hypertension, heart failure, and other cardiovascular issues have also been associated with regular NSAIDs use.[10–13] In 2015, the U.S. Food and Drug Administration updated the black box warning on OTC NSAIDS to include, "*NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease…The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID…There is an increased risk of heart failure with NSAID use.*"[14] Medical societies and professional organizations around the world have established recommendations for limiting or avoiding NSAIDs in certain high-risk populations **(Supplementary File 1)**.

Despite numerous long-standing recommendations, potentially harmful NSAIDs prescribing and OTC use persists globally.[15–18] As an example, multiple studies show that up to 30% of patients with chronic kidney disease (CKD) are prescribed long-term NSAIDs.[19,20] This high-risk use has resulted in a substantial number of adverse events; NSAIDs are a leading cause of drug-related hospitalizations and mortality.[21–23] The drivers of potentially harmful NSAIDs prescribing and use are complex and multilevel.[24–26] Clinicians' unfamiliarity with professional recommendations,

clinical inertia, limited alternative options for pain management, lack of patient knowledge or understanding, and broad availability of OTC NSAIDs are just some of the factors involved. The evolving regulatory landscape also complicates NSAIDs practice patterns and decision-making (a timeline of major NSAIDs-related regulatory events and other key historical timepoints in the U.S., as an example, is shown in **Table 1**).[27,28]

Further efforts are needed to reduce the potential harm associated with prescription and OTC NSAIDs and promote safer pain management for high-risk patients. The purpose of this paper is to provide an overview of published interventions to de-implement potentially harmful NSAIDs in healthcare settings, to identify knowledge gaps, and to suggest opportunities for subsequent interventions and future research related to NSAIDs de-implementation.

Table 1. Timeline of Major Regulatory Events and Other Key Historical Timepoints U.S. NSAID History

Year	Event
1900	Aspirin registered in the U.S., available via prescription.[29]
1915	Aspirin approved by FDA for over-the-counter distribution.[30]
1964-1976	Indomethacin, ibuprofen, diclofenac, ketoprofen, and naproxen approved by the FDA.[31,32]
1971	John Vane discovered the mechanism of action of aspirin and other NSAIDs.[33]
1976	COX enzyme discovered, recognized for role in prostaglandin synthesis.[33]
1984	Ibuprofen approved by FDA for over-the-counter distribution.[34]
1985	FDA approved aspirin for treatment of acute myocardial infarction and secondary cardiovascular prevention, CDC endorses.[35]
1991	Second COX enzyme ("COX-2") discovered, recognized as identical in structure but having important differences in substrate and inhibitor selectivity and in intracellular locations.[36]
1997	Celecoxib, the first selective COX-2 inhibitor, was introduced.[37]
2004-2005	Selective COX-2 inhibitors (rofecoxib and valdexocib) withdrawn from the market based on evidence that long-term use increases cardiovascular risk. Celecoxib remained on the market with a black box warning. The warning was also added to the over-the-counter NSAIDs' drug facts label.[38]
2007	FDA approved topical diclofenac at the prescription-level.[39]
2015	Strengthening of the black box warning over-the-counter NSAIDs' drug facts labels related to risk of heart attack and stroke.[14]

2016	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years (B recommendation).[40]
2020	Topical diclofenac approved for over-the-counter distribution.[28]
2022	Department of Health and Human Services initiates the Million Hearts Campaign, a national initiative to prevent 1 million heart attacks and strokes within 5 years. It focuses on implementing a set of evidence-based priorities that can improve cardiovascular health (including appropriate aspirin use).[41]
2022	The USPSTF recommends that for adults aged 40 to 50 years with an estimated 10% or greater 10-year cardiovascular disease (CVD) risk: The decision to initiate low-dose aspirin use for the primary prevention of CVD in this group should be an individual one. (C recommendation).[42]

CDC: Centers for Disease Control and Prevention, COX: cyclooxygenase, CRC: colorectal cancer, CVD: cardiovascular disease, FDA: Food and Drug Administration, NSAIDs: nonsteroidal anti-inflammatory drugs, USPSTF: United States Preventive Services Task Force

METHODS

We performed a scoping review of the scientific and gray literature reporting on interventions to de-implement NSAIDs in healthcare settings. Our review was guided by the PRISMA Extension for Scoping Reviews.[43] As a scoping review, this review is not eligible for PROSPERO registration, but the protocol was posted at https://osf.io/ywe62/ in January 2022. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Eligibility Criteria

Eligible studies were published in English between 2000 and 2022, employed any study design, and evaluated interventions administered with a goal of de-implementing potentially harmful NSAIDs in a healthcare setting.

Healthcare settings included any outpatient or inpatient healthcare environments within any medical specialty.

NSAIDs included prescription or over-the-counter oral or topical NSAIDs. NSAIDs that are not approved for current use were included if they had been approved at any point during the study period. For example, although rofecoxib and valdecoxib were removed from the U.S. market in 2005,[38] they were included in the literature search. Aspirin taken for cardiovascular disease prophylaxis (<100 mg) was not included since the recommended dose is lower than that commonly used for analgesic purposes. If the purpose of the intervention was to study an inappropriate prophylactic use of aspirin, an exception was made to include that study. To be

included, studies must have reported NSAID prescribing or use rates before and after the intervention, at minimum.

Potentially harmful NSAIDs included those that were prescribed or taken in a manner inconsistent with professional recommendations or otherwise recognized as high-risk by the study authors.

Interventions were defined as "any activity or set of activities aimed at modifying a process, course of action, or sequence of events in order to change one or several of their characteristics such as performance of expected outcome", as described by the World Health Organization.[44] Interventions were actively delivered to healthcare clinicians, healthcare teams, or directly to patients. All interventions included in the study involved de-implementation of NSAIDs. Passive interventions such as policy changes were not included.

De-implementation was defined as the systematic reduction or elimination of potentially harmful NSAID prescribing or use, or the modification of some aspect of NSAID prescribing or use to improve safety and/or reduce risk of harm (e.g., taking proton pump inhibitors in combination with NSAIDs).

Patient populations of focus were limited to adults ≥18 years of age and with any medical condition.

Search Strategy

With the guidance of a professional librarian, we searched PubMed, CINAHL, Embase, Cochrane Central, Google Scholar and Google for [intervention OR program OR related MESH terms] + [de-implement OR deprescribe OR reduce OR related MESH term] + [nonsteroidal anti-inflammatory drug OR NSAID OR related MESH term] in Spring 2022 (full search strategy appears in **Supplementary File 2**). Studies were limited to articles or abstracts published between 2000 and 2022. Only studies written in or translated into English were included.

Studies identified in the search were uploaded as abstracts to Covidence (Melbourne, Australia), an online systematic review management platform. Duplicate studies were auto-identified by Covidence and deleted. Two members of the research team (MR and MA) independently

screened all abstracts for inclusion in the review. Discrepancies were resolved by conference with a third team member (JE). Studies that passed the screening stage were moved to full text review. Three members of the research team (MR, MA, and ES) independently reviewed all full-text studies for alignment with eligibility criteria and reviewed reference lists for additional studies. Discrepancies were resolved via conference among the three reviewers.

Since the initial search identified some studies that focused on NSAIDs as one of multiple medications addressed in de-implementation or deprescribing interventions, we performed a second PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar search for systematic and scoping review articles related to medication de-implementation or deprescribing published between 2000 and 2022. Abstracts identified in the search were reviewed by the lead author (MR) to eliminate reviews that did not meet inclusion criteria. Each review article was independently searched by two team members (EO and JT) for studies that included NSAIDs and met all other inclusion criteria. Discrepancies were resolved via conference among the two reviewers.

Data Extraction

Studies that passed full-text review were moved to the charting/data extraction phase. Using the Covidence extraction framework, data were independently extracted by two team members (MA and ES). Two additional team members (MR and EO) downloaded the extracted data table from Covidence, independently checked a 25% data sample for accuracy, and resolved discrepancies by consensus.

The following data were extracted for each study: publication year, country, study design, intervention setting, type of intervention (de-implementation approach), intervention participants (e.g., physicians, pharmacists, patients), NSAIDs involved in intervention (prescription and/or OTC; classes and/or specific medications), and focus patient population. We also documented the effectiveness of the intervention in de-implementing NSAIDs (yes, no, or no change) and any patient-focused outcomes evaluated in relation to the intervention. Extracted data were integrated and synthesized into tables and figures based on data extraction elements listed above. The research team collectively appraised results to summarize the identified interventions and identify gaps in the literature.

RESULTS

The original search identified 7,720 studies from which 60 were included in the final review. The secondary systematic and scoping review search identified 98 articles from which eight additional papers were included in the final review. **Figure 1** details the flow of articles through identification and screening stages and **Supplementary File 3** shows all articles included in the final review (n= 68).

Characteristics of Studies

A total of 27 (39.7%) of studies were published between 2000 and 2010, with the remaining published between 2011 and 2022. The majority of studies took place in a European country (45.6%) or the United States (35.3%) (**Supplementary File 3**). A variety of study designs were represented, with randomized controlled trial (RCT) being the most common (55.9%) and prospective, interventional trials also frequently used (23.5%).

Characteristics of Interventions

Most interventions were delivered to clinicians (i.e., clinician-facing) (76.5%) **(Supplementary File 3a)**, although some were patient-facing (8.8%) **(Supplementary File 3b)** and some were both clinician and patient-facing (10.3%) **(Supplementary File 3c)**. Of the clinician-facing and both clinician and patient-facing interventions, primary care or general practice physicians were the most frequent focus (72.6%), with pharmacists, nurses, and physicians in sub-specialty settings the focus of the remaining interventions. Both single component (54.4%) and multi-component (45.6%) interventions were employed. The most common intervention approach, represented in more than half of studies, was academic detailing and/or clinician education (**Figure 2**). Interventions focused on the electronic medical record (EMR) and/or clinical decision support were common among single component interventions, while clinician performance reports or audit/feedback and medication review by a pharmacist were common among multi-component interventions (**Figure 2**).

Some interventions focused solely on NSAIDs, while 26 (59.1%) focused on de-implementation of other medications as well. For example, the EQUiPPED trial[45] aimed to reduce prescribing of multiple potentially harmful medications to older adults in the emergency department, while the study reported by Dreishulte et al.[46] focused on de-implementation of high-risk NSAIDs and antiplatelet agents in primary care. Most interventions (85.2%) aimed to de-implement all types of NSAIDS, although some (14.8%) targeted reduction of a single type or class of NSAIDs.

Interventions largely focused on prescription NSAIDs, with only 7.4% of interventions aimed to reduce potentially harmful OTC NSAIDs. All studies focused on oral NSAIDs; topical NSAIDs were not addressed in any interventions.

More than half of interventions (55.8%) aimed to de-implement NSAIDs classified as high-risk based on patient age (generally ≥65 or 70 years), with BEERS, START, and STOPP criteria frequently referenced (**Table 2**).[47] The de-implementation of potentially harmful NSAIDs among patients with gastrointestinal conditions (e.g., peptic ulcer disease, inflammatory bowel disease) or who were taking chronic NSAIDs without gastroprotective medication (e.g., proton-pump inhibitor) and kidney disease was also common (47.1% and 38.2%, respectively) (**Table 2**).

Most interventions (76.2%) were effective in reducing use of high-risk NSAIDs **(Supplementary File 3)**. Very few studies (5.9%) evaluated patients' level of pain or quality of life following discontinuation of NSAIDs. Over half of studies (51.5%) assessed other patient-focused outcomes associated with the interventions, including patient-rated quality of interaction with clinician,[48] occurrence of falls,[49] and emergency department admissions.[46]

Table 2. Criteria by which the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) was Classified as High-Risk or Potentially Harmful by Included Studies

High-risk or potentially harmful due to:	Number of Studies (%)
Age (generally >65 or 70 years)	38 (55.9)
Existing gastrointestinal conditions or lack of gastroprotective medication	32 (47.1)
Kidney disease	26 (38.2)
Cardiovascular disease or heart failure	22 (32.3)
Hypertension	19 (27.9)
Potential for medication interaction	16 (23.5)
Lower risk alternative available	10 (14.7)
Contribution to polypharmacy	7.0 (10.3)
Chronic or long-term use	6.0 (8.8)
Use of multiple medications containing NSAIDs	4.0 (5.9)

NSAIDs: nonsteroidal ant-inflammatory drugs

DISCUSSION

Although many professional organizations and societies recommend limiting or avoiding the use of NSAIDs in high-risk patients, potentially harmful prescribing and OTC use persists at undesirable rates.[15–18] This scoping review identified more than 50 studies (approximately three quarters of those reviewed) published between 2000 and 2022 that describe healthcare-based interventions effective in de-implementing potentially harmful NSAIDs. Future research should prioritize methods to adapt, scale, and disseminate these effective interventions. Such efforts stand to improve medication safety for older adults and patients with chronic conditions and other risk factors.

The interventions we reviewed spanned more than 20 years. During this time, there was a great deal of evolution in the NSAID market, in the scientific evidence related to the comparative effectiveness and safety of various NSAIDs and other analgesics, and in professional recommendations, clinical practice patterns, and regulatory policy related to NSAIDs prescribing. As such, iterative and rapid adaptations to the context, setting, and resources available are crucial to preserve internal validity and ensure the effectiveness of interventions. In addition to informed adaptation and implementation approaches, the science of de-implementation continues to evolve.[50–52] Theories, frameworks, and models for de-implementation can complement and enhance the effective interventions we reviewed, the majority of which did not report being informed by any sort of implementation or de-implementation model.

Since the interventions described in this review varied widely in terms of de-implementation approaches employed, high-risk conditions addressed, populations of interests, and NSAIDs of focus, it is difficult to directly compare studies. However, it is notable that both single and multi-component interventions were both effective in de-implementing NSAIDs, which is inconsistent with the literature for many other low-value services.[53] In several cases, interventions involving low-cost, low-burden approaches (e.g., one-time education session, online training modules, pamphlets) were associated with the same reduction in NSAIDs utilization as much more elaborate and costly approaches (e.g., pharmacist medication review, individual patient counseling, EMR workflow modification). A better understanding of intervention approaches and factors associated with effective de-implementation in different settings and for various high-risk scenarios would provide valuable insight to future efforts to improve NSAIDs safety.

We observed four additional important gaps in the literature related to NSAIDs de-implementation in healthcare settings. First, patient-facing interventions were infrequently employed. Direct engagement with patients can enhance outcomes of deprescribing and other health services interventions,[54–56] and may be especially germane to the de-implementation of OTC NSAIDs, which were barely addressed by interventions studied. Second, outcomes important to patients were inconsistently assessed in the studies reviewed. Despite some evidence that patient satisfaction and trust are not adversely impacted by low-value care de-implementation,[57,58] clinicians continue to cite concern about patient response as a predominant de-implementation barrier.[24,59–61] In addition to evaluating patient-focused outcomes, future studies should explore unintended consequences of the interventions. Of the minority of studies that evaluated adverse events or changes in pain following NSAIDs de-implementation, none showed increases in adverse event or pain outcomes.[62–66] In fact, one study reported lower pain levels among older adults who reduced NSAIDs as part of a pharmacist review program.[62] Finally, although the reviewed interventions varied in duration, sustainability of the observed effects beyond the conclusion of active interventions was infrequently evaluated.

This study has some limitations. Our initial search strategy did not consistently identify studies that focused on general healthcare deprescribing or interventions to reduce multiple medications. To incorporate these studies into our review, we added a supplemental secondary database search which was effective in identifying additional applicable studies. Additionally, our data extraction plan did not capture whether interventions focused on reducing new prescriptions for (or OTC use of) potentially harmful NSAIDs vs. reducing refills for ongoing inappropriate NSAIDs, which could be important to informing future interventions. Last, as a scoping review, we did not formally evaluate the quality of the studies reviewed.

CONCLUSION

This scoping review identified 68 interventions to de-implement potentially harmful NSAIDs published internationally from 2000 to 2022. Over three-quarters of the interventions were effective in reducing NSAIDs utilization. These interventions classified NSAID use/prescribing as high-risk for multiple reasons, employed a variety of de-implementation approaches, and took place in several different healthcare settings. Patient-facing interventions were under-represented and only two interventions included OTC NSAIDs. Few studies evaluated the sustainability of intervention outcomes or unintended consequences of interventions. Considering the large

number and diversity of effective interventions on record, future efforts should prioritize the adaptation, scaling, and dissemination initiatives to de-implement high-risk NSAIDs and enhance medication safety for older adults and patients with chronic conditions.

