VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE NON-SURGICAL MANAGEMENT OF HIP & KNEE OSTEOARTHRITIS

Department of Veterans Affairs
Department of Defense

Clinician Guideline Summary

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

The Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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Summary

According to the Centers for Disease Control and Prevention (CDC), 13.9 percent of adults age 25 years and older and 33.6 percent of adults age 65 years and older are affected by osteoarthritis (OA). Arthritis appears to be a significant burden among Veterans of the United States (US) Armed Forces. Research suggests that military service-related overuse and injuries may be a contributing factor for the increased risk of developing OA. Severe OA of the hip and knee causes debilitating pain and is a common cause of mobility impairment in elderly patients.

The Department of Veterans Affairs (VA) and Department of Defense (DoD) have an obligation to ensure that all patients with OA receive a full range of high quality care. This clinical practice guideline (CPG) recommends a framework that includes a structured evaluation and diagnosis of Veterans and Service Members who may be suffering from hip and knee OA. Additionally, the CPG provides treatment options, including pharmacological, non-pharmacological, complementary and alternative medicine, as well as options for referral for surgical consultation.

Topics discussed in this CPG include:

- Diagnosis and evaluation of OA
- Comparative effectiveness of pharmacological therapies for OA
- Comparative effectiveness of non-pharmacologic therapies
- Comparative effectiveness of complementary and alternative medicine
- Referrals for surgical consultation

OA is typically diagnosed based on the patient's medical history and a physical examination. Patients with OA may have morning joint stiffness that usually resolves within 30 minutes. As the disease progresses, prolonged joint stiffness and joint enlargement may also become evident. Although radiographs are not required to make a diagnosis of knee OA, they can be used to confirm the diagnosis and to rule out fracture, osteonecrosis, malignancy, or other conditions. Primary care providers could consider radiographs such as the weight-bearing tunnel or Rosenberg view to aid in differential diagnosis and guide the overall treatment plan.

A management plan for a patient with OA involves a partnership between the patient and primary care provider to develop an individualized course of treatment that can provide optimal results. Decisions regarding pharmacological therapy should be based on a risk benefit assessment, patient preference, and resource utilization. This process will allow selection of pharmacologic agents with proven benefit to be used in conjunction with non-pharmacologic interventions. Non-pharmacologic therapies (i.e., physical therapy (including aquatic therapy, land-based strength therapy, and manual physical therapy), as well as acupuncture and chiropractic care) should also be considered during the development of a patient's management plan. Lastly, the primary care provider may consider referral for surgical evaluation for OA patients that do not find relief through pharmacologic and/or non-pharmacologic therapies.

The goal of this CPG is to assist primary care providers in developing a comprehensive care program for patients with OA in order to achieve maximum functionality and independence, as well as improve patient and family quality of life.

Algorithm

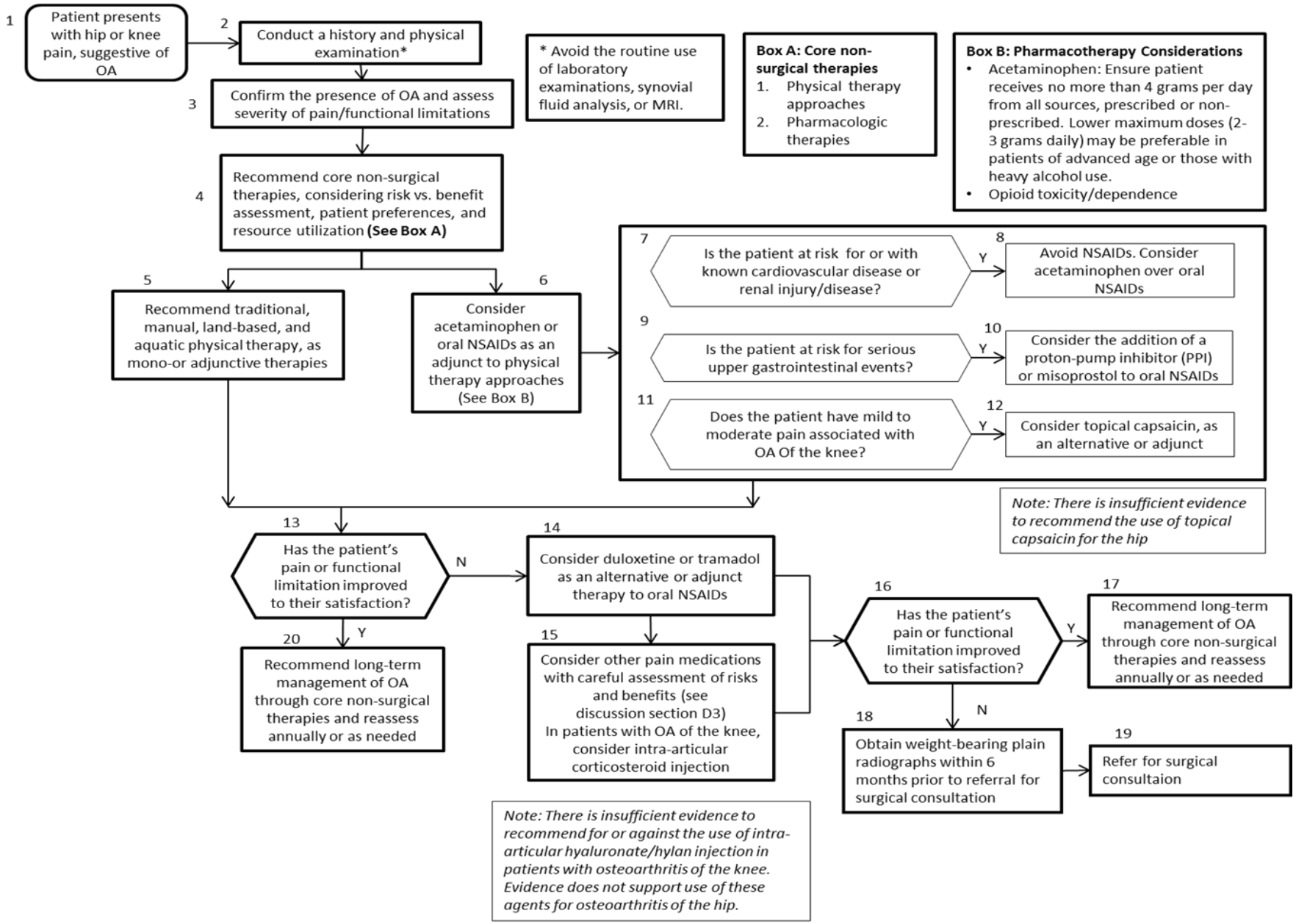
1
Patient presents with hip or knee pain, suggestive of OA
2
Conduct a history and physical examination*
3
Confirm the presence of OA and assess severity of pain/functional limitations
4
Recommend core non-surgical therapies, considering risk vs. benefit assessment, patient preferences, and resource utilization (See Box A)
* Avoid the routine use of laboratory examinations, synovial fluid analysis, or MRI.
Box A: Core non-surgical therapies
1. Physical therapy approaches
2. Pharmacologic therapies
Box B: Pharmacotherapy Considerations
• Acetaminophen: Ensure patient receives no more than 4 grams per day from all sources, prescribed or non-prescribed. Lower maximum doses (2-3 grams daily) may be preferable in patients of advanced age or those with heavy alcohol use.
• Opioid toxicity/dependence
5
Recommend traditional, manual, land-based, and aquatic physical therapy, as mono-or adjunctive therapies
6
Consider acetaminophen or oral NSAIDs as an adjunct to physical therapy approaches (See Box B)
7
Is the patient at risk for or with known cardiovascular disease or renal injury/disease?
Y
8
Avoid NSAIDs. Consider acetaminophen over oral NSAIDs
9
Is the patient at risk for serious upper gastrointestinal events?
Y
10
Consider the addition of a proton-pump inhibitor (PPI) or misoprostol to oral NSAIDs
11
Does the patient have mild to moderate pain associated with OA Of the knee?
Y
12
Consider topical capsaicin, as an alternative or adjunct
Note: There is insufficient evidence to recommend the use of topical capsaicin for the hip
13
Has the patient's pain or functional limitation improved to their satisfaction?
N
14
Consider duloxetine or tramadol as an alternative or adjunct therapy to oral NSAIDs
Y
20
Recommend long-term management of OA through core non-surgical therapies and reassess annually or as needed
15
Consider other pain medications with careful assessment of risks and benefits (see discussion section D3)
In patients with OA of the knee, consider intra-articular corticosteroid injection
16
Has the patient's pain or functional limitation improved to their satisfaction?
Y
17
Recommend long-term management of OA through core non-surgical therapies and reassess annually or as needed
N
18
Obtain weight-bearing plain radiographs within 6 months prior to referral for surgical consultation
19
Refer for surgical consultaion
Note: There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with osteoarthritis of the knee. Evidence does not support use of these agents for osteoarthritis of the hip.