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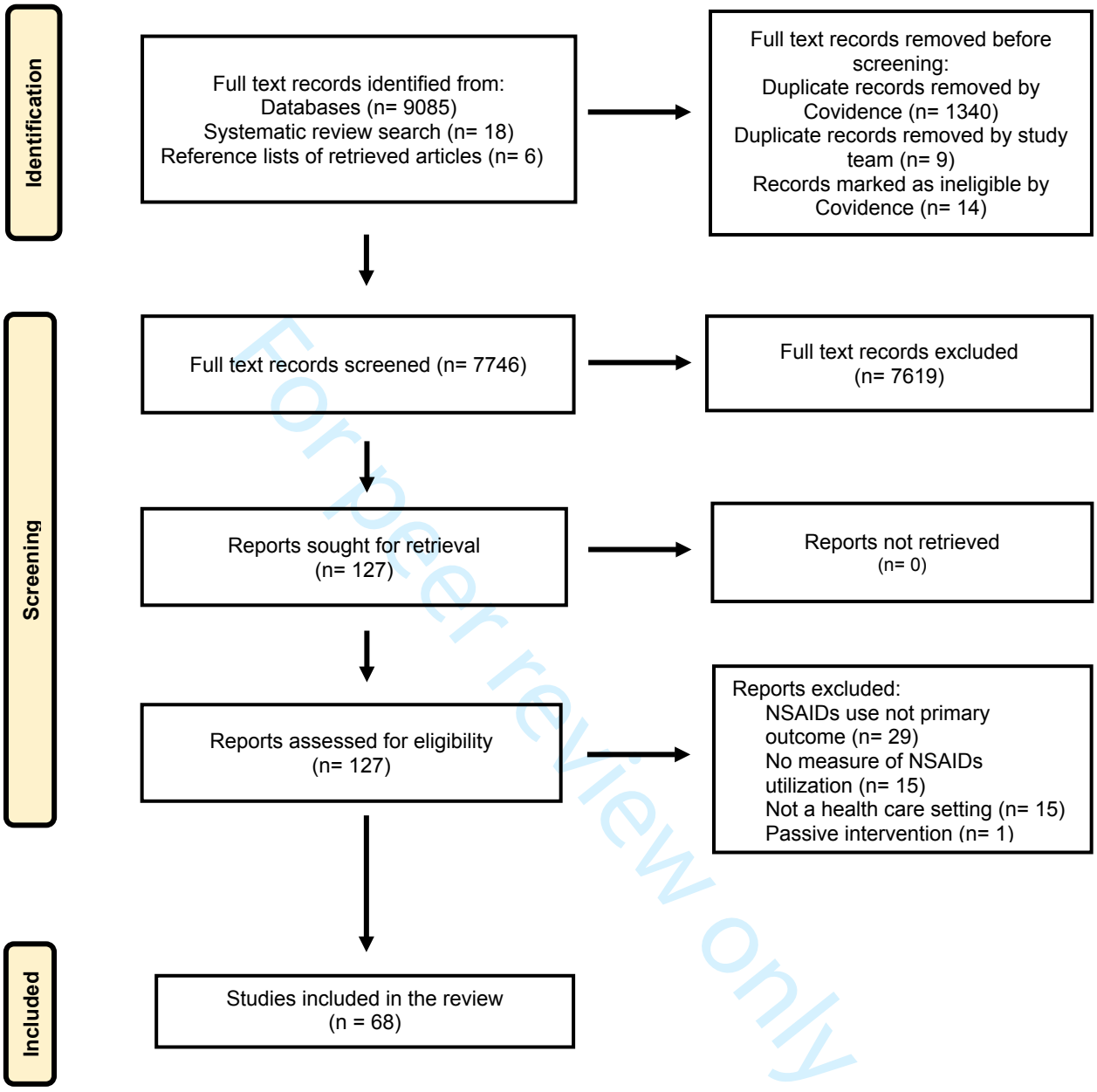

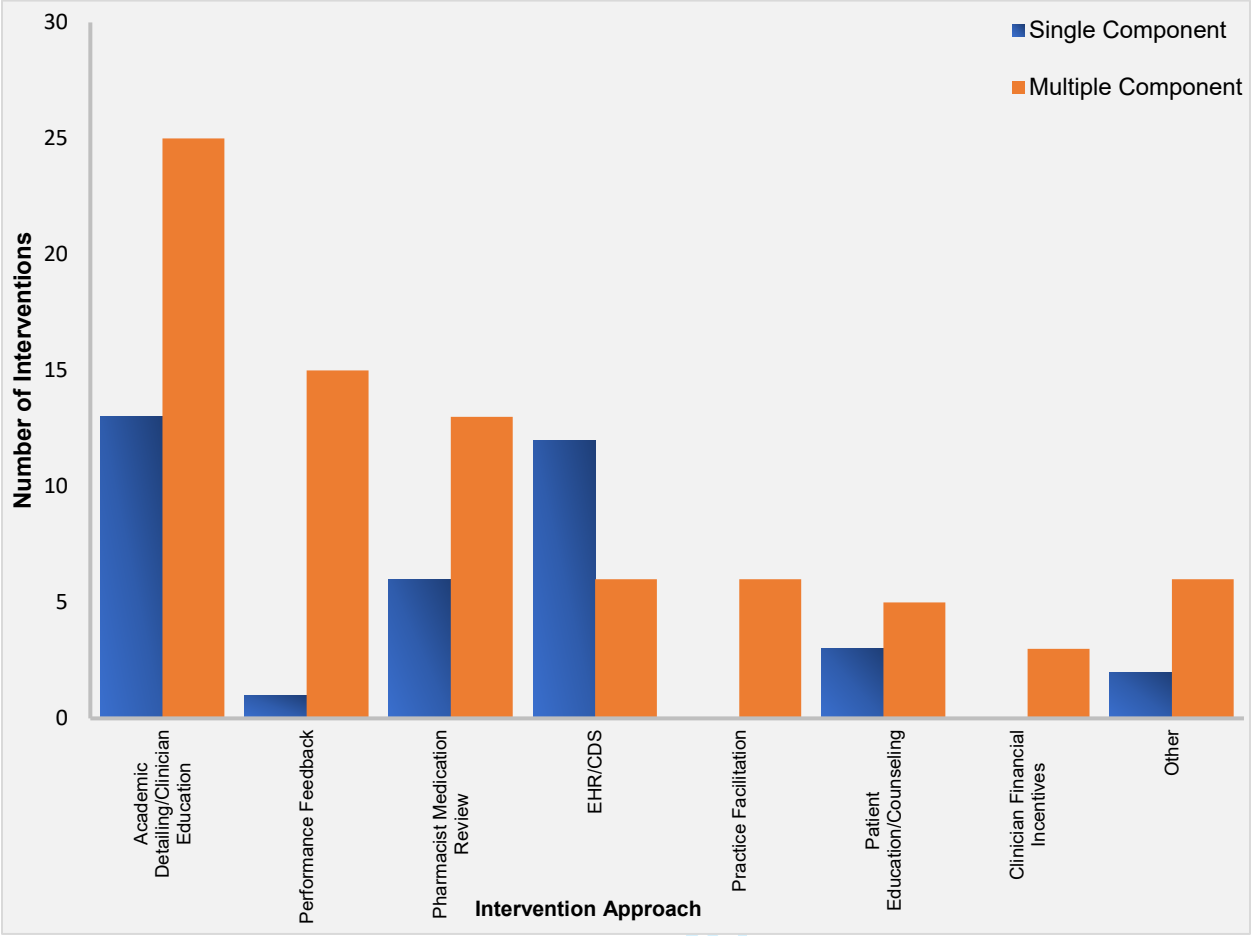

Supplementary File 1. Sample Recommendations and Prescribing Notes from Professional Medical Societies and Organizations Related to Potentially Harmful NSAIDS

Organization	Recommendation Year	Recommendation
American Association of Family Physicians (AAFP).[1]	2009	• When possible, NSAIDs should be avoided in persons with preexisting renal disease, congestive heart failure, or cirrhosis. • Consider monitoring serum creatinine levels after initiation of NSAID therapy in persons at risk of renal failure, and in those taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. • NSAIDs and aspirin should be avoided in persons taking anticoagulants. If concurrent NSAID and anticoagulant use is necessary, an increase in INR should be anticipated. There should be appropriate INR monitoring and warfarin (Coumadin) dosage adjustments, and GI prophylaxis should be initiated. • Asthma could be induced or worsened as a result of taking NSAIDs. • Ibuprofen, indomethacin, and naproxen (Naprosyn) are safe to use in breastfeeding women.
American Geriatric Society Beer's Criteria.[2]	2023	In older adults: • Avoid chronic use of NSAIDs unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol). • Avoid short-term scheduled use in combination with corticosteroids, anticoagulants, or antiplatelet agents unless other alternatives are not effective and the patient can take a gastroprotective agent. • Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: Dronedarone, NSAIDs and COX-2 inhibitors. • In patients with kidney disease and Cr/Cl <30ml/min, avoid NSAIDs (non-selective, COX-2 selective, and nonacetylated salicylates, oral and parenteral) may increase the risk of acute kidney injury and a further decline in kidney function
American Heart Association (AHA).[3]	2007	• NSAIDs should be taken at lowest effective dosage for the shortest duration possible to reduce cardiovascular risk. • COX inhibitors carry the highest cardiovascular risk and thus, naproxen is recommended as the drug of choice for patients with cardiovascular risk.
American Society of Nephrology (ASN)/ Choosing Wisely.[4]	2012	• Avoid NSAIDs in individuals with hypertension or heart failure or CKD of all causes, including diabetes.
Arthritis Society of Canada.[5]	2022	• Do not use NSAIDs before, during or after heart surgery (bypass surgery). • Patients with a history of cardiovascular disease should be careful using NSAIDs.

		• Patients with risk factors for cardiovascular disease (e.g., diabetes, smoking, elevated cholesterol, obesity and family history) should also be careful using NSAIDs. Safer alternative treatments should be used if available. • NSAIDs should be used in the lowest effective dose for the shortest possible duration of time.
Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee, Asia-Pacific Experts on Topical Analgesics Advisory Board.[6,7]	2018, 2022	• Best available evidence indicates that topical NSAIDs have a moderate effect on relief of osteoarthritic pain, comparable to that of oral NSAIDs but with a better risk-to-benefit ratio. International clinical practice guidelines recommend topical NSAIDs on par with or ahead of oral NSAIDs for pain management in patients with osteoarthritis, and as the first-line choice in persons aged ≥75 years.
European Alliance of Associations for Rheumatology (EULAR).[8]	2021	• NSAIDs, at the lowest effective dose, should be added or substituted in patients who respond inadequately to paracetamol. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor, should be used.
Health Canada.[9]	2021	• Advises pregnant women to not use NSAIDs from 20 to 28 weeks of pregnancy, unless advised by a health care professional, due to risk of kidney damage and low amniotic fluid. • NSAIDs are contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition.
Kidney Disease Improving Global Outcomes (KDIGO).[10]	2012	• Avoid NSAIDs in people with GFR <30 ml/min/1.73 m^2. • Prolonged NSAID therapy is not recommended in people with GFR <60 ml/min/1.73 m^2. • NSAIDs should not be used in people taking lithium. • Avoid NSAIDs in people taking RAAS blocking agents.
Medicines and Health care Projects Regulatory Agency (MHRA) (UK). [11,12]	2009, 2015	• Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible - if NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms - the renal function of such patients should be carefully monitored during NSAID treatment. • It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs
National Institute for Health and Care Excellence (NICE).[13]	2013	• NSAIDs should be prescribed with caution as courses of just a few days, even at doses within prescribing recommendations, can be associated with serious adverse effects in susceptible patients. • In primary care, paracetamol is recommended in preference to NSAIDs, where appropriate. If a patient is likely to benefit from NSAID treatment naproxen or ibuprofen are recommended first-line, at the lowest effective dose, for the shortest

		possible time. Patients taking NSAIDs who are at increased risk of complications require regular monitoring.
NHS Clinical guideline.[14]	2019	• Avoid NSAIDs in in severe cardiac failure, hepatic failure, and active peptic ulcer disease. • Concomitant use of NSAIDs and other nephrotoxic (e.g., ACE Inhibitors, Angiotensin Receptor Blockers, lithium, and diuretics) should be avoided where possible to prevent the risk of acute kidney injury. • Use caution with NSAIDs in the elderly and with cardiac insufficiency and mild renal impairment. • Avoid combinations of NSAIDs. • Alcohol consumption and cigarette smoking are modifiable lifestyle risk factors for serious NSAID-induced gastrointestinal adverse effects.
North American Spine Society (NASS).[15]	2020	• Non-selective NSAIDs are suggested for the treatment of low back pain. • There is insufficient evidence to make a recommendation for or against the use of selective NSAIDs for the treatment of low back pain.
Society of Hospital Pharmacists of Australia (SHPA).[16]	2018	• NSAIDs should be avoided before any surgery where postoperative bleeding would be of concern. • COX-2 selective NSAIDs may be used preoperatively as they have limited effect on platelet function.
STOPP/START Criteria.[17]	2023	The following prescriptions are potentially inappropriate to use in patients aged 65 years and older: • Long-term systemic i.e., non-topical NSAIDs with known history of coronary, cerebral or peripheral vascular disease (increased risk of thrombosis). • NSAIDs or systemic corticosteroids with heart failure requiring loop diuretic therapy (risk of exacerbation of heart failure). • Long-term aspirin at doses greater than 100mg per day (increased risk of bleeding, no evidence for increased efficacy). • NSAIDs and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding). • NSAIDs if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function). • NSAIDs other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).

		• NSAIDs with severe hypertension i.e., systolic blood pressure consistently above 170 mmHg and/or diastolic blood pressure consistently above 100 mmHg (risk of exacerbation of hypertension). • Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief and safer). • Long-term NSAID or colchicine (>3 months) for prophylactic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor. • NSAID with concurrent corticosteroids for treatment of arthritis/rheumatism of any kind (increased risk of peptic ulcer disease).

ACE: angiotensin-converting enzyme, CKD: chronic kidney disease, COX: cyclooxygenase, eGFR/GFR: estimated glomerular filtration rate/glomerular filtration rate, H2: histamine 2-receptor, GI: gastrointestinal, INR: international normalization ratio, NSAIDs: nonsteroidal ant-inflammatory drugs, PPI: proton pump inhibitors, PRN: pro re nata, RAAS: renin–angiotensin–aldosterone system.

Supplementary File 2. Terms Used in Literature Search

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS	DE-IMPLEMENTATION	INTERVENTION
Acetylsalicylic acid	Cease, ceasing, ceased	Academic detailing
Advil	Decrease, decreasing. decreased	Audit and feedback
Aleve	De-escalate, de-escalating, decreased, de-escalation	Clinical decision support
Anti-inflammatory	De-implement, de-implementing, de-implemented, de-implementation	CME
Anti-inflammatory agent	Deimplement, deimplementing, deimplementation, deimplementation	Continuing medical education
Aspirin	Deprescribe, deprescribing	Counseling
Bextra	Discontinue, discontinuing, discontinued, discontinuation	Education
Celebrex	Mitigate, mitigating, mitigated, mitigation	Inappropriate prescribing
Celocoxib	Phase out, phasing out, phased out	Initiative
Daypro	Reduce, reducing, reduced, reduction	Intervention
Diclofenac	Remove, removing, removed, removal	Measure
Etodolac	Stop, stopping, stopped	Medication review
Etoricoxib	Taper, taper off, tapering, tapered	Pharmacist counseling
Fenoprofen	Terminate, terminating, terminated, termination	Pharmacist review
Flurbiprofen	Withdraw, withdrawing, withdrawn, withdrawal	Program
Ibuprofen		Strategy
Indocin		Electronic medical record tool
Indomethacin		Electronic medical record strategy
Ketoprofen		EMR tool
Ketorolac		EMR strategy
Lodine		Electronic health record tool
Mefanamic acid		Electronic health record strategy
Meloxicam		EHR tool
Motrin		EHR strategy
Nabumetone		Financial incentive
Nalfon		Performance feedback
Naproxen		Performance improvement
Non-opiate		Performance incentive
Non-opioid		Performance report
Nonsteroidal anti-inflammatory drugs		Practice coaching
Nonsteroidal anti-inflammatory medication		Practice facilitation
NSAID		Quality
Oxaprozin		Quality improvement
Piroxicam		Safety
Ponstel		
Relafen		
Rovecoxib		
Salicylic acid		
Steroidal, non		
Sulindac		
Toradol		
Valdecoxib		
Vioxx		
Voltaren		

Supplementary File 3. Articles Included in the Final Review (n=68)

Supplementary File 3a. Clinician Facing Interventions (n=55)					
Study title	**Author (Year)**	**Country**	**Health care setting**	**Type of intervention**	**Intervention reduced NSAIDs use?**
• A pharmacist-led information technology intervention for medication errors (PINCER): a multicenter, cluster-randomized, controlled trial and cost-effectiveness analysis.[18]	Avery (2012)	United Kingdom	General Practice/ Primary Care	Pharmacist-led information technology intervention composed of clinician education, feedback, and dedicated support	Yes
• CURATA: A patient health management program for the treatment of osteoarthritis in Québec: An integrated approach to improving the appropriate utilization of anti-inflammatory/analgesic medications.[19]	Beaulieu (2004)	Canada	General Practice/ Primary Care	Clinician education workshop	Yes
• Evidence-based educational outreach visits: Effects on prescriptions of non-steroidal anti-inflammatory drugs.[20]	Bernal-Delgardo (2002)	Spain	General Practice/ Primary Care	Academic detailing	Yes
• Improving ambulatory prescribing safety with a handheld decision support system: A randomized controlled trial.[21]	Berner (2006)	United States	General Practice/ Primary Care	A personal digital assistant (PDA)–based clinical decision support system	Yes
• Influencing NSAID prescribing in primary care using different feedback strategies.[22]	Braybrook (2000)	United Kingdom	General Practice/ Primary Care	Clinician education, active or passive practice-specific prescribing feedback, and prescribing workbook	Yes
• The implementation of academic detailing and its effectiveness on appropriate prescribing of pain relief medication: A real-world cluster randomized trial in Belgian General Practice/ Primary Care.[23]	Bruyndonck (2018)	Belgium	General Practice/ Primary Care	Academic detailing	Yes
• A group randomized trial to improve safe use of nonsteroidal anti-inflammatory drugs.[24]	Curtis (2005)	United States	Managed Care Organization	Continuing medical education and audit & feedback with peer-derived benchmarks	No
• Safer prescribing — A trial of education, informatics, and financial incentives.[25]	Dreischulte (2016)	Scotland	General Practice/ Primary Care	Clinician education, computerized clinical decision support, and financial incentives to practices to review patients' charts for appropriateness of NSAIDs use	Yes
• Academic detailing as a method of continuing medical education.[26]	Dyrkorn (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A large-scale initiative to improve NSAID prescribing safety.[27]	Eskildsen (2017)	New Zealand	General Practice/ Primary Care	Practice facilitation including academic detailing, workflow coaching, performance feedback,	Yes

				and other safe prescribing resources	
• Computerized clinical decision support during medication ordering for long-term care residents with renal insufficiency.[28]	Field (2009)	Canada	Long-term Care Facility	Computerized clinical decision support system alerts	Yes
• One-to-one versus group sessions to improve prescription in primary care: A pragmatic randomized controlled trial.[29]	Figueiras (2001)	Spain	General Practice/ Primary Care	One-on-one and group clinician education and reminders	Yes
• Prevention of potentially inappropriate prescribing for elderly patients: A randomized controlled trial using STOPP/START criteria.[30]	Gallagher (2011)	Ireland	Inpatient Care	Screening by pharmacist using STOPP/START criteria and follow-up visit with primary care	Yes
• Impact of EHR-based clinical decision support on adherence to guidelines for patients on NSAIDs: A randomized controlled trial.[31]	Gill (2011)	United States	General Practice/ Primary Care	EHR-based clinical decision support alerts for high-risk patients	Yes
• Effect of an academic detailing intervention on the utilization rate of cyclooxygenase-2 inhibitors in the elderly.[32]	Graham (2008)	Canada	Tertiary Medical Center	Academic detailing	Yes
• Guided medication dosing for elderly emergency patients using real-time, computerized decision support.[33]	Griffey (2012)	United States	Tertiary Medical Center	Computerized decision support tool	Yes
• Data feedback and behavioral change intervention to improve primary care prescribing safety (EFIPPS): Multicenter, three-arm, cluster randomized controlled trial.[34]	Guthrie (2016)	Scotland	General Practice/ Primary Care	Emailed educational material with support for identifying high-risk patients or feedback on high-risk prescribing, with or without a behavioral change component	Yes
• A physician-focused intervention to reduce potentially inappropriate medication prescribing in older people.[35]	Keith (2013)	Italy	General Practice/ Primary Care	Academic detailing, alternative drug list for potentially avoidable medications, prescribing reviews	Yes
• Reducing inappropriate non-steroidal anti-inflammatory prescription in primary care patients with chronic kidney disease.[36]	Keohane (2017)	Ireland	General Practice/ Primary Care	Automated EHR alert	Yes
• Toward safer prescribing: Evaluation of a prospective drug utilization review system on inappropriate prescriptions, prescribing patterns, and adverse drug events and related health expenditure in South Korea.[37]	Kim (2018)	South Korea	General Practice/Primary Care	Drug utilization review system	No
• The prevalence of 'triple whammy' prescriptions in surgical inpatients and associated pharmacist recommendations.[38]	Koeck (2021)	Germany	Inpatient Surgical Wards	Pharmacist medication review	Yes
• Pharmacist-led medication review in patients over 65: A randomized, controlled trial in primary care.[39]	Krska (2001)	Scotland	General Practice/ Primary Care	Pharmacist medication review	Yes