Table 1: Evidence-Based Clinical Practice Recommendations for the Non-Surgical Management of Osteoarthritis

Recommendation	Grade
Diagnosis and Evaluation	
1. Clinicians should conduct a history and physical examination for all patients, with an emphasis on the musculoskeletal examination.	EO
2. Clinicians may use plain radiography to confirm the clinical diagnosis of hip and knee osteoarthritis.	C
3. Clinicians should not use magnetic resonance imaging (MRI) as an evaluative tool to diagnose, confirm, or manage the treatment of osteoarthritis.	D
4. Clinicians should avoid routine use of laboratory examinations or synovial fluid analysis to diagnose osteoarthritis of the hip and/or knee.	EO
Core Non-Surgical Treatment Principles	
5. The decision to prescribe any intervention should be based on consideration of assessment findings, risk vs. benefit analysis, pain severity, functional status, patient preference, and resource utilization.	EO
6. For patients with osteoarthritis of the hip and/or knee, clinicians should attempt the core non-surgical therapies prior to referral to surgery.	C
7. For patients with osteoarthritis of the hip and/or knee, clinicians should refer for physical therapist services early on, as part of a comprehensive management plan.	B
8. Clinicians should refer overweight or obese patients (defined by a BMI > 25 kg/m^2) with osteoarthritis of the knee to a weight management program to lose a minimum of five percent body weight and maintain this new level of weight.	C
9. Clinicians should refer overweight or obese patients (defined by a BMI > 25 kg/m^2) with osteoarthritis of the hip to a weight management program to lose a minimum of five percent body weight and maintain this new level of weight.	EO
Physical Therapy Approaches	
10. For patients with osteoarthritis of the knee, the addition of manual physical therapy as an adjunct to traditional physical therapy and supervised exercise can improve pain, function, and walking distance.	B
11. For patients with osteoarthritis of the hip, the addition of manual physical therapy as an adjunct to traditional physical therapy and supervised exercise can improve pain, function, and range of motion.	B
12. For adults with osteoarthritis of the knee who do not tolerate land-based therapeutic exercise, clinicians should consider adjunctive aquatic physical therapy.	C
13. For patients with osteoarthritis of the knee or hip, the prescription and training of ambulation or walking aids should be carried out by a physical therapist or the referring provider.	EO
Pharmacologic Therapies	
14. In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral non-steroidal anti-inflammatory drugs (NSAIDs) as first line treatment.	B
15. Clinicians should ensure that patients receive no more than four grams of acetaminophen daily from all sources of prescribed and non-prescribed medications.	A
16. In patients requiring treatment with oral NSAIDs and who are at risk for serious upper gastrointestinal (GI) adverse events, clinicians should consider the addition of a proton-pump inhibitor (PPI) or misoprostol.	A

Recommendation	Grade
17. Clinicians should consider the balance of benefit and potential harm in prescribing oral NSAIDs in patients at risk for or with known cardiovascular disease or renal injury/disease.	B
18. In patients with mild to moderate pain associated with osteoarthritis of the knee, topical capsaicin can be considered as first line or adjunctive therapy.	C
19. There is insufficient evidence to recommend for or against the use of topical capsaicin for the hip as first line or adjunctive therapy.	I
20. For patients with persistent moderate or moderately severe osteoarthritis pain, clinicians may offer duloxetine or tramadol as an alternative or adjunct to oral NSAIDs.	B
21. For patients with persistent severe osteoarthritis pain who have contraindications, inadequate response, or intolerable adverse effects with non-opioid therapies and tramadol, clinicians may consider prescribing non-tramadol opioids.	C
22. For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection.	C
23. There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with osteoarthritis of the knee; however, it may be considered for patients who have not responded adequately to nonpharmacologic measures and who have an inadequate response, intolerable adverse events, or contraindications to other pharmacologic therapies.	I
24. For patients with moderate to severe osteoarthritis of the hip, clinicians may consider imaging/ultrasound directed corticosteroid injection to reduce pain.	C
25. Intra-articular injection of hyaluronate/hylan is not recommended for patients with osteoarthritis of the hip.	EO
Complementary and Alternative Therapies	
26. In patients with hip and/or knee osteoarthritis, there is insufficient evidence to recommend for or against the use of dietary supplements for relief of pain and improved function.	I
27. In patients with hip and/or knee osteoarthritis, clinicians should not prescribe chondroitin sulfate, glucosamine, and/or any combination of the two, to treat joint pain or improve function.	D
28. In adults with hip and/or knee osteoarthritis, there is insufficient evidence to recommend for or against referral for short term trial needle acupuncture or chiropractic therapy for relief of pain and improved function.	I
Referrals for Surgical Consultation	
29. For patients with osteoarthritis of the hip and/or knee, who experience joint symptoms (such as pain, stiffness, and reduced function) with substantial impact on their quality of life (individualized based upon patient assessment), and who have not benefited from the core non-surgical therapies, clinicians may offer referral for joint replacement surgery.	B
30. In patients with osteoarthritis of the hip and/or knee considered for surgical consultations, clinicians should obtain weight-bearing plain radiographs within 6 months prior to the referral to surgical consultation.	B
31. In candidates for joint replacement of the hip and/or knee, joint injections should not be given into the involved joint if surgery is anticipated within three months.	EO

Strength of Recommendations

In order for the clinician to be aware of the evidence base behind the recommendations and the weight that should be given to each recommendation, the recommendations are keyed according to the level of confidence with which each recommendation is made. The graded recommendations are based on two main dimensions: 1) net benefit of an intervention and 2) certainty of evidence associated with that net benefit. When evidence is limited, the level of confidence also incorporates clinical consensus with regard to a particular clinical decision. The strength of recommendation is based on the level of the evidence and graded using the USPSTF rating system (see Table 2. Strength of Recommendation Rating).

Table 2. Strength of Recommendation Rating (SR)

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Grade of EO for Expert Opinion: To grade the recommendations for the guideline, the Working Group members used a variation of the USPSTF grading framework to provide a grade of EO for "Expert Opinion." Given that evidence-based clinical practice guidelines have to be used in real practice settings for Veterans and Service Members, a grade of I for insufficient evidence may not provide useful guidance for supporting clinical decisions. In particular, we considered certain instances in which evidence suggests a Substantial or Moderate net benefit, but the certainty/strength of that evidence is Low. In those instances, rather than concluding that the evidence is insufficient to support a clinical decision, we relied on Expert Opinion to support a recommendation. A grade of EO does not imply that the evidence is strong (it is still Low). Rather, it suggests that the magnitude of net benefit (Substantial or Moderate) is of sufficient clinical importance to make a recommendation, even if it is based on Low certainty (weak evidence).