• Interdisciplinary geriatric and psychiatric care reduces potentially inappropriate prescribing in the hospital: Interventional study in 150 acutely Ill elderly patients with mental and somatic comorbid conditions.[40]	Lang (2012)	Switzerland	Inpatient Medical-Psychiatric Unit	Integrated care (a daily collaboration between a geriatrician and a psychiatrist providing interdisciplinary health care management)	No
• Effectiveness of an academic detailing intervention in Primary Care on the prescribing of non-steroidal anti-inflammatory drugs.[41]	Langaas (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients.[42]	Lenander (2017)	Sweden	General Practice/ Primary Care	Clinician self-assessment, peer review & feedback and written change agreements	Yes
• Evaluation of a complex intervention to improve primary care prescribing: A phase IV segmented regression interrupted time series analysis.[43]	MacBride-Stewart (2017)	Scotland	General Practice/ Primary Care	Clinician education, performance feedback, pharmacist support, and financial incentives	Yes
• Improving medication use in newly admitted home health care patients: A randomized controlled trial.[44]	Meredith (2002)	United States	Home Health Care	Medication improvement program (pharmacist consultations with home health nurses)	No
• Leveraging practice-based research networks to accelerate implementation and diffusion of chronic kidney disease guidelines in primary care practices: A prospective cohort study.[45]	Mold (2014)	United States	General Practice/ Primary Care	Practice facilitation including academic detailing and performance feedback	Yes
• Improving quality of NSAID prescribing by internal medicine trainees with an educational intervention.[46]	Naughton (2010)	United States	Ambulatory Care Internal Medicine	Clinician education program, local practice data & consensus conferences, polypharmacy journals, and audit & feedback	Yes
• Can a practice pharmacist improve prescribing safety and reduce costs in polypharmacy patients? A pilot study of an intervention in an Irish general practice setting.[47]	Ó Ciardha (2022)	Ireland	General Practice/ Primary Care	Pharmacist conducting holistic medication reviews in the study group over a 6 month period.	Yes
• Effectiveness of educational outreach visits compared with usual guideline dissemination to improve family physician prescribing—an 18-month open cluster-randomized trial.[48]	Pinto (2018)	Portugal	General Practice/ Primary Care	Clinician education outreach visits or online resources	No
• A quality use of medicines program for general practitioners and older people: A cluster randomized controlled trial.[49]	Pit (2007)	Australia	General Practice/ Primary Care	Academic detailing, medication risk assessment, performance feedback, and financial incentives	Yes
• Education to reduce potentially harmful medication use among residents of assisted living facilities: A randomized controlled trial.[50]	Pitkala (2014)	Finland	Assisted Living Facilities	Nurse education and training	Yes
• Reporting of estimated glomerular filtration rate: Effect on physician recognition of chronic	Quartarolo (2007)	United States	Inpatient Care	GFR reporting	No

kidney disease and prescribing practices for elderly hospitalized patients.[51]					
• Randomized trial to improve prescribing safety in ambulatory elderly patients.[52]	Raebel (2007)	United States	Health Maintenance Organization.	Medication prescribing alerts	No
• Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population.[53]	Rahme (2005)	Canada	General Practice/ Primary Care	Clinician education workshop and prescribing decision tree	Yes
• Clinically important drug-drug interactions in poly-treated elderly outpatients: A campaign to improve appropriateness in general practice.[54]	Raschi (2015)	Italy	General Practice/ Primary Care	Academic detailing	Yes
• Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: A randomized controlled trial.[55]	Ray (2001)	United States	Community Health Care	Clinician education program	Yes
• Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes.[56]	Roberts (2001)	Australia	Long-term Care Facility	Clinical pharmacy interventions in nursing homes, relationship building, nurse education, and medication reviews	Yes
• Potentially inappropriate prescribing to older patients: Criteria, prevalence, and an intervention to reduce It: The prescription peer academic detailing (Rx-PAD) study – A cluster-randomized, educational intervention in Norwegian general practice.[57]	Rognstad (2018)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A multifactorial intervention to lower potentially inappropriate medication use in older adults in Argentina.[58]	Schapira (2021)	Argentina	General Practice/Primary Care	Clinician education workshops, deprescribing algorithms, and email alerts	Yes
• Computerized prescribing alerts and group academic detailing to reduce the use of potentially inappropriate medications in older people.[59]	Simon (2006)	United States	General Practice/ Primary Care	Academic detailing and computerized alerts	No
• Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: A randomized controlled trial.[60]	Stein (2001)	United States	Long-term Care Facility	Clinician education	Yes
• Enhancing Quality of Provider Practices for Older Adults in the Emergency Department (EQUiPPED).[61]	Stevens (2017)	United States	Emergency Department	Clinician education, clinical decision support, individual performance feedback	Yes
• Randomized clinical trial of a customized electronic alert requiring an affirmative response compared to a control group receiving a commercial passive CPOE alert:	Strom (2010)	United States	Inpatient Care	EHR alerts	No

NSAID—warfarin co-prescribing as a test case.[62]					
• The medical office of the 21st Century (MOXXI): Effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care.[63]	Tamblyn (2003)	Canada	General Practice/ Primary Care	Computerized clinical decision support	No
• Effectiveness of interventions by community pharmacists to reduce risk of gastrointestinal side effects in nonselective nonsteroidal anti-inflammatory drug users.[64]	Teichert (2014)	Netherlands	Pharmacies	Performance feedback	Yes
• Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: A randomized, controlled trial.[65]	Terrell (2009)	United States	Emergency Department	Computerized clinical decision support	Yes
• Intervention to improve appropriate prescribing and reduce polypharmacy in elderly patients admitted to an internal medicine unit.[66]	Urfer (2016)	Switzerland	Inpatient Care/Internal Medicine Unit	Clinical decision support checklist tool	Yes
• A cluster randomized trial to measure the impact on nonsteroidal anti-inflammatory drug and proton pump inhibitor prescribing in Italy of distributing cost-free paracetamol to osteoarthritic patients.[67]	Vicentini (2019)	Italy	General Practice/ Primary Care	Clinician education	No
• Electronic health record alerts decreased non-steroidal anti-inflammatory drug prescriptions in patients with congestive heart failure: A quality improvement initiative.[68]	Vincent (2020)	United States	Inpatient Care	EHR alerts	Yes
• Guidelines and educational outreach visits from community pharmacists to improve prescribing in general practice: A randomized controlled trial.[69]	Watson (2001)	England	General Practice/ Primary Care	Clinician education plus mailed printed guidelines	No
• Assessment of clinical pharmacy interventions to reduce outpatient use of high-risk medications in the elderly.[70]	Weddle (2017)	United States	General Practice/ Primary Care	Pharmacist medication review and electronic alerts	Yes
• Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function.[71]	Wei (2013)	Scotland	General Practice/ Primary Care	GFR reporting	Yes
• Pharmacist-led provider education on inappropriate NSAID prescribing rates.[72]	Whitner (2020)	United States	General Practice/ Primary Care	Academic detailing	Yes
Supplementary File 3b. Patient Facing Interventions (n=6)					
• Pharmacist counseling and the use of nonsteroidal anti-inflammatory drugs by older adults.[73]	Bear (2017)	United States	General Practice/ Primary Care	Counseling from pharmacist	Yes

• A nurse-delivered advice intervention can reduce chronic non-steroidal anti-inflammatory drug use in general practice: A randomized controlled trial.[74]	Jones (2002)	United Kingdom	General Practice/ Primary Care	Advice and education from nurse	Yes
• Can a nurse-directed intervention reduce the exposure of patients with knee osteoarthritis to nonsteroidal anti-inflammatory drugs?[75]	Mazzuca (2004)	United States	Health Maintenance Organization	Advice and education from nurse about non-pharmacological self-management of osteoarthritis	Yes
• Evaluating the effectiveness of a patient storytelling DVD intervention to encourage patient-physician communication about nonsteroidal anti-inflammatory drug (NSAID) use.[76]	Miller (2016)	United States	General Practice/ Primary Care	Video modeling patient-physician communication about NSAID use	No
• Effect of mobile device-assisted N-of-1 trial participation on analgesic prescribing for chronic pain: Randomized controlled trial.[77]	Odineal (2020)	United States	General Practice/ Primary Care	Mobile educational app	Yes
• Evaluation of a pharmacist-managed nonsteroidal anti-inflammatory drugs deprescribing program in an integrated health care system.[78]	Rashid (2020)	United States	Integrated Health System	A pharmacist managed NSAID deprescribing program	Yes
Supplementary File 3c. Clinician and Patient-Facing Interventions (n=7)					
• Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling poly-medicated elderly people.[79]	Campins (2017)	Spain	General Practice/ Primary Care	Medication evaluation program	Yes
• Effectiveness of a multifaceted intervention for potentially inappropriate prescribing in older patients in primary care: A cluster-randomized controlled trial (OPTI-SCRIPT Study).[80]	Clyne (2015)	Ireland	General Practice/ Primary Care	Academic detailing, pharmacist medicine review, and tailored patient information leaflets	No
• Pharmacist intervention reduces gastropathy risk in patients using NSAIDs.[81]	Ibanez-Cuevas (2008)	Spain	Pharmacies	Structured interviews with patients and performance feedback reports with clinicians	Yes
• Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: The D-PRESCRIBE randomized clinical trial.[82]	Martin (2018)	Canada	Pharmacies	Pharmacist-generated educational brochure to patients and deprescribing recommendation to physicians	Yes
• Effect of pharmaceutical care services on outcomes for home care patients with heart failure.[83]	Triller (2007)	United States	Hospital/ Home Health care	Pharmacist in-home medication review with patients and feedback/recommendations to clinicians	No
• Safer Prescribing and Care for the Elderly (SPACE): A pilot study in general practice.[84]	Wallis (2018)	New Zealand	General Practice/ Primary Care	Academic detailing, audit & feedback, and educational mailings to patients	Yes

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• NSAID use after bariatric surgery: A randomized controlled intervention study.[85]	Yska (2016)	Netherlands	Inpatient Surgical Health Care	Mailings to patients and their general practitioners on the risks of NSAIDs after bariatric surgery	No

CPOE: commercial computerized provider order entry, EHR: electronic health record, GFR: glomerular filtration rate, NSAIDs: nonsteroidal ant-inflammatory drugs, Rx-PAD: prescription peer academic detailing, STOPP/START: screening tool of older persons' potentially inappropriate prescriptions/Screening tool to alert to right treatment.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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A Scoping Review of Interventions to De-implement Potentially Harmful Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Healthcare Settings

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A Scoping Review of Interventions to De-implement Potentially Harmful Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Healthcare Settings

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ABSTRACT

Objectives: Potentially harmful nonsteroidal anti-inflammatory drugs (NSAIDs) utilization persists at undesirable rates throughout the world. The purpose of this paper is to review the literature on interventions to de-implement potentially harmful NSAIDs in healthcare settings and to suggest directions for future research.

Design: Scoping review

Data Sources: PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar (2000-May 31, 2022).

Study Selection: Studies reporting on the effectiveness of interventions to systematically reduce potentially harmful NSAID utilization in healthcare settings.

Data Extraction: Using Covidence systematic review software, we extracted study and intervention characteristics, including the effectiveness of interventions in reducing NSAID utilization.

Results: From 7,818 articles initially identified, 68 were included in the review. Most studies took place in European countries (45.6%) or the U.S. (35.3%), with randomized controlled trial as the most common design (55.9%). Interventions were largely clinician-facing (76.2%) and delivered in primary care (60.2%), but were rarely (14.9%) guided by an implementation model, framework, or theory Academic detailing, clinical decision support or electronic medical record interventions, performance reports, and pharmacist review were frequent approaches employed. NSAID use was most commonly classified as potentially harmful based on patients' age (55.8%) or history of gastrointestinal disorders (47.1%) or kidney disease (38.2%). Only 7.4% of interventions focused on over-the-counter (OTC) NSAIDs in addition to prescription. The majority of studies (76.2%) reported a reduction in the utilization of potentially harmful NSAIDs. Few studies (5.9%) evaluated pain or quality of life following NSAIDs discontinuation.

Conclusion: Many varied interventions to de-implement potentially harmful NSAIDs have been applied in healthcare settings worldwide. Based on these findings and identified knowledge gaps, further efforts to comprehensively evaluate the effectiveness of interventions and combination of intervention characteristics associated with effective de-implementation are needed. In addition, future efforts should be guided by de-implementation theory, focus on OTC NSAIDs, and incorporate patient-focused strategies and outcomes, including the evaluation of unintended consequences of the intervention.

Key words: deprescribe, medication overuse, safety, low-value care

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review included the 20+ year period during which all currently available NSAID classes were on the market in many countries.
- Interventions focused on only NSAIDs vs. NSAIDs as one of multiple medications were included, but the literature search used to identify the latter was limited to published systematic and scoping reviews.
- As a scoping review, this study did not assess the quality of included studies.
- Aside from broad classifications of interventions as effective or not effective in de-implementing NSAIDs

BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation through inhibition of cyclooxygenase (COX-1 and -2) enzymes, thereby limiting the production of inflammatory prostaglandins (1). Representing 5 to 10% of global medication utilization, NSAIDs are commonly used to treat arthritis and musculoskeletal pain, injuries, headache, and other sources of acute and chronic pain (2). There are six classes of NSAIDs: salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, anthranilic acid derivatives, and selective COX-2 inhibitors (3). NSAIDs are available in prescription and over-the-counter (OTC) strengths, a variety of different formulations, and oral (most common), intravenous, injectable, and topical forms. The use of NSAIDs has risen globally throughout the last twenty years (4–8), in part due to increasing rates of chronic and persistent pain and an increasing aging population.

In addition to anti-inflammatory and analgesic properties, NSAIDs have numerous other physiologic effects, which differ by NSAIDs class. For example, NSAIDs can reduce the integrity of the gastrointestinal mucosal barrier and limit submucosal blood flow, increasing risk of ulceration, hemorrhage, or perforation, particularly among vulnerable individuals; COX-2 selective NSAIDs are associated with lower gastrointestinal risk (1,9). Taking NSAIDs can reduce renal blood flow, alter fluid-electrolyte balance, and increase risk of acute kidney injury (10). Risk for and worsening of hypertension, heart failure, and other cardiovascular issues have also been associated with regular NSAIDs use (10–13). In 2015, the U.S. Food and Drug Administration updated the black box warning on OTC NSAIDS to include, "*NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease…The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID…There is an increased risk of heart failure with NSAID use.*" (14) Medical societies and professional organizations around the world have established recommendations for limiting or avoiding NSAIDs in certain high-risk populations **(Supplementary File 1)**.

Despite numerous long-standing recommendations, potentially harmful NSAIDs prescribing and OTC use persists globally (15–18). As an example, multiple studies show that up to 30% of patients with chronic kidney disease (CKD) are prescribed long-term NSAIDs (19,20). This high-risk use has resulted in a substantial number of adverse events; NSAIDs are a leading cause of drug-related hospitalizations and mortality (21–23). The drivers of potentially harmful NSAIDs prescribing and use are complex and multilevel (24–26). Clinicians' unfamiliarity with professional

recommendations, clinical inertia, limited alternative options for pain management, lack of patient knowledge or understanding, and broad availability of OTC NSAIDs are just some of the factors involved. The evolving regulatory landscape also complicates NSAIDs practice patterns and decision-making (a timeline of major NSAIDs-related regulatory events and other key historical timepoints in the U.S., as an example, is shown in **Table 1**) (27,28).

Further efforts are needed to reduce the potential harm associated with prescription and OTC NSAIDs and promote safer pain management for high-risk patients. The purpose of this paper is to provide an overview of published interventions to de-implement potentially harmful NSAIDs in healthcare settings, to identify knowledge gaps, and to suggest opportunities for subsequent interventions and future research related to NSAIDs de-implementation.

Table 1. Timeline of Major Regulatory Events and Other Key Historical Timepoints U.S. NSAID History

Year	Event
1900	Aspirin registered in the U.S., available via prescription (29).
1915	Aspirin approved by FDA for over-the-counter distribution (30).
1964-1976	Indomethacin, ibuprofen, diclofenac, ketoprofen, and naproxen approved by the FDA (31,32).
1971	John Vane discovered the mechanism of action of aspirin and other NSAIDs (33).
1976	COX enzyme discovered, recognized for role in prostaglandin synthesis (33).
1984	Ibuprofen approved by FDA for over-the-counter distribution (34).
1985	FDA approved aspirin for treatment of acute myocardial infarction and secondary cardiovascular prevention, CDC endorses (35).
1991	Second COX enzyme ("COX-2") discovered, recognized as identical in structure but having important differences in substrate and inhibitor selectivity and in intracellular locations (36).
1999	Celecoxib, the first selective COX-2 inhibitor, available via prescription (37).
2004-2005	Selective COX-2 inhibitors (rofecoxib and valdexocib) withdrawn from the market based on evidence that long-term use increases cardiovascular risk. Celecoxib remained on the market with a black box warning. The warning was also added to the over-the-counter NSAIDs' drug facts label (38).
2007	FDA approved topical diclofenac at the prescription-level (39).
2015	Strengthening of the black box warning over-the-counter NSAIDs' drug facts labels related to risk of heart attack and stroke (14).
2016	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years (B recommendation) (40).

2020	Topical diclofenac approved for over-the-counter distribution (28).
2022	Department of Health and Human Services initiates the Million Hearts Campaign, a national initiative to prevent 1 million heart attacks and strokes within 5 years. It focuses on implementing a set of evidence-based priorities that can improve cardiovascular health (including appropriate aspirin use) (41).
2022	The USPSTF recommends that for adults aged 40 to 50 years with an estimated 10% or greater 10-year cardiovascular disease (CVD) risk: The decision to initiate low-dose aspirin use for the primary prevention of CVD in this group should be an individual one. (C recommendation) (42).

CDC: Centers for Disease Control and Prevention, COX: cyclooxygenase, CRC: colorectal cancer, CVD: cardiovascular disease, FDA: Food and Drug Administration, NSAIDs: nonsteroidal anti-inflammatory drugs, USPSTF: United States Preventive Services Task Force

METHODS

We performed a scoping review of the scientific and gray literature reporting on interventions to de-implement NSAIDs in healthcare settings. Our review was guided by the PRISMA Extension for Scoping Reviews (43). As a scoping review, this review is not eligible for PROSPERO registration, but the protocol was posted at https://osf.io/ywe62/ in January 2022.

Eligibility Criteria

Eligible studies were published in English between January 1, 2000 and May 31, 2022, employed any study design, and evaluated interventions administered with a goal of de-implementing potentially harmful NSAIDs in a healthcare setting. We selected 2000 as the earliest eligibility year since it was the first full year in which selective COX-2 inhibitors were available for use in several countries, including the United States and United Kingdom. Thus, all six NSAIDs classes were available throughout the study period.

Healthcare settings included any outpatient or inpatient healthcare environments within any medical specialty.

NSAIDs included prescription or over-the-counter oral or topical NSAIDs. NSAIDs that are not approved for current use were included if they had been approved at any point during the study period. For example, although rofecoxib and valdecoxib were removed from the U.S. market in 2005, (38) they were included in the literature search. Aspirin taken for cardiovascular disease prophylaxis (<100 mg) was not included since the recommended dose is lower than that commonly used for analgesic purposes. If the purpose of the intervention was to study an inappropriate prophylactic use of aspirin, an exception was made to include that study. To be

included, studies must have reported NSAID prescribing or use rates before and after the intervention, at minimum.

Potentially harmful NSAIDs included those that were prescribed or taken in a manner inconsistent with professional recommendations or otherwise recognized as high-risk by the study authors.