Table 3: Pharmacologic Agents for the Treatment of Osteoarthritis*+

Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
COX-2 selective NSAIDs:[a]						
Celecoxib	CELEBREX	C	100-200 mg	200 mg	once or twice daily	Max 200 mg/day for OA
Partially selective NSAIDs:[a]						
Etodolac	generic only/XR	C, T; C (XR)	200 mg	400 mg	2-4 times daily	XR up to 1200/daily
Meloxicam	MOBIC/generics	T, Susp	7.5 mg	15 mg	once daily	Max dose is 15 mg daily
Nabumetone	generic only	T	1000 mg	2000 mg	once daily	May divide twice daily. Max dose is 2000 mg daily
Non-aspirin, nonselective NSAIDs:[a]						
Diclofenac potassium/sodium	generics	several	50 mg	75 mg	2-3 times daily	Max total daily dose is 150 mg. May divide up to 3 times daily
Diclofenac sodium	VOLTAREN XR	T	100 mg	100 mg	once daily	Max dose is 100 mg daily
Diflunisal	generic only	T	250 mg	750 mg	twice daily	Max dose is 1500 mg daily
Fenoprofen	NALFON/generics	C, T	300 mg	600 mg	3-4 times daily	Higher renal risk. Total daily dose should not exceed 3,200 mg
Flurbiprofen	ANSAID/generics	T	50-100 mg	100 mg	twice daily	Max daily dose is 300 mg
Ibuprofen	generics	several	400 mg	800 mg	3-4 times daily	Max dose in chronic pain is 2400 mg daily
Indomethacin	INDOCIN/SR/generics	C, Supp, Susp	25-50 mg (IR) 75 mg (SR)	50 mg 75 mg	2-3 times daily 1-2 times daily	May divide up to 4 times daily (IR). Max dose is 150 mg daily
Ketoprofen IR	generic only	C; OTC T	50 mg	75 mg	3 or 4 times daily	Max dose is 300 mg daily
Ketoprofen ER	generic only	C	200 mg		once daily	
Meclofenamate sodium	generic only	C	50 mg	100 mg	4 times daily	May give 3 times daily. Max dose is 400 mg daily
Naproxen/-EC	NAPROSYN/generics	T, susp	250 mg	500 mg	twice daily	Max dose in chronic pain is 1000 mg daily
Naproxen Sodium	ANAPROX/generics	T	275 mg	550 mg	twice daily	Max dose in chronic pain is 1100 mg daily
Oxaprozin	DAYPRO/generics	T	1200 mg	1800 mg	once daily	Max dose is 26 mg/kg up to 1800 mg, whichever is lower
Piroxicam	FELDENE/generics	C	10 mg	20 mg	once daily	Max dose is 20 mg daily. May divide twice daily
Sulindac	CLINORIL/generics	T	150 mg	200 mg	twice daily	Max dose is 400 mg daily
Tolmetin	generic only	T, C	400-600 mg	600 mg	3 times daily	Max dose is 1800 mg daily
Aspirin and Salsalate						

Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Aspirin	several	T, Supp	1000 mg	1000 mg	3 times daily	May increase to 4 times daily Max dose is 4000 mg daily
Salsalate	several	T	500 mg-750 mg	1000 mg	2-3 times daily	May increase to 3 times daily Max dose is 3000 mg daily
Acetaminophen and Supplements						
Acetaminophen	several	several	650 mg	1300 mg	3-4 times daily (Max dose 2-4 grams daily, depending upon the patient)	Max 3000-4000 mg/day Consider lower total daily doses (e.g., 2-3 grams) in elderly patients or in those with heavy use of alcohol The total daily dose of acetaminophen from all sources (single and multiple ingredient products) must not exceed 4000 mg/day
Chondroitin	several	several	400 mg		3 times daily	Large variation in delivered dose Not recommended due to lack of evidence showing benefit
Glucosamine	several	several	500 mg		3 times daily	Large variation in delivered dose Not recommended due to lack of evidence showing benefit
Topical Therapies						
Capsaicin	generics	cream, gel, liquid, lotion Varied concentrations: 0.025%-0.075%	--	--	Apply 3-4 times daily	Patients may experience burning/tingling sensation in the first few days of use. Instruct patients to wash their hands with soap and water after application.
Diclofenac	Pennsaid	Soln 1.5 and 2%	40 drops	40 drops	4 times daily	Local skin irritation
Diclofenac	Flector	Patch 1.3%	1 patch (180 mg)	1 patch (180mg)	twice daily	Not FDA approved for OA Local skin irritation
Diclofenac	Solaraze	Gel 3%	--	--	twice daily	Local skin irritation
Other Therapies						

Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Duloxetine	Cymbalta/generics	Delayed release C	30 mg for 1 week, increase to 60 mg conce daily	60 mg	Once daily	Max dose is 60 mg daily. Higher doses are not associated with improved outcomes but a higher rate of adverse events is reported Avoid in end-stage renal disease or CrCl <30 ml/min or in patients with substantial alcohol intake Refer to prescribing information for other details including contraindications, drug-drug interactions, warnings and precautions and adverse events.
Tramadol (IR)	generics	T, several	25-50 mg	100 mg	Every 4-6 hours Max daily dose 400 mg	For patients not requiring rapid onset of pain relief, initiate dosing at 25 mg 4 times daily, increasing by 25 mg every 3 days until reaching 25 mg 4 times daily, and so on. When combined with certain drugs or in those patients with a history of seizure disorder, tramadol may increase the risk of seizures.

Hyaluronate/Hylan Injections: Treatment Course (Each injection is given at weekly intervals)			
Hyaluronate/Hylan	**Frequency**	**Volume**	**Notes**
Euflexxa	3 weekly; repeat approved	2.0 ml	---
Gel-One	Single injection	3.0 ml	Caution in those with avian allergy
Hyalgan	3 or 5 weekly	2.0 ml	Caution in those with avian allergy
Orthovisc	3 to 4 weekly	2.0 ml	---
Supartz	3 or 5 weekly	2.5 ml	Caution in those with avian allergy
Synvisc	3 weekly	2.0 ml	Caution in those with avian allergy
Synvisc-One	Single injection	6.0 ml	Caution in those with avian allergy

*Refer to VA or DoD formularies for availability of agents or comparable agents. The list of available formulations may not be all-inclusive or may change with time as will generic availability. +For additional details on warnings and precautions, drug-drug interactions, etc., refer to the prescribing information for the individual agents of interest.

[a]All NSAIDs have the potential to increase the risk for cardiovascular (CV) events and therefore should be used at the lowest effective dose for the shortest possible duration. Naproxen has a neutral or lowest risk for adverse CV events. Use with caution or avoid use of NSAIDs in patients with renal impairment, history of gastrointestinal bleeding, uncontrolled hypertension, congestive heart failure, advanced liver diseases, known cardiovascular disease, patients receiving anticoagulants, etc.

Table 4: Key Findings from Studies on Nutraceuticals/Dietary Supplements (Glucosamine and Chondroitin)