Interventions were defined as "any activity or set of activities aimed at modifying a process, course of action, or sequence of events in order to change one or several of their characteristics such as performance of expected outcome", as described by the World Health Organization (44). Interventions were actively delivered to healthcare clinicians, healthcare teams, or directly to patients. All interventions included in the study involved de-implementation of NSAIDs. Passive interventions such as policy changes were not included.

De-implementation was defined as the systematic reduction or elimination of potentially harmful NSAID prescribing or use, or the modification of some aspect of NSAID prescribing or use to improve safety and/or reduce risk of harm (e.g., taking proton pump inhibitors in combination with NSAIDs).

Patient populations were limited to adults ≥18 years of age. Patients with or without specific medical conditions and of any health status were included.

Search Strategy

With the guidance of a professional librarian, we searched PubMed, CINAHL, Embase, Cochrane Central, Google Scholar and Google for [intervention OR program OR related MESH terms] + [de-implement OR deprescribe OR reduce OR related MESH term] + [nonsteroidal anti-inflammatory drug OR NSAID OR related MESH term] in Spring 2022 (full search strategy appears in **Supplementary File 2**). Studies were limited to articles or abstracts published between January 1, 2000 and May 31, 2022. Only studies written in or translated into English were included.

Studies identified in the search were uploaded as abstracts to Covidence (Melbourne, Australia), an online systematic review management platform. Duplicate studies were auto-identified by

Covidence and deleted. Two members of the research team (MR and MA) independently screened all abstracts for inclusion in the review. Discrepancies were resolved by conference with a third team member (JE). Studies that passed the screening stage were moved to full text review. Three members of the research team (MR, MA, and ES) independently reviewed all full-text studies for alignment with eligibility criteria and reviewed reference lists for additional studies. Discrepancies were resolved via conference among the three reviewers.

Since the reference list review identified some studies that focused on NSAIDs as one of multiple medications addressed in de-implementation or deprescribing interventions that were not captured in our initial search, we performed a second PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar search for systematic and scoping review articles related to medication de-implementation, deprescribing, or polypharmacy interventions published between January 1, 2000 and May 31, 2022. Abstracts identified in the search were reviewed by the lead author (MR) to eliminate reviews that did not meet inclusion criteria. Each review article was independently searched by two team members (EO and JT) for studies that included NSAIDs and met all other inclusion criteria. Discrepancies were resolved via conference among the two reviewers.

Data Extraction

Studies that passed full-text review were moved to the charting/data extraction phase. Using the Covidence extraction framework, data were independently extracted by two team members (MA and ES). Two additional team members (MR and EO) downloaded the extracted data table from Covidence, independently checked a 25% data sample for accuracy, and resolved discrepancies by consensus.

The following data were extracted for each study: publication year, country, study design, intervention setting, type of intervention (de-implementation approach), participants (e.g., physicians, pharmacists, patients), NSAIDs involved in intervention (prescription and/or OTC; classes and/or specific medications), focus patient population, guiding model/framework/theory. Intervention types were categorized as academic detailing/clinician education, clinician financial incentives, EHR/clinical decision support, patient counseling, patient education, performance feedback (a.k.a., audit and feedback), pharmacist medication review, practice facilitation or coaching, or other as informed by the work of Cliff et al (45) and Colla et al (46) and the authors'

knowledge of the literature. During the analysis, we combined patient counseling and patient education since these categories were defined differently across studies, and because of substantial overlap in categories.

We documented the general effectiveness of the intervention in de-implementing NSAIDs (yes, no, or no change) and any patient-focused outcomes evaluated in relation to the intervention. An intervention was scored as 'yes' for effectiveness if any significant ($p<0.05$) improvement in the utilization or prescribing of any NSAID was reported. For multiple-drug interventions, we focused only on NSAIDs results.

Extracted data were integrated and synthesized into tables and figures based on data extraction elements listed above. The research team collectively appraised results to summarize the identified interventions and identify gaps in the literature.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

The original search identified 7,720 studies from which 60 were included in the final review. The secondary systematic and scoping review search identified 98 articles from which eight additional papers were included in the final review. **Figure 1** details the flow of articles through identification and screening stages and **Supplementary File 3** shows all articles included in the final review (n= 68).

Characteristics of Studies

A total of 27 (39.7%) of studies were published between 2000 and 2010, with the remaining published between 2011 and May 31, 2022. The majority of studies took place in a European country (45.6%) or the United States (35.3%) (**Supplementary File 3**). A variety of study designs were represented, with randomized controlled trial (RCT) being the most common (55.9%) and prospective, interventional trials also frequently used (23.5%).

Characteristics of Interventions

A minority of interventions (14.7%) were guided or informed by a specified conceptual theory, model, or framework. Most interventions were delivered to clinicians (i.e., clinician-facing) (76.5%) **(Supplementary File 3a)**, although some were patient-facing (8.8%) **(Supplementary File 3b)** and some were both clinician and patient-facing (10.3%) **(Supplementary File 3c)**. Of the clinician-facing and both clinician and patient-facing interventions, primary care or general practice physicians were the most frequent focus (72.6%), with pharmacists, nurses, and physicians in sub-specialty settings the focus of the remaining interventions. Both single component (54.4%) and multi-component (45.6%) interventions were employed. The most common intervention approach, represented in more than half of studies, was academic detailing and/or clinician education (**Figure 2**). Interventions focused on the electronic health record (EHR) and/or clinical decision support were common among single component interventions, while clinician performance reports or audit/feedback and medication review by a pharmacist were common among multi-component interventions (**Figure 2**).

Some interventions focused solely on NSAIDs, while 26 (38.1%) focused on de-implementation of other medications as well. For example, the EQUiPPED trial (47) aimed to reduce prescribing of multiple potentially harmful medications to older adults in the emergency department, while the study reported by Dreishulte et al.(48) focused on de-implementation of high-risk NSAIDs and antiplatelet agents in primary care. Most interventions (85.2%) aimed to de-implement all types of NSAIDS, although some (14.8%) targeted reduction of a single type or class of NSAIDs. Interventions largely focused on prescription NSAIDs, with only 7.4% of interventions aimed to reduce potentially harmful OTC NSAIDs. All studies focused on oral NSAIDs; topical NSAIDs were not addressed in any interventions.

More than half of interventions (55.8%) aimed to de-implement NSAIDs classified as high-risk based on patient age (generally ≥65 or 70 years), with BEERS, START, and STOPP criteria frequently referenced (**Table 2**) (49). The de-implementation of potentially harmful NSAIDs among patients with gastrointestinal conditions (e.g., peptic ulcer disease, inflammatory bowel disease) or who were taking chronic NSAIDs without gastroprotective medication (e.g., proton-pump inhibitor) and kidney disease was also common (47.1% and 38.2%, respectively) (**Table 2**).

Most interventions (76.2%) were effective in reducing use of high-risk NSAIDs **(Supplementary File 3)**. Very few studies (5.9%) evaluated patients' level of pain or quality of life following discontinuation of NSAIDs. Over half of studies (51.5%) assessed other patient-focused outcomes associated with the interventions, including patient-rated quality of interaction with clinician, (50) occurrence of falls, (51) and emergency department admissions (48).

Table 2. Criteria by which the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) was Classified as High-Risk or Potentially Harmful by Included Studies

High-risk or potentially harmful due to:	Number of Studies (%)
Age (generally >65 or 70 years)	38 (55.9)
Existing gastrointestinal conditions or lack of gastroprotective medication	32 (47.1)
Kidney disease	26 (38.2)
Cardiovascular disease or heart failure	22 (32.3)
Hypertension	19 (27.9)
Potential for medication interaction	16 (23.5)
Lower risk alternative available	10 (14.7)
Contribution to polypharmacy	7.0 (10.3)
Chronic or long-term use	6.0 (8.8)
Use of multiple medications containing NSAIDs	4.0 (5.9)

NSAIDs: nonsteroidal ant-inflammatory drugs

DISCUSSION

Although many professional organizations and societies recommend limiting or avoiding NSAIDs in high-risk patients, potentially harmful prescribing and OTC use persists at undesirable rates (15–18). This scoping review identified 68 studies describing healthcare-based interventions to de-implement potentially harmful NSAIDs published between January 1, 2000 and May 31, 2022. A broad range of intervention types and characteristics were represented, with multi-component, clinician-facing interventions targeting older adult and those with gastrointestinal or renal risk factors in primary care being the most common. This review exposed several knowledge gaps, many of which suggest opportunities for subsequent research, as highlighted below.

Based on the identified research gaps, we have identified several opportunities for future research. First, a more comprehensive analysis of the effectiveness of prior interventions may best inform subsequent interventions to de-implement potentially harmful NSAIDs. The present

review identified interventions reported as effective vs. not effective in reducing potentially harmful NSAIDs, but, as a scoping review with a stated purpose of overviewing the available literature, did not evaluate effect size, degree of effectiveness, or clinical relevance of results. Although identified interventions varied widely in terms of de-implementation approaches employed, high-risk conditions addressed, populations of interests, NSAIDs of focus, and methods for assessing outcomes, our team did attempt to uncover general patterns in the data about interventions reported as effective vs. not effective and those that reported patient-focused outcomes vs. did not. Few clear patterns emerged, but we observed that all but one patient-facing or clinician and patient-facing interventions were effective in reducing NSAID utilization and that, compared with other countries, a greater proportion of studies taking place in the U.S. (34% vs. <20% for other countries) reported on an intervention that was not effective in reducing NSAID utilization. It is unclear to what extent publication bias influenced the reporting of negative outcome interventions, but further efforts to de-implement potentially harmful NSAIDs are needed in the U.S., regardless.

Second, we noted that both single and multi-component interventions were effective in de-implementing NSAIDs, which is inconsistent with some, (45,46) but not all, (52) previous literature for reducing utilization of low-value health services. In several cases, interventions involving low-cost, low-burden approaches (e.g., one-time education session, online training modules, pamphlets) were associated with the same reduction in NSAID utilization as much more elaborate and costly approaches (e.g., pharmacist medication review, individual patient counseling, EHR workflow modification). Further research to identify characteristics of the simplest or most feasible and sustainable interventions is needed, keeping in mind the many contextual variables that influence effectiveness (53) and that the effectiveness of intervention components is not additive (i.e., a greater number of components in a multicomponent intervention is not always better) (45).

Third, some intervention approaches were infrequently tested in comparison to academic detailing and clinician education (most common), performance feedback, pharmacist medication review, and EHR modification. One option warranting further evaluation is practice facilitation, which leverages external facilitators to employ a variety of practice change strategies and tailor interventions to context, Although more commonly used to implement evident into practice rather than de-implement practice that is not supported by the evidence, (54) there are examples of successful practice facilitation de-implementation interventions (55,56). Direct patient education and counseling was effective for some interventions in the present study (57–59) and aligns with

our observation that patient-facing interventions tended to be effective. Engagement with patients can enhance outcomes of deprescribing and other health services interventions, (60–62) and may be especially germane to the de-implementation of OTC NSAIDs, which were barely addressed by interventions studied. Finally, as many real-world efforts to change clinician behavior involve financial incentives (e.g., insurance pay-for-performance), further evaluation of that approach should be pursued. As the lowest proportion of effective interventions occurred in U.S. studies, considering the unique barriers and facilitators to de-implementation within different health systems is important.

Fourth, as there are many scenarios for which long-term NSAID use may be potentially harmful, interventions focused largely on older adults and those with gastrointestinal or renal risk factors. While these are very important populations to target, their findings are not necessarily generalizable to other patient populations. Despite need for de-implementing NSAIDs in patients with cardiovascular disease, heart failure, and hypertension, (10,11) they were the focus of less than one-third of interventions. Additionally, despite evidence that patients may have limited NSAID literacy, (63–66) the issue of duplicate NSAID use was minimally addressed by previous interventions. Thus, moving forward, there are numerous opportunities to focus and tailor de-implementation approaches to the patient populations and contexts where needs exist.

Fifth, outcomes important to patients were inconsistently assessed in the studies reviewed. Despite some evidence that patient satisfaction and trust are not adversely impacted by low-value care de-implementation, (67,68) clinicians continue to cite concern about patient response as a predominant de-implementation barrier (24,69–71). In addition to evaluating patient-focused outcomes, future studies should explore unintended consequences of the interventions. Of the minority of studies that evaluated adverse events or changes in pain following NSAIDs de-implementation, none showed increases in adverse event or pain outcomes (72–76). In fact, one study reported lower pain levels among older adults who reduced NSAIDs as part of a pharmacist review program (72).

Finally, we observed that very few of the identified interventions employed an implementation or de-implementation theory, framework, or model. Although there appeared to be no difference in effectiveness of interventions that did vs. did not use such a theory, framework, or model, their use facilitates thorough exploration of factors that led or did not lead to an effective intervention.

Further, the use of these theories, frameworks, and models can guide successful implementation, adaptation, and dissemination of interventions and should be applied in future efforts (77–79). One excellent example is provided by the intervention reported by Pinto et al. (80) who included their TIDieR checklist (81) in their published manuscript. Future researchers may benefit from categorizing interventions based on the 4R's framework of Norton et al. (82) (did the intervention involve removing, replacing, reducing, or restricting the inappropriate service?).

This study has some limitations. Our initial search strategy did not comprehensively identify studies that focused on interventions to de-implement NSAIDs as one of multiple target medications. To incorporate these studies into our review, we added a supplemental secondary database search that was effective in identifying eight additional applicable studies. Although it is possible that this approach may have missed some multiple medication interventions, the process of reviewing reference lists and numerous systematic or scoping review articles was the best available approach for including as many appropriate studies as possible with the resources available. Future literature searches may benefit from the inclusion of 'polypharmacy' and associated terms. Additionally, our data extraction plan did not capture whether interventions focused on reducing new prescriptions for (or OTC use of) potentially harmful NSAIDs vs. reducing refills for ongoing inappropriate NSAIDs, which could be important to informing future interventions. It is also possible that some authors may have reported data we extracted in separate publications (e.g., implementation or de-implementation theory, framework, or model). Last, as a scoping review, we did not formally evaluate the quality of the studies reviewed.

CONCLUSION

This scoping review identified 68 interventions to de-implement potentially harmful NSAIDs published internationally from January 1, 2000 to May 31, 2022. During this time, there was a great deal of evolution in the NSAID market, in the scientific evidence related to the comparative effectiveness and safety of various NSAIDs and other analgesics, and in professional recommendations, clinical practice patterns, and regulatory policy related to NSAIDs prescribing. Yet, many interventions with varying characteristics were effective in de-implementing potentially harmful NSAIDs during this timeframe. These interventions classified NSAID use/prescribing as high-risk for multiple reasons, employed a variety of de-implementation approaches, and took place in several different healthcare settings. We highlight six opportunities to enhance scientific knowledge on NSAID de-implementation interventions in healthcare settings: 1) a

comprehensive, systematic analysis of the effectiveness of prior interventions; 2) an evaluation of characteristics and combinations of characteristics associated with highly effective interventions; 3) an assessment of the effectiveness of less-used intervention strategies such as practice facilitation and clinician financial incentives; 4) the evaluation of interventions for varying high-risk patient populations and to de-implement OTC NSAIDs as well as prescription; 5) the inclusion of patient-focused outcomes; and 6) the incorporation of implementation or de-implementation theories, frameworks, or models to guide the planning, delivery, and evaluation of interventions. This subsequent knowledge stands to de-implement a common health service (NSAIDs) and improve medication safety and healthcare quality for a very large number of patients living with common health conditions.

CONTRIBUTORSHIP STATEMENT

MR: study design and strategy, literature review, data extraction, interpretation, preparation of manuscript first draft. JE: study design and strategy, interpretation. EO, ES, JT: abstract review, data extraction. IY, MV: literature review, interpretation. All authors approved the final manuscript.

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DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

ETHICAL APPROVAL STATEMENT

This study is a scoping review that does not involve human participants.

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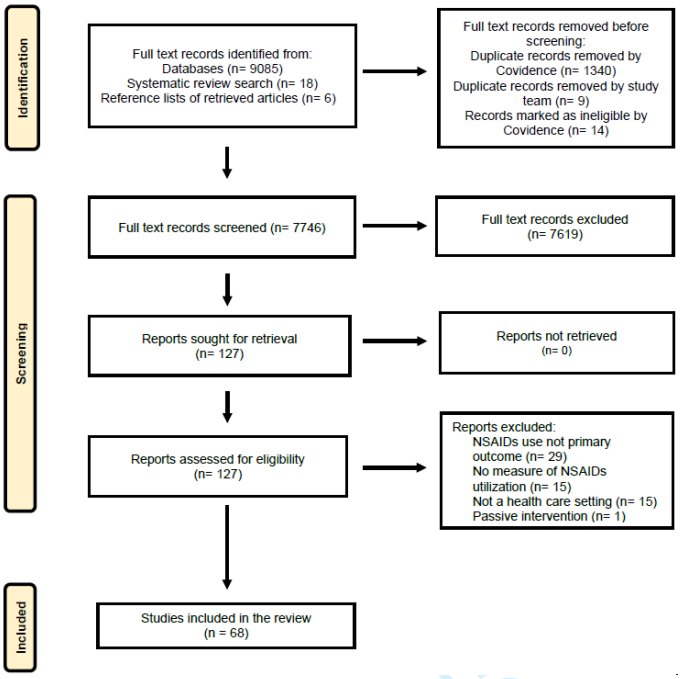

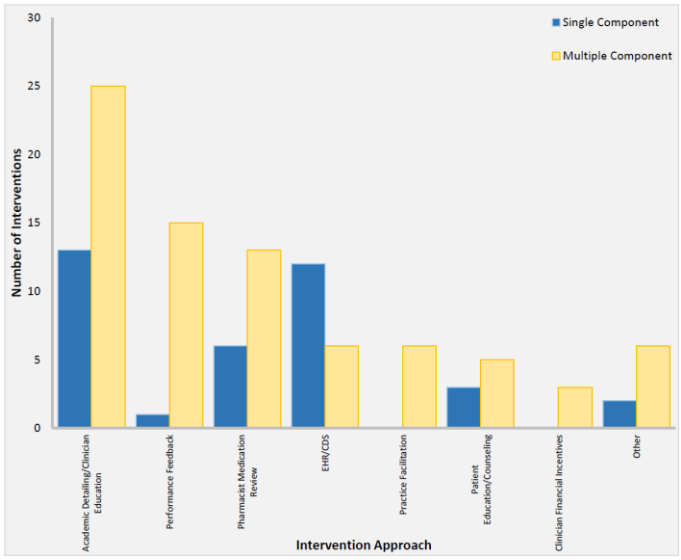

NSAIDs: nonsteroidal ant-inflammatory drugs; EHR: electronic health record; CDS: clinical decision support

Figure 2. Single and Multiple Component Intervention Approaches to De-implement Potentially Harmful NSAIDs in Health Care Settings

Supplementary File 1. Sample Recommendations and Prescribing Notes from Professional Medical Societies and Organizations Related to Potentially Harmful NSAIDS

Organization	Recommendation Year	Recommendation
American Association of Family Physicians (AAFP).[1]	2009	• When possible, NSAIDs should be avoided in persons with preexisting renal disease, congestive heart failure, or cirrhosis. • Consider monitoring serum creatinine levels after initiation of NSAID therapy in persons at risk of renal failure, and in those taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. • NSAIDs and aspirin should be avoided in persons taking anticoagulants. If concurrent NSAID and anticoagulant use is necessary, an increase in INR should be anticipated. There should be appropriate INR monitoring and warfarin (Coumadin) dosage adjustments, and GI prophylaxis should be initiated. • Asthma could be induced or worsened as a result of taking NSAIDs. • Ibuprofen, indomethacin, and naproxen (Naprosyn) are safe to use in breastfeeding women.
American Geriatric Society Beer's Criteria.[2]	2023	In older adults: • Avoid chronic use of NSAIDs unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol). • Avoid short-term scheduled use in combination with corticosteroids, anticoagulants, or antiplatelet agents unless other alternatives are not effective and the patient can take a gastroprotective agent. • Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: Dronedarone NSAIDs and COX-2 inhibitors. • In patients with kidney disease and Cr/Cl <30ml/min, avoid NSAIDs (non-selective, COX-2 selective, and nonacetylated salicylates, oral and parenteral) may increase the risk of acute kidney injury and a further decline in kidney function
American Heart Association (AHA).[3]	2007	• NSAIDs should be taken at lowest effective dosage for the shortest duration possible to reduce cardiovascular risk. • COX inhibitors carry the highest cardiovascular risk and thus, naproxen is recommended as the drug of choice for patients with cardiovascular risk.
American Society of Nephrology (ASN)/ Choosing Wisely.[4]	2012	• Avoid NSAIDs in individuals with hypertension or heart failure or CKD of all causes, including diabetes.
Arthritis Society of Canada.[5]	2022	• Do not use NSAIDs before, during or after heart surgery (bypass surgery). • Patients with a history of cardiovascular disease should be careful using NSAIDs.

		• Patients with risk factors for cardiovascular disease (e.g., diabetes, smoking, elevated cholesterol, obesity and family history) should also be careful using NSAIDs. Safer alternative treatments should be used if available. • NSAIDs should be used in the lowest effective dose for the shortest possible duration of time.
Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee, Asia-Pacific Experts on Topical Analgesics Advisory Board.[6,7]	2018, 2022	• Best available evidence indicates that topical NSAIDs have a moderate effect on relief of osteoarthritic pain, comparable to that of oral NSAIDs but with a better risk-to-benefit ratio. International clinical practice guidelines recommend topical NSAIDs on par with or ahead of oral NSAIDs for pain management in patients with osteoarthritis, and as the first-line choice in persons aged ≥75 years.
European Alliance of Associations for Rheumatology (EULAR).[8]	2021	• NSAIDs, at the lowest effective dose, should be added or substituted in patients who respond inadequately to paracetamol. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor, should be used.
Health Canada.[9]	2021	• Advises pregnant women to not use NSAIDs from 20 to 28 weeks of pregnancy, unless advised by a health care professional, due to risk of kidney damage and low amniotic fluid. • NSAIDs are contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition.
Kidney Disease Improving Global Outcomes (KDIGO).[10]	2012	• Avoid NSAIDs in people with GFR <30 ml/min/1.73 m^2. • Prolonged NSAID therapy is not recommended in people with GFR <60 ml/min/1.73 m^2. • NSAIDs should not be used in people taking lithium. • Avoid NSAIDs in people taking RAAS blocking agents.
Medicines and Health care Projects Regulatory Agency (MHRA) (UK). [11,12]	2009, 2015	• Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible - if NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms - the renal function of such patients should be carefully monitored during NSAID treatment. • It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs
National Institute for Health and Care Excellence (NICE).[13]	2013	• NSAIDs should be prescribed with caution as courses of just a few days, even at doses within prescribing recommendations, can be associated with serious adverse effects in susceptible patients. • In primary care, paracetamol is recommended in preference to NSAIDs, where appropriate. If a patient is likely to benefit from NSAID treatment naproxen or ibuprofen are recommended first-line, at the lowest effective dose, for the shortest possible time. Patients

		taking NSAIDs who are at increased risk of complications require regular monitoring.
NHS Clinical guideline.[14]	2019	• Avoid NSAIDs in in severe cardiac failure, hepatic failure, and active peptic ulcer disease. • Concomitant use of NSAIDs and other nephrotoxics (e.g., ACE Inhibitors, Angiotensin Receptor Blockers, lithium, and diuretics) should be avoided where possible to prevent the risk of acute kidney injury. • Use caution with NSAIDs in the elderly and with hepatic insufficiency and mild renal impairment. • Avoid combinations of NSAIDs. • Alcohol consumption and cigarette smoking are possible lifestyle risk factors for serious NSAID-induced gastrointestinal adverse effects.
North American Spine Society (NASS).[15]	2020	• Non-selective NSAIDs are suggested for the treatment of low back pain. • There is insufficient evidence to make a recommendation for or against the use of selective NSAIDs for the treatment of low back pain.
Society of Hospital Pharmacists of Australia (SHPA).[16]	2018	• NSAIDs should be avoided before any surgery where postoperative bleeding would be of concern. • COX-2 selective NSAIDs may be used preoperatively as they have limited effect on platelet function.
STOPP/START Criteria.[17]	2023	The following prescriptions are potentially inappropriate to use in patients aged 65 years and older: • Long-term systemic i.e., non-topical NSAIDs with known history of coronary, cerebral or peripheral vascular disease (increased risk of thrombosis). • NSAIDs or systemic corticosteroids with heart failure requiring loop diuretic therapy (risk of exacerbation of heart failure). • Long-term aspirin at doses greater than 100mg per day (increased risk of bleeding, no evidence for increased efficacy). • NSAIDs and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding). • NSAIDs if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function). • NSAIDs other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse). • NSAIDs with severe hypertension i.e., systolic blood pressure consistently above 170 mmHg and/or diastolic blood pressure consistently above 100 mmHg (risk of exacerbation of hypertension). • Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been

		tried (simple analgesics preferable and usually as effective for pain relief and safer). • Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor. • NSAID with concurrent corticosteroids for treatment of arthritis/rheumatism of any kind (increased risk of peptic ulcer disease).

ACE: angiotensin-converting enzyme, CKD: chronic kidney disease, COX: cyclooxygenase, eGFR/GFR: estimated glomerular filtration rate/glomerular filtration rate, H2: histamine 2-receptor, GI: gastrointestinal, INR: international normalization ratio, NSAIDs: nonsteroidal ant-inflammatory drugs, PPI: proton pump inhibitors, PRN: pro re nata, RAAS: renin–angiotensin–aldosterone system.

Supplementary File 2. Terms Used in Literature Search

The literature search used keywords related to nonsteroidal anti-inflammatory drugs (NSAIDs), de-implementation, and intervention using the following query:

("nonsteroidal anti-inflammatory drug"[mh] OR advil[tiab] OR aleve[tiab] OR aspirin[tiab] OR bextra[tiab] OR Celebrex[tiab] OR celocoxib[tiab] OR daypro[tiab] OR diclofenac[tiab] OR etodolac[tiab] OR etoricoxib[tiab] OR fenoprofen[tiab] OR ibuprofen[tiab] OR Indocin[tiab] OR indomethacin[tiab] OR ketoprofen[tiab] OR ketorolac[tiab] OR lodine[tiab] OR "mefenamic acid" [tiab] OR meloxicam[tiab] OR motrin[tiab] OR nabumetone[tiab] OR nalfon[tiab] OR naproxen[tiab] OR "non-opiate"[mh] OR "non opiate"[mh] OR nsaid[tiab] OR oxaprozin[tiab] OR piroxicam[tiab] OR ponstel[tiab] OR Relafen[tiab] OR rovecoxib[tiab] OR "salicylic acid" [tiab] OR toradol[tiab] OR valdecoxib[tiab] OR voltaren[tiab] OR vioxx[tiab]) AND (deimplement*[mh] OR ceas*[tiab] OR decreas*[tiab] OR de-escal*[tiab] OR deprescrib*[mh] OR discontin[tiab] OR mitigate[tiab] OR "phas* out" [tiab] OR reduc*[tiab] OR remov*[tiab] OR taper[tiab] OR termin*[tiab] OR withdraw[tiab]) AND (interven*[mh] OR initiative[mh] OR program [mh] OR "academic detail*"[tiab] OR "audit and feedback"[mh] OR "decision support"[mh] OR CME[tiab] OR "continuing medical education"[tiab] OR counsel*[tiab] OR educat*[tiab] OR measur*[tiab] OR "medication review"[mh] OR strateg*[tiab] OR "electronic medical record"[mh] OR incentive*[tiab] OR feedback[tiab] OR quality[tiab] OR safe[tiab] OR facilitate*[tiab])

Supplementary File 3. Articles Included in the Final Review (n=68)

Supplementary File 3a. Clinician Facing Interventions (n=55)					
Study title	**Author (Year)**	**Country**	**Health care setting**	**Type of intervention**	**Intervention reduced NSAIDs use?**
• A pharmacist-led information technology intervention for medication errors (PINCER): a multicenter, cluster-randomized, controlled trial and cost-effectiveness analysis.[18]	Avery (2012)	United Kingdom	General Practice/ Primary Care	Pharmacist-led information technology intervention composed of clinician education, feedback, and dedicated support	Yes
• CURATA: A patient health management program for the treatment of osteoarthritis in Québec: An integrated approach to improving the appropriate utilization of anti-inflammatory/analgesic medications.[19]	Beaulieu (2004)	Canada	General Practice/ Primary Care	Clinician education workshop	Yes
• Evidence-based educational outreach visits: Effects on prescriptions of non-steroidal anti-inflammatory drugs.[20]	Bernal-Delgardo (2002)	Spain	General Practice/ Primary Care	Academic detailing	Yes
• Improving ambulatory prescribing safety with a handheld decision support system: A randomized controlled trial.[21]	Berner (2006)	United States	General Practice/ Primary Care	A personal digital assistant (PDA)–based clinical decision support system	Yes
• Influencing NSAID prescribing in primary care using different feedback strategies.[22]	Braybrook (2000)	United Kingdom	General Practice/ Primary Care	Clinician education, active or passive practice-specific prescribing feedback, and prescribing workbook	Yes
• The implementation of academic detailing and its effectiveness on appropriate prescribing of pain relief medication: A real-world cluster randomized trial in Belgian General Practice/ Primary Care.[23]	Bruyndonck (2018)	Belgium	General Practice/ Primary Care	Academic detailing	Yes
• A group randomized trial to improve safe use of nonsteroidal anti-inflammatory drugs.[24]	Curtis (2005)	United States	Managed Care Organization	Continuing medical education and audit & feedback with peer-derived benchmark	No
• Safer prescribing — A trial of education, informatics, and financial incentives.[25]	Dreischulte (2016)	Scotland	General Practice/ Primary Care	Clinician education, computerized clinical decision support, and financial incentives to practices to review patients' charts for appropriateness of NSAIDs use	Yes
• Academic detailing as a method of continuing medical education.[26]	Dyrkorn (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A large-scale initiative to improve NSAID prescribing safety.[27]	Eskildsen (2017)	New Zealand	General Practice/ Primary Care	Practice facilitation including academic detailing, workflow coaching, performance feedback,	Yes

				and other safe prescribing resources	
• Computerized clinical decision support during medication ordering for long-term care residents with renal insufficiency.[28]	Field (2009)	Canada	Long-term Care Facility	Computerized clinical decision support system alerts	Yes
• One-to-one versus group sessions to improve prescription in primary care: A pragmatic randomized controlled trial.[29]	Figueiras (2001)	Spain	General Practice/ Primary Care	One-on-one and group clinician education and reminders	Yes
• Prevention of potentially inappropriate prescribing for elderly patients: A randomized controlled trial using STOPP/START criteria.[30]	Gallagher (2011)	Ireland	Inpatient Care	Screening by pharmacist using STOPP/START criteria and follow-up visit with primary care	Yes
• Impact of EHR-based clinical decision support on adherence to guidelines for patients on NSAIDs: A randomized controlled trial.[31]	Gill (2011)	United States	General Practice/ Primary Care	EHR-based clinical decision support alerts for high-risk patients	Yes
• Effect of an academic detailing intervention on the utilization rate of cyclooxygenase-2 inhibitors in the elderly.[32]	Graham (2008)	Canada	Tertiary Medical Center	Academic detailing	Yes
• Guided medication dosing for elderly emergency patients using real-time, computerized decision support.[33]	Griffey (2012)	United States	Tertiary Medical Center	Computerized decision support tool	Yes
• Data feedback and behavioral change intervention to improve primary care prescribing safety (EFIPPS): Multicenter, three-arm, cluster randomized controlled trial.[34]	Guthrie (2016)	Scotland	General Practice/ Primary Care	Emailed educational material with support for identifying high-risk patients or feedback on high-risk prescribing, with or without a behavioral change component	Yes
• A physician-focused intervention to reduce potentially inappropriate medication prescribing in older people.[35]	Keith (2013)	Italy	General Practice/ Primary Care	Academic detailing, alternative drug list for potentially avoidable medications, prescribing reviews	Yes
• Reducing inappropriate non-steroidal anti-inflammatory prescription in primary care patients with chronic kidney disease.[36]	Keohane (2017)	Ireland	General Practice/ Primary Care	Automated EHR alert	Yes
• Toward safer prescribing: Evaluation of a prospective drug utilization review system on inappropriate prescriptions, prescribing patterns, and adverse drug events and related health expenditure in South Korea.[37]	Kim (2018)	South Korea	General Practice/Primary Care	Drug utilization review system	No
• The prevalence of 'triple whammy' prescriptions in surgical inpatients and associated pharmacist recommendations.[38]	Koeck (2021)	Germany	Inpatient Surgical Wards	Pharmacist medication review	Yes
• Pharmacist-led medication review in patients over 65: A randomized, controlled trial in primary care.[39]	Krska (2001)	Scotland	General Practice/ Primary Care	Pharmacist medication review	Yes

• Interdisciplinary geriatric and psychiatric care reduces potentially inappropriate prescribing in the hospital: Interventional study in 150 acutely Ill elderly patients with mental and somatic comorbid conditions.[40]	Lang (2012)	Switzerland	Inpatient Medical-Psychiatric Unit	Integrated care (a daily collaboration between a geriatrician and a psychiatrist providing interdisciplinary health care management)	No
• Effectiveness of an academic detailing intervention in Primary Care on the prescribing of non-steroidal anti-inflammatory drugs.[41]	Langaas (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients.[42]	Lenander (2017)	Sweden	General Practice/ Primary Care	Clinician self-assessment, peer review & feedback and written change agreements	Yes
• Evaluation of a complex intervention to improve primary care prescribing: A phase IV segmented regression interrupted time series analysis.[43]	MacBride-Stewart (2017)	Scotland	General Practice/ Primary Care	Clinician education, performance feedback, pharmacist support, and financial incentives	Yes
• Improving medication use in newly admitted home health care patients: A randomized controlled trial.[44]	Meredith (2002)	United States	Home Health Care	Medication improvement program (pharmacist consultations with home health nurses)	No
• Leveraging practice-based research networks to accelerate implementation and diffusion of chronic kidney disease guidelines in primary care practices: A prospective cohort study.[45]	Mold (2014)	United States	General Practice/ Primary Care	Practice facilitation including academic detailing and performance feedback	Yes
• Improving quality of NSAID prescribing by internal medicine trainees with an educational intervention.[46]	Naughton (2010)	United States	Ambulatory Care Internal Medicine	Clinician education program, local practice data & consensus conferences, polypharmacy journals, and audit & feedback	Yes
• Can a practice pharmacist improve prescribing safety and reduce costs in polypharmacy patients? A pilot study of an intervention in an Irish general practice setting.[47]	Ó Ciardha (2022)	Ireland	General Practice/ Primary Care	Pharmacist conducting holistic medication reviews in the study group over a 6 month period.	Yes
• Effectiveness of educational outreach visits compared with usual guideline dissemination to improve family physician prescribing—an 18-month open cluster-randomized trial.[48]	Pinto (2018)	Portugal	General Practice/ Primary Care	Clinician education, outreach visits or online resources	No
• A quality use of medicines program for general practitioners and older people: A cluster randomized controlled trial.[49]	Pit (2007)	Australia	General Practice/ Primary Care	Academic detailing, medication risk assessment, performance feedback, and financial incentives	Yes
• Education to reduce potentially harmful medication use among residents of assisted living facilities: A randomized controlled trial.[50]	Pitkala (2014)	Finland	Assisted Living Facilities	Nurse education and training	Yes
• Reporting of estimated glomerular filtration rate: Effect on physician recognition of chronic	Quartarolo (2007)	United States	Inpatient Care	GFR reporting	No

kidney disease and prescribing practices for elderly hospitalized patients.[51]					
• Randomized trial to improve prescribing safety in ambulatory elderly patients.[52]	Raebel (2007)	United States	Health Maintenance Organization.	Medication prescribing alerts	No
• Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population.[53]	Rahme (2005)	Canada	General Practice/ Primary Care	Clinician education workshop and prescribing decision tree	Yes
• Clinically important drug-drug interactions in poly-treated elderly outpatients: A campaign to improve appropriateness in general practice.[54]	Raschi (2015)	Italy	General Practice/ Primary Care	Academic detailing	Yes
• Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: A randomized controlled trial.[55]	Ray (2001)	United States	Community Health Care	Clinician education program	Yes
• Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes.[56]	Roberts (2001)	Australia	Long-term Care Facility	Clinical pharmacy interventions in nursing homes, relationship building, nurse education, and medication reviews	Yes
• Potentially inappropriate prescribing to older patients: Criteria, prevalence, and an intervention to reduce It: The prescription peer academic detailing (Rx-PAD) study – A cluster-randomized, educational intervention in Norwegian general practice.[57]	Rognstad (2018)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A multifactorial intervention to lower potentially inappropriate medication use in older adults in Argentina.[58]	Schapira (2021)	Argentina	General Practice/Primary Care	Clinician education, workshops, deprescribing algorithms, and email alerts	Yes
• Computerized prescribing alerts and group academic detailing to reduce the use of potentially inappropriate medications in older people.[59]	Simon (2006)	United States	General Practice/ Primary Care	Academic detailing and computerized alerts	No
• Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: A randomized controlled trial.[60]	Stein (2001)	United States	Long-term Care Facility	Clinician education	Yes
• Enhancing Quality of Provider Practices for Older Adults in the Emergency Department (EQUiPPED).[61]	Stevens (2017)	United States	Emergency Department	Clinician education, clinical decision support, individual performance feedback	Yes
• Randomized clinical trial of a customized electronic alert requiring an affirmative response compared to a control group receiving a commercial passive CPOE alert:	Strom (2010)	United States	Inpatient Care	EHR alerts	No