Dietary Supplement	Summary of Study Characteristics	Key Findings
Ayurvedic formulations (components: Shunthi and Guduchi)	One RCT rated as Good quality; 5 Ayurvedic formulations were compared to placebo and glucosamine sulfate; total n = 245 Chopra et al. 2011	No statistically significant improvements in pain or function for any group.
Boiogito (Sinomenium Stem)	One RCT (unblinded) rated as fair compared Boiogito with loxoprofen vs. loxoprefen alone; n = 50 Majima et al. 2012	Both groups experienced improvements in pain from baseline and physical function.
Collagen Derivatives (Indentured Collagen; Gelatin; Collagen Hydrolysate)	One systematic review of 8 trials included 6 RCTs, 1 quasi-RCT, and 1 crossover design study, total n = 1187. The review was rated as Good quality, but the studies included were low to moderate in quality. VanVijven et al. 2012	For both pain and function, Collagen (various forms) did not appear to be more effective than placebo, based on meta-analysis of 3 trials.
Curcuma (domestica and longa)	Two RCT's, both rated as Fair quality (lack of blinding); compared curcuma to placebo plus rescue medication or curcuma to ibuprofen. Madhu et al. 2012 Kuptniratsaikul et al. 2009	One trial found statistically significant improvements in pain and function for patients treated with curcuma vs placebo; the other did not.
Derris Scandens	One RCT rated as Fair for lack of blinding; compared Derris Sandens to naproxen, n=107. Kuptniratsaikul et al. 2011	No statistically significant findings by treatment group in mean pain reduction or for function.
Duhuo Jisheng Wan	One RCT rated as Good, n =200, compared Duhuo Jisheng Wan to diclofenac. Teekachunhatean et al. 2004	No statistically significant difference in measures of pain or function seen between groups.
Eggshell membrane	One RCT rated as Good quality, n =60, compared eggshell membrane to placebo. Ruff et al. 2009	Eggshell group showed a statistically significant but not clinically meaningful reduction in pain compared to placebo; there was no statistically significant improvement in function.
Flavocoxid ("Limbrel" proprietary product)	One RCT with a quality rating of Good, n=223; compared product to naproxen. Levy et al. 2010	There were no between group differences in pain or function.
Ginger	One Good quality systematic narrative review and one Good quality RCT. Leach et al. 2008 Zakeri et al. 2011	Within the Leach review, 3 trials compared ginger to placebo; one trial found a statistically significant improvement in pain in the ginger group. In the Leach review, 2 trials compared ginger to ibuprofen; there was no statistically significant difference between groups. Improvements in function favored ibuprofen only.
MESACA (Methylsulfonylmethane and	One RCT of Good quality compared MESACA to placebo (total n = 30).	Both groups experienced statistically significant improvements in pain from baseline, but the between group difference

Dietary Supplement	Summary of Study Characteristics	Key Findings
Boswellia Acid Combination)	Notarnicola et al. 2012	favored placebo; however, the MESACA group used significantly less rescue medication than at baseline. There was no statistically significant difference in measures of function between groups.
Phytalgic (proprietary blend of fish oil; vitamin E; uritica dioica)	One RCT rated as Good quality compared Phytalgic to placebo (total n = 81). Jacquet et al. 2009	There was a statistically significant reduction in pain and improved function for the Phytalgic group compared to placebo.
Pycnogenol	One RCT rated as Good quality compared Pycnogenol to placebo (total n = 100). Cisar et al. 2008	There was no statistically significant difference between Pycnogenol and placebo for pain or daily activities; patients on Pycnogenol were able to decrease their analgesic doses, but statistical significance was not reported. Total WOMAC score was improved significantly for the Pycnogenol group.
SKI 306X (Clematis Radix, Trichosanthes Root, Prunella Spike)	N – 249, OA of the knee, patients aged 35-75 years; SK1306X with placebo, administered 200 mg 3 x/d for 4 weeks, vs 100 mg dicolfenac 100 mg/d plus placebo. Jung et al. 2001	Statistically significant difference vbetween groups in favor of diclofenac for function; no between group difference for pain.
SAMe	A systematic review was rated as Good, but included trials of low quality rating; trials compared SAMe to placebo. One recently published RCT was considered Good quality and compared SAMe to nabumetone. Rutjes et al. 2009 Kim et al. 2009	Rutjes et al. performed a meta-analysis of 2 RCTs and found no between group difference in pain reduction or improved function. In the RCT by Kim, there was no statistically significant difference for pain or function between groups.
Sierrasil	One RCT with a Good quality rating compared high dose Sierrasil, low dose Sierrasil and placebo (total n = 107). Miller et al. 2003	There was no statistically significant between group difference for pain scores; all groups improved from baseline for measures of function, but it was not stated if groups differed in the improvement.
Siriraj Wattama Recipe (proprietary blend of 15 herbs)	One RCT of Fair quality with unblinded design compared the supplement to diclofenac (total n = 60). Pengkhum et al. 2012	No statistically significant between group difference for pain score or function.