NSAID—warfarin co-prescribing as a test case.[62]					
• The medical office of the 21st Century (MOXXI): Effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care.[63]	Tamblyn (2003)	Canada	General Practice/ Primary Care	Computerized clinical decision support	No
• Effectiveness of interventions by community pharmacists to reduce risk of gastrointestinal side effects in nonselective nonsteroidal anti-inflammatory drug users.[64]	Teichert (2014)	Netherlands	Pharmacies	Performance feedback	Yes
• Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: A randomized, controlled trial.[65]	Terrell (2009)	United States	Emergency Department	Computerized clinical decision support	Yes
• Intervention to improve appropriate prescribing and reduce polypharmacy in elderly patients admitted to an internal medicine unit.[66]	Urfer (2016)	Switzerland	Inpatient Care/Internal Medicine Unit	Clinical decision support checklist tool	Yes
• A cluster randomized trial to measure the impact on nonsteroidal anti-inflammatory drug and proton pump inhibitor prescribing in Italy of distributing cost-free paracetamol to osteoarthritic patients.[67]	Vicentini (2019)	Italy	General Practice/ Primary Care	Clinician education	No
• Electronic health record alerts decreased non-steroidal anti-inflammatory drug prescriptions in patients with congestive heart failure: A quality improvement initiative.[68]	Vincent (2020)	United States	Inpatient Care	EHR alerts	Yes
• Guidelines and educational outreach visits from community pharmacists to improve prescribing in general practice: A randomized controlled trial.[69]	Watson (2001)	England	General Practice/ Primary Care	Clinician education plus mailed printed guidelines	No
• Assessment of clinical pharmacy interventions to reduce outpatient use of high-risk medications in the elderly.[70]	Weddle (2017)	United States	General Practice/ Primary Care	Pharmacist medication review and electronic alerts	Yes
• Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function.[71]	Wei (2013)	Scotland	General Practice/ Primary Care	GFR reporting	Yes
• Pharmacist-led provider education on inappropriate NSAID prescribing rates.[72]	Whitner (2020)	United States	General Practice/ Primary Care	Academic detailing	Yes
Supplementary File 3b. Patient Facing Interventions (n=6)					
• Pharmacist counseling and the use of nonsteroidal anti-inflammatory drugs by older adults.[73]	Bear (2017)	United States	General Practice/ Primary Care	Counseling from pharmacist	Yes

• A nurse-delivered advice intervention can reduce chronic non-steroidal anti-inflammatory drug use in general practice: A randomized controlled trial.[74]	Jones (2002)	United Kingdom	General Practice/ Primary Care	Advice and education from nurse	Yes
• Can a nurse-directed intervention reduce the exposure of patients with knee osteoarthritis to nonsteroidal anti-inflammatory drugs?[75]	Mazzuca (2004)	United States	Health Maintenance Organization	Advice and education from nurse about non-pharmacological self-management of osteoarthritis	Yes
• Evaluating the effectiveness of a patient storytelling DVD intervention to encourage patient-physician communication about nonsteroidal anti-inflammatory drug (NSAID) use.[76]	Miller (2016)	United States	General Practice/ Primary Care	Video modeling patient-physician communication about NSAID use	No
• Effect of mobile device-assisted N-of-1 trial participation on analgesic prescribing for chronic pain: Randomized controlled trial.[77]	Odineal (2020)	United States	General Practice/ Primary Care	Mobile educational app	Yes
• Evaluation of a pharmacist-managed nonsteroidal anti-inflammatory drugs deprescribing program in an integrated health care system.[78]	Rashid (2020)	United States	Integrated Health System	A pharmacist managed NSAID deprescribing program	Yes
Supplementary File 3c. Clinician and Patient-Facing Interventions (n=7)					
• Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling poly-medicated elderly people.[79]	Campins (2017)	Spain	General Practice/ Primary Care	Medication evaluation program	Yes
• Effectiveness of a multifaceted intervention for potentially inappropriate prescribing in older patients in primary care: A cluster-randomized controlled trial (OPTI-SCRIPT Study).[80]	Clyne (2015)	Ireland	General Practice/ Primary Care	Academic detailing, pharmacist medicine review, and tailored patient information leaflets	No
• Pharmacist intervention reduces gastropathy risk in patients using NSAIDs.[81]	Ibanez-Cuevas (2008)	Spain	Pharmacies	Structured interviews with patients and performance feedback reports with clinicians	Yes
• Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: The D-PRESCRIBE randomized clinical trial.[82]	Martin (2018)	Canada	Pharmacies	Pharmacist-generated educational brochure to patients and deprescribing recommendation to physicians	Yes
• Effect of pharmaceutical care services on outcomes for home care patients with heart failure.[83]	Triller (2007)	United States	Hospital/ Home Health care	Pharmacist in-home medication review with patients and feedback/recommendations to clinicians	No
• Safer Prescribing and Care for the Elderly (SPACE): A pilot study in general practice.[84]	Wallis (2018)	New Zealand	General Practice/ Primary Care	Academic detailing, audit & feedback, and educational mailings to patients	Yes

• NSAID use after bariatric surgery: A randomized controlled intervention study.[85]	Yska (2016)	Netherlands	Inpatient Surgical Health Care	Mailings to patients and their general practitioners on the risks of NSAIDs after bariatric surgery	No

CPOE: commercial computerized provider order entry, EHR: electronic health record, GFR: glomerular filtration rate, NSAIDs: nonsteroidal ant-inflammatory drugs, Rx-PAD: prescription peer academic detailing, STOPP/START: screening tool of older persons' potentially inappropriate prescriptions/Screening tool to alert to right treatment.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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A Scoping Review of Interventions to De-implement Potentially Harmful Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Healthcare Settings

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ABSTRACT

Objectives: Potentially harmful nonsteroidal anti-inflammatory drugs (NSAIDs) utilization persists at undesirable rates throughout the world. The purpose of this paper is to review the literature on interventions to de-implement potentially harmful NSAIDs in healthcare settings and to suggest directions for future research.

Design: Scoping review

Data Sources: PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar (2000-May 31, 2022).

Study Selection: Studies reporting on the effectiveness of interventions to systematically reduce potentially harmful NSAID utilization in healthcare settings.

Data Extraction: Using Covidence systematic review software, we extracted study and intervention characteristics, including the effectiveness of interventions in reducing NSAID utilization.

Results: From 7,818 articles initially identified, 68 were included in the review. Most studies took place in European countries (45.6%) or the U.S. (35.3%), with randomized controlled trial as the most common design (55.9%). Interventions were largely clinician-facing (76.2%) and delivered in primary care (60.2%) but were rarely (14.9%) guided by an implementation model, framework, or theory Academic detailing, clinical decision support or electronic medical record interventions, performance reports, and pharmacist review were frequent approaches employed. NSAID use was most commonly classified as potentially harmful based on patients' age (55.8%) or history of gastrointestinal disorders (47.1%) or kidney disease (38.2%). Only 7.4% of interventions focused on over-the-counter (OTC) NSAIDs in addition to prescription. The majority of studies (76.2%) reported a reduction in the utilization of potentially harmful NSAIDs. Few studies (5.9%) evaluated pain or quality of life following NSAIDs discontinuation.

Conclusion: Many varied interventions to de-implement potentially harmful NSAIDs have been applied in healthcare settings worldwide. Based on these findings and identified knowledge gaps, further efforts to comprehensively evaluate the effectiveness of interventions and combination of intervention characteristics associated with effective de-implementation are needed. In addition, future efforts should be guided by de-implementation theory, focus on OTC NSAIDs, and incorporate patient-focused strategies and outcomes, including the evaluation of unintended consequences of the intervention.

Key words: deprescribe, medication overuse, safety, low-value care

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review identified 68 studies published during the 20+ year period during which all currently available NSAID classes were on the market in many countries.
- Interventions focused on only NSAIDs vs. NSAIDs as one of multiple medications were included, but the literature search used to identify the latter was limited to published systematic and scoping reviews.
- Multiple characteristics of interventions and author-reported effectiveness are reported for each of the 68 studies identified.
- As a scoping review, this study did not systematically assess the quality of included studies.

BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation through inhibition of cyclooxygenase (COX-1 and -2) enzymes, thereby limiting the production of inflammatory prostaglandins (1). Representing 5 to 10% of global medication utilization, NSAIDs are commonly used to treat arthritis and musculoskeletal pain, injuries, headache, and other sources of acute and chronic pain (2). There are six classes of NSAIDs: salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, anthranilic acid derivatives, and selective COX-2 inhibitors (3). NSAIDs are available in prescription and over-the-counter (OTC) strengths, a variety of different formulations, and oral (most common), intravenous, injectable, and topical forms. The use of NSAIDs has risen globally throughout the last twenty years (4–8), in part due to increasing rates of chronic and persistent pain and an increasing aging population.

In addition to anti-inflammatory and analgesic properties, NSAIDs have numerous other physiologic effects, which differ by NSAIDs class. For example, NSAIDs can reduce the integrity of the gastrointestinal mucosal barrier and limit submucosal blood flow, increasing risk of ulceration, hemorrhage, or perforation, particularly among vulnerable individuals; COX-2 selective NSAIDs are associated with lower gastrointestinal risk (1,9). Taking NSAIDs can reduce renal blood flow, alter fluid-electrolyte balance, and increase risk of acute kidney injury (10). Risk for and worsening of hypertension, heart failure, and other cardiovascular issues have also been associated with regular NSAIDs use (10–13). In 2015, the U.S. Food and Drug Administration updated the black box warning on OTC NSAIDS to include, "*NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease…The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID…There is an increased risk of heart failure with NSAID use.*" (14) Medical societies and professional organizations around the world have established recommendations for limiting or avoiding NSAIDs in certain high-risk populations **(Supplementary File 1)**.

Despite numerous long-standing recommendations, potentially harmful NSAIDs prescribing and OTC use persists globally (15–18). As an example, multiple studies show that up to 30% of patients with chronic kidney disease (CKD) are prescribed long-term NSAIDs (19,20). This high-risk use has resulted in a substantial number of adverse events; NSAIDs are a leading cause of drug-related hospitalizations and mortality (21–23). The drivers of potentially harmful NSAIDs prescribing and use are complex and multilevel (24–26). Clinicians' unfamiliarity with professional

recommendations, clinical inertia, limited alternative options for pain management, lack of patient knowledge or understanding, and broad availability of OTC NSAIDs are just some of the factors involved. The evolving regulatory landscape also complicates NSAIDs practice patterns and decision-making (a timeline of major NSAIDs-related regulatory events and other key historical timepoints in the U.S., as an example, is shown in **Table 1**) (27,28).

Further efforts are needed to reduce the potential harm associated with prescription and OTC NSAIDs and promote safer pain management for high-risk patients. The purpose of this paper is to provide an overview of published interventions to de-implement potentially harmful NSAIDs in healthcare settings, to identify knowledge gaps, and to suggest opportunities for subsequent interventions and future research related to NSAIDs de-implementation.

Table 1. Timeline of Major Regulatory Events and Other Key Historical Timepoints U.S. NSAID History

Year	Event
1900	Aspirin registered in the U.S., available via prescription (29).
1915	Aspirin approved by FDA for over-the-counter distribution (30).
1964-1976	Indomethacin, ibuprofen, diclofenac, ketoprofen, and naproxen approved by the FDA (31,32).
1971	John Vane discovered the mechanism of action of aspirin and other NSAIDs (33).
1976	COX enzyme discovered, recognized for role in prostaglandin synthesis (33).
1984	Ibuprofen approved by FDA for over-the-counter distribution (34).
1985	FDA approved aspirin for treatment of acute myocardial infarction and secondary cardiovascular prevention, CDC endorses (35).
1991	Second COX enzyme ("COX-2") discovered, recognized as identical in structure but having important differences in substrate and inhibitor selectivity and in intracellular locations (36).
1999	Celecoxib, the first selective COX-2 inhibitor, available via prescription (37).
2004-2005	Selective COX-2 inhibitors (rofecoxib and valdexocib) withdrawn from the market based on evidence that long-term use increases cardiovascular risk. Celecoxib remained on the market with a black box warning. The warning was also added to the over-the-counter NSAIDs' drug facts label (38).
2007	FDA approved topical diclofenac at the prescription-level (39).
2015	Strengthening of the black box warning over-the-counter NSAIDs' drug facts labels related to risk of heart attack and stroke (14).
2016	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years (B recommendation) (40).

2020	Topical diclofenac approved for over-the-counter distribution (28).
2022	Department of Health and Human Services initiates the Million Hearts Campaign, a national initiative to prevent 1 million heart attacks and strokes within 5 years. It focuses on implementing a set of evidence-based priorities that can improve cardiovascular health (including appropriate aspirin use) (41).
2022	The USPSTF recommends that for adults aged 40 to 50 years with an estimated 10% or greater 10-year cardiovascular disease (CVD) risk: The decision to initiate low-dose aspirin use for the primary prevention of CVD in this group should be an individual one. (C recommendation) (42).

CDC: Centers for Disease Control and Prevention, COX: cyclooxygenase, CRC: colorectal cancer, CVD: cardiovascular disease, FDA: Food and Drug Administration, NSAIDs: nonsteroidal anti-inflammatory drugs, USPSTF: United States Preventive Services Task Force

METHODS

We performed a scoping review of the scientific and gray literature reporting on interventions to de-implement NSAIDs in healthcare settings. Our review was guided by the PRISMA Extension for Scoping Reviews (43). As a scoping review, this review is not eligible for PROSPERO registration, but the protocol was posted at https://osf.io/ywe62/ in January 2022.

Eligibility Criteria

Eligible studies were published in English between January 1, 2000 and May 31, 2022, employed any study design, and evaluated interventions administered with a goal of de-implementing potentially harmful NSAIDs in a healthcare setting. We selected 2000 as the earliest eligibility year since it was the first full year in which selective COX-2 inhibitors were available for use in several countries, including the United States and United Kingdom. Thus, all six NSAIDs classes were available throughout the study period.

Healthcare settings included any outpatient or inpatient healthcare environments within any medical specialty.

NSAIDs included prescription or over-the-counter oral or topical NSAIDs. NSAIDs that are not approved for current use were included if they had been approved at any point during the study period. For example, although rofecoxib and valdecoxib were removed from the U.S. market in 2005, (38) they were included in the literature search. Aspirin taken for cardiovascular disease prophylaxis (<100 mg) was not included since the recommended dose is lower than that commonly used for analgesic purposes. If the purpose of the intervention was to study an inappropriate prophylactic use of aspirin, an exception was made to include that study. To be

included, studies must have reported NSAID prescribing or use rates before and after the intervention, at minimum.

Potentially harmful NSAIDs included those that were prescribed or taken in a manner inconsistent with professional recommendations or otherwise recognized as high-risk by the study authors.

Interventions were defined as "any activity or set of activities aimed at modifying a process, course of action, or sequence of events in order to change one or several of their characteristics such as performance of expected outcome", as described by the World Health Organization (44). Interventions were actively delivered to healthcare clinicians, healthcare teams, or directly to patients. All interventions included in the study involved de-implementation of NSAIDs. Passive interventions such as policy changes were not included.

De-implementation was defined as the systematic reduction or elimination of potentially harmful NSAID prescribing or use, or the modification of some aspect of NSAID prescribing or use to improve safety and/or reduce risk of harm (e.g., taking proton pump inhibitors in combination with NSAIDs).

Patient populations were limited to adults ≥18 years of age. Patients with or without specific medical conditions and of any health status were included.

Search Strategy

With the guidance of a professional librarian, we searched PubMed, CINAHL, Embase, Cochrane Central, Google Scholar and Google for [intervention OR program OR related MESH terms] + [de-implement OR deprescribe OR reduce OR related MESH term] + [nonsteroidal anti-inflammatory drug OR NSAID OR related MESH term] in Spring 2022 (full search strategy appears in **Supplementary File 2**). Studies were limited to articles or abstracts published between January 1, 2000 and May 31, 2022. Only studies written in or translated into English were included.

Studies identified in the search were uploaded as abstracts to Covidence (Melbourne, Australia), an online systematic review management platform. Duplicate studies were auto-identified by

Covidence and deleted. Two members of the research team (MR and MA) independently screened all abstracts for inclusion in the review. Discrepancies were resolved by conference with a third team member (JE). Studies that passed the screening stage were moved to full text review. Three members of the research team (MR, MA, and ES) independently reviewed all full-text studies for alignment with eligibility criteria and reviewed reference lists for additional studies. Discrepancies were resolved via conference among the three reviewers.

Since the reference list review identified some studies that focused on NSAIDs as one of multiple medications addressed in de-implementation or deprescribing interventions that were not captured in our initial search, we performed a second PubMed, CINAHL, Embase, Cochrane Central, and Google Scholar search for systematic and scoping review articles related to medication de-implementation, deprescribing, or polypharmacy interventions published between January 1, 2000 and May 31, 2022. Abstracts identified in the search were reviewed by the lead author (MR) to eliminate reviews that did not meet inclusion criteria. Each review article was independently searched by two team members (EO and JT) for studies that included NSAIDs and met all other inclusion criteria. Discrepancies were resolved via conference among the two reviewers.

Data Extraction

Studies that passed full-text review were moved to the charting/data extraction phase. Using the Covidence extraction framework, data were independently extracted by two team members (MA and ES). Two additional team members (MR and EO) downloaded the extracted data table from Covidence, independently checked a 25% data sample for accuracy, and resolved discrepancies by consensus.

The following data were extracted for each study: publication year, country, study design, intervention setting, type of intervention (de-implementation approach), participants (e.g., physicians, pharmacists, patients), NSAIDs involved in intervention (prescription and/or OTC; classes and/or specific medications), focus patient population, guiding model/framework/theory. Intervention types were categorized as academic detailing/clinician education, clinician financial incentives, EHR/clinical decision support, patient counseling, patient education, performance feedback (a.k.a., audit and feedback), pharmacist medication review, practice facilitation or coaching, or other as informed by the work of Cliff et al (45) and Colla et al (46) and the authors'

knowledge of the literature. During the analysis, we combined patient counseling and patient education since these categories were defined differently across studies, and because of substantial overlap in categories.

We documented the general effectiveness of the intervention in de-implementing NSAIDs (yes, no, or no change) and any patient-focused outcomes evaluated in relation to the intervention. An intervention was scored as 'yes' for effectiveness if any significant ($p<0.05$) improvement in the utilization or prescribing of any NSAID was reported. For multiple-drug interventions, we focused only on NSAIDs results.

Extracted data were integrated and synthesized into tables and figures based on data extraction elements listed above. The research team collectively appraised results to summarize the identified interventions and identify gaps in the literature.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

The original search identified 7,720 studies from which 60 were included in the final review. The secondary systematic and scoping review search identified 98 articles from which eight additional papers were included in the final review. **Figure 1** details the flow of articles through identification and screening stages and **Supplementary File 3** shows all articles included in the final review (n= 68).

Characteristics of Studies

A total of 27 (39.7%) of studies were published between 2000 and 2010, with the remaining published between 2011 and May 31, 2022. The majority of studies took place in a European country (45.6%) or the United States (35.3%) (**Supplementary File 3**). A variety of study designs were represented, with randomized controlled trial (RCT) being the most common (55.9%) and prospective, interventional trials also frequently used (23.5%).

Characteristics of Interventions

A minority of interventions (14.7%) were guided or informed by a specified conceptual theory, model, or framework. Most interventions were delivered to clinicians (i.e., clinician-facing) (76.5%) **(Supplementary File 3a)**, although some were patient-facing (8.8%) **(Supplementary File 3b)** and some were both clinician and patient-facing (10.3%) **(Supplementary File 3c)**. Of the clinician-facing and both clinician and patient-facing interventions, primary care or general practice physicians were the most frequent focus (72.6%), with pharmacists, nurses, and physicians in sub-specialty settings the focus of the remaining interventions. Both single component (54.4%) and multi-component (45.6%) interventions were employed. The most common intervention approach, represented in more than half of studies, was academic detailing and/or clinician education (**Figure 2**). Interventions focused on the electronic health record (EHR) and/or clinical decision support were common among single component interventions, while clinician performance reports or audit/feedback and medication review by a pharmacist were common among multi-component interventions (**Figure 2**).

Some interventions focused solely on NSAIDs, while 26 (38.1%) focused on de-implementation of other medications as well. For example, the EQUiPPED trial (47) aimed to reduce prescribing of multiple potentially harmful medications to older adults in the emergency department, while the study reported by Dreishulte et al.(48) focused on de-implementation of high-risk NSAIDs and antiplatelet agents in primary care. Most interventions (85.2%) aimed to de-implement all types of NSAIDS, although some (14.8%) targeted reduction of a single type or class of NSAIDs. Interventions largely focused on prescription NSAIDs, with only 7.4% of interventions aimed to reduce potentially harmful OTC NSAIDs. All studies focused on oral NSAIDs; topical NSAIDs were not addressed in any interventions.

More than half of interventions (55.8%) aimed to de-implement NSAIDs classified as high-risk based on patient age (generally ≥65 or 70 years), with BEERS, START, and STOPP criteria frequently referenced (**Table 2**) (49). The de-implementation of potentially harmful NSAIDs among patients with gastrointestinal conditions (e.g., peptic ulcer disease, inflammatory bowel disease) or who were taking chronic NSAIDs without gastroprotective medication (e.g., proton-pump inhibitor) and kidney disease was also common (47.1% and 38.2%, respectively) (**Table 2**).

Most interventions (76.2%) were effective in reducing use of high-risk NSAIDs **(Supplementary File 3)**. There was minimal difference in the reported effectiveness of interventions that incorporated an implementation theory/model/framework vs. those that did not (68% effective, 78% effective), were clinician vs. patient-facing or both clinician and patient-facing (78% effective, 70% effective), single vs. multicomponent (74% effective, 77% effective), involved only NSAIDs vs. multiple medications (76% effective, 71% effective). Effectiveness was similar across intervention types [academic detailing/clinician education (66% effective), clinician financial incentives (79% effective), EHR/clinical decision support (71% effective), patient counseling or education (68% effective), performance feedback (77% effective), pharmacist medication review (70% effective), practice facilitation or coaching (75% effective), or other (80% effective)]. A lower proportion of studies taking place in the U.S. (64% vs. 82% for other countries) reported on an intervention that was effective in reducing NSAID utilization.

Very few studies (5.9%) evaluated patients' level of pain or quality of life following discontinuation of NSAIDs. Over half of studies (51.5%) assessed other patient-focused outcomes associated with the interventions, including patient-rated quality of interaction with clinician, (50) occurrence of falls, (51) and emergency department admissions (48).

Table 2. Criteria by which the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) was Classified as High-Risk or Potentially Harmful by Included Studies

High-risk or potentially harmful due to:	Number of Studies (%)
Age (generally >65 or 70 years)	38 (55.9)
Existing gastrointestinal conditions or lack of gastroprotective medication	32 (47.1)
Kidney disease	26 (38.2)
Cardiovascular disease or heart failure	22 (32.3)
Hypertension	19 (27.9)
Potential for medication interaction	16 (23.5)
Lower risk alternative available	10 (14.7)
Contribution to polypharmacy	7.0 (10.3)
Chronic or long-term use	6.0 (8.8)
Use of multiple medications containing NSAIDs	4.0 (5.9)

NSAIDs: nonsteroidal ant-inflammatory drugs

DISCUSSION

Although many professional organizations and societies recommend limiting or avoiding NSAIDs in high-risk patients, potentially harmful prescribing and OTC use persists at undesirable rates (15–18). This scoping review identified 68 studies describing healthcare-based interventions to de-implement potentially harmful NSAIDs published between January 1, 2000 and May 31, 2022. A broad range of intervention types and characteristics were represented, with multi-component, clinician-facing interventions targeting older adults and those with gastrointestinal or renal risk factors in primary care being the most common. This review exposed several knowledge gaps, many of which suggest opportunities for subsequent research, as highlighted below.

Based on the identified research gaps, we suggest several recommendations for future research. First, a more comprehensive analysis of the effectiveness of prior interventions may best inform subsequent interventions to de-implement potentially harmful NSAIDs. The present review identified interventions reported as effective vs. not effective in reducing potentially harmful NSAIDs, but, as a scoping review with a stated purpose of overviewing the available literature, did not evaluate effect size, degree of effectiveness, or clinical relevance of results. Our evaluation of effective vs. not effective interventions yielded few differences with the exception of a greater proportion of not effective interventions reported by U.S. research teams compared with those from other countries. It is unclear to what extent publication bias influenced the reporting of negative outcome interventions, but further efforts to de-implement potentially harmful NSAIDs are needed in the U.S., regardless.

Second, we noted that both single and multi-component interventions were similarly effective in de-implementing NSAIDs, which is inconsistent with some, (45,46) but not all, (52) previous literature for reducing utilization of low-value health services. In several cases, interventions involving low-cost, low-burden approaches (e.g., one-time education session, online training modules, pamphlets) were associated with the same reduction in NSAID utilization as much more elaborate and costly approaches (e.g., pharmacist medication review, individual patient counseling, EHR workflow modification). Further research to identify characteristics of the simplest or most feasible and sustainable interventions is needed, keeping in mind the many contextual variables that influence effectiveness (53) and that the effectiveness of intervention components is not additive (i.e., a greater number of components in a multicomponent intervention is not always better) (45).

Third, some intervention approaches were infrequently tested in comparison to academic detailing and clinician education (most common), performance feedback, pharmacist medication review, and EHR modification. One option warranting further evaluation is practice facilitation, which leverages external facilitators to employ a variety of practice change strategies and tailor interventions to context, Although more commonly used to implement evident into practice rather than de-implement practice that is not supported by the evidence, (54) there are examples of successful practice facilitation de-implementation interventions (55,56). Direct patient education and counseling was effective for some interventions in the present study (57–59) and aligns with our observation that patient-facing interventions tended to be effective. Engagement with patients can enhance outcomes of deprescribing and other health services interventions, (60–62) and may be especially germane to the de-implementation of OTC NSAIDs, which were barely addressed by interventions studied. Finally, as many real-world efforts to change clinician behavior involve financial incentives (e.g., insurance pay-for-performance), further evaluation of that approach should be pursued. As the lowest proportion of effective interventions occurred in U.S. studies, considering the unique barriers and facilitators to de-implementation within different health systems is important.

Fourth, as there are many scenarios for which long-term NSAID use may be potentially harmful, interventions focused largely on older adults and those with gastrointestinal or renal risk factors. While these are very important populations to target, their findings are not necessarily generalizable to other patient populations. Despite need for de-implementing NSAIDs in patients with cardiovascular disease, heart failure, and hypertension, (10,11) they were the focus of less than one-third of interventions. Additionally, despite evidence that patients may have limited NSAID literacy, (63–66) the issue of duplicate NSAID use was minimally addressed by previous interventions. Thus, moving forward, there are numerous opportunities to focus and tailor de-implementation approaches to the patient populations and contexts where needs exist.

Fifth, outcomes important to patients were inconsistently assessed in the studies reviewed. Despite some evidence that patient satisfaction and trust are not adversely impacted by low-value care de-implementation, (67,68) clinicians continue to cite concern about patient response as a predominant de-implementation barrier (24,69–71). In addition to evaluating patient-focused outcomes, future studies should explore unintended consequences of the interventions. Of the minority of studies that evaluated adverse events or changes in pain following NSAIDs de-

implementation, none showed increases in adverse event or pain outcomes (72–76). In fact, one study reported lower pain levels among older adults who reduced NSAIDs as part of a pharmacist review program (72).

Finally, we observed that very few of the identified interventions employed an implementation or de-implementation theory, framework, or model. Although there appeared to be no difference in effectiveness of interventions that did vs. did not use such a theory, framework, or model, their use facilitates thorough exploration of factors that led or did not lead to an effective intervention. Further, the use of these theories, frameworks, and models can guide successful implementation, adaptation, and dissemination of interventions and should be applied in future efforts (77–79). One excellent example is provided by the intervention reported by Pinto et al. (80) who included their TIDieR checklist (81) in their published manuscript. Future researchers may benefit from categorizing interventions based on the 4R's framework of Norton et al. (82) (did the intervention involve removing, replacing, reducing, or restricting the inappropriate service?).

This study has some limitations. Our initial search strategy did not comprehensively identify studies that focused on interventions to de-implement NSAIDs as one of multiple target medications. To incorporate these studies into our review, we added a supplemental secondary database search that was effective in identifying eight additional applicable studies. Although it is possible that this approach may have missed some multiple medication interventions, the process of reviewing reference lists and numerous systematic or scoping review articles was the best available approach for including as many appropriate studies as possible with the resources available. Future literature searches may benefit from the inclusion of 'polypharmacy' and associated terms. Additionally, our data extraction plan did not capture whether interventions focused on reducing new prescriptions for (or OTC use of) potentially harmful NSAIDs vs. reducing refills for ongoing inappropriate NSAIDs, which could be important to informing future interventions. It is also possible that some authors may have reported data we extracted in separate publications (e.g., implementation or de-implementation theory, framework, or model). Last, as a scoping review, we did not formally evaluate the quality of the studies reviewed.

CONCLUSION

This scoping review identified 68 interventions to de-implement potentially harmful NSAIDs published internationally from January 1, 2000 to May 31, 2022. During this time, there was a

great deal of evolution in the NSAID market, in the scientific evidence related to the comparative effectiveness and safety of various NSAIDs and other analgesics, and in professional recommendations, clinical practice patterns, and regulatory policy related to NSAIDs prescribing. Yet, many interventions with varying characteristics were effective in de-implementing potentially harmful NSAIDs during this timeframe. These interventions classified NSAID use/prescribing as high-risk for multiple reasons, employed a variety of de-implementation approaches, and took place in several different healthcare settings. We highlight six opportunities to enhance scientific knowledge on NSAID de-implementation interventions in healthcare settings: 1) a comprehensive, systematic analysis of the effectiveness of prior interventions; 2) an evaluation of characteristics and combinations of characteristics associated with highly effective interventions; 3) an assessment of the effectiveness of less-used intervention strategies such as practice facilitation and clinician financial incentives; 4) the evaluation of interventions for varying high-risk patient populations and to de-implement OTC NSAIDs as well as prescription; 5) the inclusion of patient-focused outcomes; and 6) the incorporation of implementation or de-implementation theories, frameworks, or models to guide the planning, delivery, and evaluation of interventions. This subsequent knowledge stands to de-implement a common health service (NSAIDs) and improve medication safety and healthcare quality for a very large number of patients living with common health conditions.

CONTRIBUTORSHIP STATEMENT

MR: study design and strategy, literature review, data extraction, interpretation, preparation of manuscript first draft. JE: study design and strategy, interpretation. EO, ES, JT: abstract review, data extraction. IY, MV: literature review, interpretation. All authors approved the final manuscript.

COMPETING INTERESTS

None declared.

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DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

ETHICAL APPROVAL STATEMENT

This study is a scoping review that does not involve human participants.

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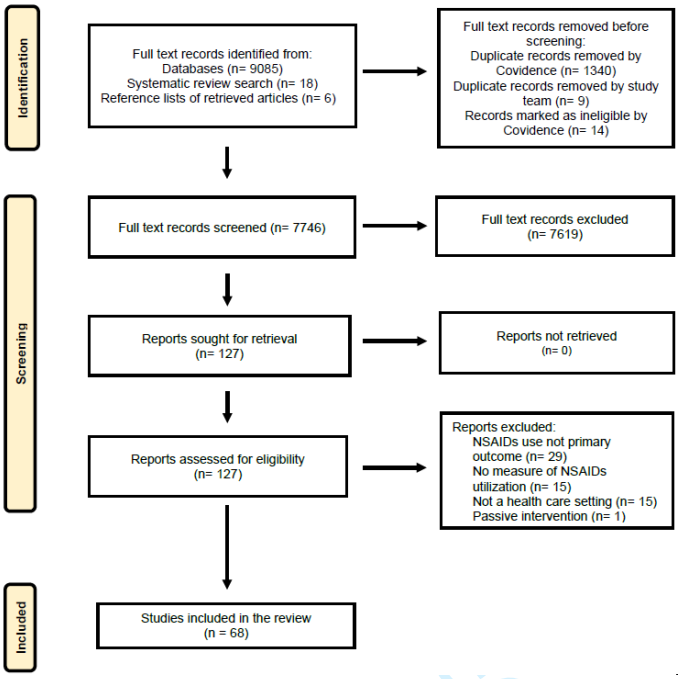

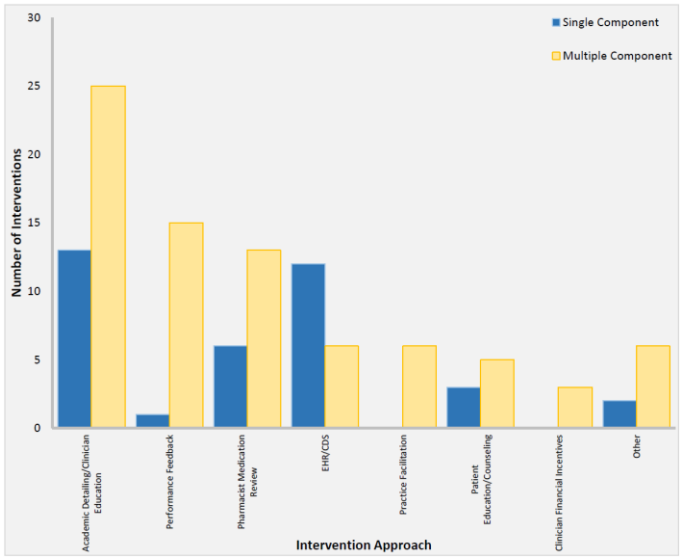

NSAIDs: nonsteroidal ant-inflammatory drugs; EHR: electronic health record; CDS: clinical decision support

Figure 2. Single and Multiple Component Intervention Approaches to De-implement Potentially Harmful NSAIDs in Health Care Settings

Supplementary File 1. Sample Recommendations and Prescribing Notes from Professional Medical Societies and Organizations Related to Potentially Harmful NSAIDS

Organization	Recommendation Year	Recommendation
American Association of Family Physicians (AAFP).[1]	2009	• When possible, NSAIDs should be avoided in persons with preexisting renal disease, congestive heart failure, or cirrhosis. • Consider monitoring serum creatinine levels after initiation of NSAID therapy in persons at risk of renal failure, and in those taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. • NSAIDs and aspirin should be avoided in persons taking anticoagulants. If concurrent NSAID and anticoagulant use is necessary, an increase in INR should be anticipated. There should be appropriate INR monitoring and warfarin (Coumadin) dosage adjustments, and GI prophylaxis should be initiated. • Asthma could be induced or worsened as a result of taking NSAIDs. • Ibuprofen, indomethacin, and naproxen (Naprosyn) are safe to use in breastfeeding women.
American Geriatric Society Beer's Criteria.[2]	2023	In older adults: • Avoid chronic use of NSAIDs unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol). • Avoid short-term scheduled use in combination with corticosteroids, anticoagulants, or antiplatelet agents unless other alternatives are not effective and the patient can take a gastroprotective agent. • Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: Dronedarone NSAIDs and COX-2 inhibitors. • In patients with kidney disease and Cr/Cl <30ml/min, avoid NSAIDs (non-selective, COX-2 selective, and nonacetylated salicylates, oral and parenteral) may increase the risk of acute kidney injury and a further decline in kidney function
American Heart Association (AHA).[3]	2007	• NSAIDs should be taken at lowest effective dosage for the shortest duration possible to reduce cardiovascular risk. • COX inhibitors carry the highest cardiovascular risk and thus, naproxen is recommended as the drug of choice for patients with cardiovascular risk.
American Society of Nephrology (ASN)/ Choosing Wisely.[4]	2012	• Avoid NSAIDs in individuals with hypertension or heart failure or CKD of all causes, including diabetes.
Arthritis Society of Canada.[5]	2022	• Do not use NSAIDs before, during or after heart surgery (bypass surgery). • Patients with a history of cardiovascular disease should be careful using NSAIDs.

		• Patients with risk factors for cardiovascular disease (e.g., diabetes, smoking, elevated cholesterol, obesity and family history) should also be careful using NSAIDs. Safer alternative treatments should be used if available. • NSAIDs should be used in the lowest effective dose for the shortest possible duration of time.
Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee, Asia-Pacific Experts on Topical Analgesics Advisory Board.[6,7]	2018, 2022	• Best available evidence indicates that topical NSAIDs have a moderate effect on relief of osteoarthritic pain, comparable to that of oral NSAIDs but with a better risk-to-benefit ratio. International clinical practice guidelines recommend topical NSAIDs on par with or ahead of oral NSAIDs for pain management in patients with osteoarthritis, and as the first-line choice in persons aged ≥75 years.
European Alliance of Associations for Rheumatology (EULAR).[8]	2021	• NSAIDs, at the lowest effective dose, should be added or substituted in patients who respond inadequately to paracetamol. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor, should be used.
Health Canada.[9]	2021	• Advises pregnant women to not use NSAIDs from 20 to 28 weeks of pregnancy, unless advised by a health care professional, due to risk of kidney damage and low amniotic fluid. • NSAIDs are contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition.
Kidney Disease Improving Global Outcomes (KDIGO).[10]	2012	• Avoid NSAIDs in people with GFR <30 ml/min/1.73 m^2. • Prolonged NSAID therapy is not recommended in people with GFR <60 ml/min/1.73 m^2. • NSAIDs should not be used in people taking lithium. • Avoid NSAIDs in people taking RAAS blocking agents.
Medicines and Health care Projects Regulatory Agency (MHRA) (UK). [11,12]	2009, 2015	• Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible - if NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms - the renal function of such patients should be carefully monitored during NSAID treatment. • It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs
National Institute for Health and Care Excellence (NICE).[13]	2013	• NSAIDs should be prescribed with caution as courses of just a few days, even at doses within prescribing recommendations, can be associated with serious adverse effects in susceptible patients. • In primary care, paracetamol is recommended in preference to NSAIDs, where appropriate. If a patient is likely to benefit from NSAID treatment naproxen or ibuprofen are recommended first-line, at the lowest effective dose, for the shortest possible time. Patients

		taking NSAIDs who are at increased risk of complications require regular monitoring.
NHS Clinical guideline.[14]	2019	• Avoid NSAIDs in in severe cardiac failure, hepatic failure, and active peptic ulcer disease. • Concomitant use of NSAIDs and other nephrotoxics (e.g., ACE Inhibitors, Angiotensin Receptor Blockers, lithium, and diuretics) should be avoided where possible to prevent the risk of acute kidney injury. • Use caution with NSAIDs in the elderly and with hepatic insufficiency and mild renal impairment. • Avoid combinations of NSAIDs. • Alcohol consumption and cigarette smoking are possible lifestyle risk factors for serious NSAID-induced gastrointestinal adverse effects.
North American Spine Society (NASS).[15]	2020	• Non-selective NSAIDs are suggested for the treatment of low back pain. • There is insufficient evidence to make a recommendation for or against the use of selective NSAIDs for the treatment of low back pain.
Society of Hospital Pharmacists of Australia (SHPA).[16]	2018	• NSAIDs should be avoided before any surgery where postoperative bleeding would be of concern. • COX-2 selective NSAIDs may be used preoperatively as they have limited effect on platelet function.
STOPP/START Criteria.[17]	2023	The following prescriptions are potentially inappropriate to use in patients aged 65 years and older: • Long-term systemic i.e., non-topical NSAIDs with known history of coronary, cerebral or peripheral vascular disease (increased risk of thrombosis). • NSAIDs or systemic corticosteroids with heart failure requiring loop diuretic therapy (risk of exacerbation of heart failure). • Long-term aspirin at doses greater than 100mg per day (increased risk of bleeding, no evidence for increased efficacy). • NSAIDs and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding). • NSAIDs if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function). • NSAIDs other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse). • NSAIDs with severe hypertension i.e., systolic blood pressure consistently above 170 mmHg and/or diastolic blood pressure consistently above 100 mmHg (risk of exacerbation of hypertension). • Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been

		tried (simple analgesics preferable and usually as effective for pain relief and safer). • Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor. • NSAID with concurrent corticosteroids for treatment of arthritis/rheumatism of any kind (increased risk of peptic ulcer disease).

ACE: angiotensin-converting enzyme, CKD: chronic kidney disease, COX: cyclooxygenase, eGFR/GFR: estimated glomerular filtration rate/glomerular filtration rate, H2: histamine 2-receptor, GI: gastrointestinal, INR: international normalization ratio, NSAIDs: nonsteroidal ant-inflammatory drugs, PPI: proton pump inhibitors, PRN: pro re nata, RAAS: renin–angiotensin–aldosterone system.

Supplementary File 2. Terms Used in Literature Search

The literature search used keywords related to nonsteroidal anti-inflammatory drugs (NSAIDs), de-implementation, and intervention using the following query in PubMed, CINAHL, Embase, Cochrane Central, Google Scholar and Google:

("nonsteroidal anti-inflammatory drug"[mh] OR advil[tiab] OR aleve[tiab] OR aspirin[tiab] OR bextra[tiab] OR Celebrex[tiab] OR celocoxib[tiab] OR daypro[tiab] OR diclofenac[tiab] OR etodolac[tiab] OR etoricoxib[tiab] OR fenoprofen[tiab] OR ibuprofen[tiab] OR Indocin[tiab] OR indomethacin[tiab] OR ketoprofen[tiab] OR ketorolac[tiab] OR lodine[tiab] OR "mefenamic acid" [tiab] OR meloxicam[tiab] OR motrin[tiab] OR nabumetone[tiab] OR nalfon[tiab] OR naproxen[tiab] OR "non-opiate"[mh] OR "non opiate"[mh] OR nsaid[tiab] OR oxaprozin[tiab] OR piroxicam[tiab] OR ponstel[tiab] OR Relafen[tiab] OR rovecoxib[tiab] OR "salicylic acid" [tiab] OR toradol[tiab] OR valdecoxib[tiab] OR voltaren[tiab] OR vioxx[tiab]) AND (deimplement*[mh] OR ceas*[tiab] OR decreas*[tiab] OR de-escal*[tiab] OR deprescrib*[mh] OR discontin[tiab] OR mitigate[tiab] OR "phas* out" [tiab] OR reduc*[tiab] OR remov*[tiab] OR taper[tiab] OR termin*[tiab] OR withdraw[tiab]) AND (interven*[mh] OR initiative[mh] OR program [mh] OR "academic detail*"[tiab] OR "audit and feedback"[mh] OR "decision support"[mh] OR CME[tiab] OR "continuing medical education"[tiab] OR counsel*[tiab] OR educat*[tiab] OR measur*[tiab] OR "medication review"[mh] OR strateg*[tiab] OR "electronic medical record"[mh] OR incentive*[tiab] OR feedback[tiab] OR quality[tiab] OR safe[tiab] OR facilitate*[tiab])

Supplementary File 3. Articles Included in the Final Review (n=68)

Supplementary File 3a. Clinician Facing Interventions (n=55)					
Study title	**Author (Year)**	**Country**	**Health care setting**	**Type of intervention**	**Intervention reduced NSAIDs use?**
• A pharmacist-led information technology intervention for medication errors (PINCER): a multicenter, cluster-randomized, controlled trial and cost-effectiveness analysis.[18]	Avery (2012)	United Kingdom	General Practice/ Primary Care	Pharmacist-led information technology intervention composed of clinician education, feedback, and dedicated support	Yes
• CURATA: A patient health management program for the treatment of osteoarthritis in Québec: An integrated approach to improving the appropriate utilization of anti-inflammatory/analgesic medications.[19]	Beaulieu (2004)	Canada	General Practice/ Primary Care	Clinician education workshop	Yes
• Evidence-based educational outreach visits: Effects on prescriptions of non-steroidal anti-inflammatory drugs.[20]	Bernal-Delgardo (2002)	Spain	General Practice/ Primary Care	Academic detailing	Yes
• Improving ambulatory prescribing safety with a handheld decision support system: A randomized controlled trial.[21]	Berner (2006)	United States	General Practice/ Primary Care	A personal digital assistant (PDA)–based clinical decision support system	Yes
• Influencing NSAID prescribing in primary care using different feedback strategies.[22]	Braybrook (2000)	United Kingdom	General Practice/ Primary Care	Clinician education, active or passive practice-specific prescribing feedback, and prescribing workbook	Yes
• The implementation of academic detailing and its effectiveness on appropriate prescribing of pain relief medication: A real-world cluster randomized trial in Belgian General Practice/ Primary Care.[23]	Bruyndonck (2018)	Belgium	General Practice/ Primary Care	Academic detailing	Yes
• A group randomized trial to improve safe use of nonsteroidal anti-inflammatory drugs.[24]	Curtis (2005)	United States	Managed Care Organization	Continuing medical education and audit & feedback with peer-derived benchmark	No
• Safer prescribing — A trial of education, informatics, and financial incentives.[25]	Dreischulte (2016)	Scotland	General Practice/ Primary Care	Clinician education, computerized clinical decision support, and financial incentives to practices to review patients' charts for appropriateness of NSAIDs use	Yes
• Academic detailing as a method of continuing medical education.[26]	Dyrkorn (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A large-scale initiative to improve NSAID prescribing safety.[27]	Eskildsen (2017)	New Zealand	General Practice/ Primary Care	Practice facilitation including academic detailing, workflow coaching, performance feedback,	Yes

				and other safe prescribing resources	
• Computerized clinical decision support during medication ordering for long-term care residents with renal insufficiency.[28]	Field (2009)	Canada	Long-term Care Facility	Computerized clinical decision support system alerts	Yes
• One-to-one versus group sessions to improve prescription in primary care: A pragmatic randomized controlled trial.[29]	Figueiras (2001)	Spain	General Practice/ Primary Care	One-on-one and group clinician education and reminders	Yes
• Prevention of potentially inappropriate prescribing for elderly patients: A randomized controlled trial using STOPP/START criteria.[30]	Gallagher (2011)	Ireland	Inpatient Care	Screening by pharmacist using STOPP/START criteria and follow-up visit with primary care	Yes
• Impact of EHR-based clinical decision support on adherence to guidelines for patients on NSAIDs: A randomized controlled trial.[31]	Gill (2011)	United States	General Practice/ Primary Care	EHR-based clinical decision support alerts for high-risk patients	Yes
• Effect of an academic detailing intervention on the utilization rate of cyclooxygenase-2 inhibitors in the elderly.[32]	Graham (2008)	Canada	Tertiary Medical Center	Academic detailing	Yes
• Guided medication dosing for elderly emergency patients using real-time, computerized decision support.[33]	Griffey (2012)	United States	Tertiary Medical Center	Computerized decision support tool	Yes
• Data feedback and behavioral change intervention to improve primary care prescribing safety (EFIPPS): Multicenter, three-arm, cluster randomized controlled trial.[34]	Guthrie (2016)	Scotland	General Practice/ Primary Care	Emailed educational material with support for identifying high-risk patients or feedback on high-risk prescribing, with or without a behavioral change component	Yes
• A physician-focused intervention to reduce potentially inappropriate medication prescribing in older people.[35]	Keith (2013)	Italy	General Practice/ Primary Care	Academic detailing, alternative drug list for potentially avoidable medications, prescribing reviews	Yes
• Reducing inappropriate non-steroidal anti-inflammatory prescription in primary care patients with chronic kidney disease.[36]	Keohane (2017)	Ireland	General Practice/ Primary Care	Automated EHR alert	Yes
• Toward safer prescribing: Evaluation of a prospective drug utilization review system on inappropriate prescriptions, prescribing patterns, and adverse drug events and related health expenditure in South Korea.[37]	Kim (2018)	South Korea	General Practice/Primary Care	Drug utilization review system	No
• The prevalence of 'triple whammy' prescriptions in surgical inpatients and associated pharmacist recommendations.[38]	Koeck (2021)	Germany	Inpatient Surgical Wards	Pharmacist medication review	Yes
• Pharmacist-led medication review in patients over 65: A randomized, controlled trial in primary care.[39]	Krska (2001)	Scotland	General Practice/ Primary Care	Pharmacist medication review	Yes

• Interdisciplinary geriatric and psychiatric care reduces potentially inappropriate prescribing in the hospital: Interventional study in 150 acutely Ill elderly patients with mental and somatic comorbid conditions.[40]	Lang (2012)	Switzerland	Inpatient Medical-Psychiatric Unit	Integrated care (a daily collaboration between a geriatrician and a psychiatrist providing interdisciplinary health care management)	No
• Effectiveness of an academic detailing intervention in Primary Care on the prescribing of non-steroidal anti-inflammatory drugs.[41]	Langaas (2019)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients.[42]	Lenander (2017)	Sweden	General Practice/ Primary Care	Clinician self-assessment, peer review & feedback and written change agreements	Yes
• Evaluation of a complex intervention to improve primary care prescribing: A phase IV segmented regression interrupted time series analysis.[43]	MacBride-Stewart (2017)	Scotland	General Practice/ Primary Care	Clinician education, performance feedback, pharmacist support, and financial incentives	Yes
• Improving medication use in newly admitted home health care patients: A randomized controlled trial.[44]	Meredith (2002)	United States	Home Health Care	Medication improvement program (pharmacist consultations with home health nurses)	No
• Leveraging practice-based research networks to accelerate implementation and diffusion of chronic kidney disease guidelines in primary care practices: A prospective cohort study.[45]	Mold (2014)	United States	General Practice/ Primary Care	Practice facilitation including academic detailing and performance feedback	Yes
• Improving quality of NSAID prescribing by internal medicine trainees with an educational intervention.[46]	Naughton (2010)	United States	Ambulatory Care Internal Medicine	Clinician education program, local practice data & consensus conferences, polypharmacy journals, and audit & feedback	Yes
• Can a practice pharmacist improve prescribing safety and reduce costs in polypharmacy patients? A pilot study of an intervention in an Irish general practice setting.[47]	Ó Ciardha (2022)	Ireland	General Practice/ Primary Care	Pharmacist conducting holistic medication reviews in the study group over a 6 month period.	Yes
• Effectiveness of educational outreach visits compared with usual guideline dissemination to improve family physician prescribing—an 18-month open cluster-randomized trial.[48]	Pinto (2018)	Portugal	General Practice/ Primary Care	Clinician education, outreach visits or online resources	No
• A quality use of medicines program for general practitioners and older people: A cluster randomized controlled trial.[49]	Pit (2007)	Australia	General Practice/ Primary Care	Academic detailing, medication risk assessment, performance feedback, and financial incentives	Yes
• Education to reduce potentially harmful medication use among residents of assisted living facilities: A randomized controlled trial.[50]	Pitkala (2014)	Finland	Assisted Living Facilities	Nurse education and training	Yes
• Reporting of estimated glomerular filtration rate: Effect on physician recognition of chronic	Quartarolo (2007)	United States	Inpatient Care	GFR reporting	No

kidney disease and prescribing practices for elderly hospitalized patients.[51]					
• Randomized trial to improve prescribing safety in ambulatory elderly patients.[52]	Raebel (2007)	United States	Health Maintenance Organization.	Medication prescribing alerts	No
• Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population.[53]	Rahme (2005)	Canada	General Practice/ Primary Care	Clinician education workshop and prescribing decision tree	Yes
• Clinically important drug-drug interactions in poly-treated elderly outpatients: A campaign to improve appropriateness in general practice.[54]	Raschi (2015)	Italy	General Practice/ Primary Care	Academic detailing	Yes
• Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: A randomized controlled trial.[55]	Ray (2001)	United States	Community Health Care	Clinician education program	Yes
• Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes.[56]	Roberts (2001)	Australia	Long-term Care Facility	Clinical pharmacy interventions in nursing homes, relationship building, nurse education, and medication reviews	Yes
• Potentially inappropriate prescribing to older patients: Criteria, prevalence, and an intervention to reduce It: The prescription peer academic detailing (Rx-PAD) study – A cluster-randomized, educational intervention in Norwegian general practice.[57]	Rognstad (2018)	Norway	General Practice/ Primary Care	Academic detailing	Yes
• A multifactorial intervention to lower potentially inappropriate medication use in older adults in Argentina.[58]	Schapira (2021)	Argentina	General Practice/Primary Care	Clinician education, workshops, deprescribing algorithms, and email alerts	Yes
• Computerized prescribing alerts and group academic detailing to reduce the use of potentially inappropriate medications in older people.[59]	Simon (2006)	United States	General Practice/ Primary Care	Academic detailing and computerized alerts	No
• Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: A randomized controlled trial.[60]	Stein (2001)	United States	Long-term Care Facility	Clinician education	Yes
• Enhancing Quality of Provider Practices for Older Adults in the Emergency Department (EQUiPPED).[61]	Stevens (2017)	United States	Emergency Department	Clinician education, clinical decision support, individual performance feedback	Yes
• Randomized clinical trial of a customized electronic alert requiring an affirmative response compared to a control group receiving a commercial passive CPOE alert:	Strom (2010)	United States	Inpatient Care	EHR alerts	No

NSAID—warfarin co-prescribing as a test case.[62]					
• The medical office of the 21st Century (MOXXI): Effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care.[63]	Tamblyn (2003)	Canada	General Practice/ Primary Care	Computerized clinical decision support	No
• Effectiveness of interventions by community pharmacists to reduce risk of gastrointestinal side effects in nonselective nonsteroidal anti-inflammatory drug users.[64]	Teichert (2014)	Netherlands	Pharmacies	Performance feedback	Yes
• Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: A randomized, controlled trial.[65]	Terrell (2009)	United States	Emergency Department	Computerized clinical decision support	Yes
• Intervention to improve appropriate prescribing and reduce polypharmacy in elderly patients admitted to an internal medicine unit.[66]	Urfer (2016)	Switzerland	Inpatient Care/Internal Medicine Unit	Clinical decision support checklist tool	Yes
• A cluster randomized trial to measure the impact on nonsteroidal anti-inflammatory drug and proton pump inhibitor prescribing in Italy of distributing cost-free paracetamol to osteoarthritic patients.[67]	Vicentini (2019)	Italy	General Practice/ Primary Care	Clinician education	No
• Electronic health record alerts decreased non-steroidal anti-inflammatory drug prescriptions in patients with congestive heart failure: A quality improvement initiative.[68]	Vincent (2020)	United States	Inpatient Care	EHR alerts	Yes
• Guidelines and educational outreach visits from community pharmacists to improve prescribing in general practice: A randomized controlled trial.[69]	Watson (2001)	England	General Practice/ Primary Care	Clinician education plus mailed printed guidelines	No
• Assessment of clinical pharmacy interventions to reduce outpatient use of high-risk medications in the elderly.[70]	Weddle (2017)	United States	General Practice/ Primary Care	Pharmacist medication review and electronic alerts	Yes
• Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function.[71]	Wei (2013)	Scotland	General Practice/ Primary Care	GFR reporting	Yes
• Pharmacist-led provider education on inappropriate NSAID prescribing rates.[72]	Whitner (2020)	United States	General Practice/ Primary Care	Academic detailing	Yes
Supplementary File 3b. Patient Facing Interventions (n=6)					
• Pharmacist counseling and the use of nonsteroidal anti-inflammatory drugs by older adults.[73]	Bear (2017)	United States	General Practice/ Primary Care	Counseling from pharmacist	Yes

• A nurse-delivered advice intervention can reduce chronic non-steroidal anti-inflammatory drug use in general practice: A randomized controlled trial.[74]	Jones (2002)	United Kingdom	General Practice/ Primary Care	Advice and education from nurse	Yes
• Can a nurse-directed intervention reduce the exposure of patients with knee osteoarthritis to nonsteroidal anti-inflammatory drugs?[75]	Mazzuca (2004)	United States	Health Maintenance Organization	Advice and education from nurse about non-pharmacological self-management of osteoarthritis	Yes
• Evaluating the effectiveness of a patient storytelling DVD intervention to encourage patient-physician communication about nonsteroidal anti-inflammatory drug (NSAID) use.[76]	Miller (2016)	United States	General Practice/ Primary Care	Video modeling patient-physician communication about NSAID use	No
• Effect of mobile device-assisted N-of-1 trial participation on analgesic prescribing for chronic pain: Randomized controlled trial.[77]	Odineal (2020)	United States	General Practice/ Primary Care	Mobile educational app	Yes
• Evaluation of a pharmacist-managed nonsteroidal anti-inflammatory drugs deprescribing program in an integrated health care system.[78]	Rashid (2020)	United States	Integrated Health System	A pharmacist managed NSAID deprescribing program	Yes
Supplementary File 3c. Clinician and Patient-Facing Interventions (n=7)					
• Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling poly-medicated elderly people.[79]	Campins (2017)	Spain	General Practice/ Primary Care	Medication evaluation program	Yes
• Effectiveness of a multifaceted intervention for potentially inappropriate prescribing in older patients in primary care: A cluster-randomized controlled trial (OPTI-SCRIPT Study).[80]	Clyne (2015)	Ireland	General Practice/ Primary Care	Academic detailing, pharmacist medicine review, and tailored patient information leaflets	No
• Pharmacist intervention reduces gastropathy risk in patients using NSAIDs.[81]	Ibanez-Cuevas (2008)	Spain	Pharmacies	Structured interviews with patients and performance feedback reports with clinicians	Yes
• Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: The D-PRESCRIBE randomized clinical trial.[82]	Martin (2018)	Canada	Pharmacies	Pharmacist-generated educational brochure to patients and deprescribing recommendation to physicians	Yes
• Effect of pharmaceutical care services on outcomes for home care patients with heart failure.[83]	Triller (2007)	United States	Hospital/ Home Health care	Pharmacist in-home medication review with patients and feedback/recommendations to clinicians	No
• Safer Prescribing and Care for the Elderly (SPACE): A pilot study in general practice.[84]	Wallis (2018)	New Zealand	General Practice/ Primary Care	Academic detailing, audit & feedback, and educational mailings to patients	Yes

• NSAID use after bariatric surgery: A randomized controlled intervention study.[85]	Yska (2016)	Netherlands	Inpatient Surgical Health Care	Mailings to patients and their general practitioners on the risks of NSAIDs after bariatric surgery	No

CPOE: commercial computerized provider order entry, EHR: electronic health record, GFR: glomerular filtration rate, NSAIDs: nonsteroidal ant-inflammatory drugs, Rx-PAD: prescription peer academic detailing, STOPP/START: screening tool of older persons' potentially inappropriate prescriptions/Screening tool to alert to right treatment.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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