1. A man, 66 years of age, with a history of knee osteoarthritis (OA) is experiencing increasing pain at rest and with physical activity. He also has a history of depression and coronary artery disease. He currently takes sertraline 100 mg po daily, aspirin 81 mg po daily, pravastatin 20 mg po daily, and lisinopril 10 mg po daily. His primary care provider is considering NSAID therapy. Which risk factors may predispose this patient to gastrointestinal (GI) complications from the addition of nonsteroidal anti-inflammatory drug (NSAID) therapy?

A. Age and gender
B. Age, history of OA, and pravastatin use
C. Age, use of sertraline, and use of low-dose aspirin***
D. Age and use of low-dose aspirin

Correct Answer: C

Risk factors for NSAID-associated GI complications include age older than 65 years, history of prior complicated peptic ulcer disease or upper GI bleed, history of chronic debilitating conditions, including RA and cardiovascular disease, Helicobacter pylori infection, use of multiple NSAIDs, use of NSAIDs at high doses, and concurrent use of low-dose aspirin, antiplatelets, anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors (SSRIs). The use of low-dose aspirin alone, in the absence of other risk factors, is associated with an increased risk for both GI bleeding and death from GI complications.

2. Based on a meta-analysis of observational studies, which one of the following NSAIDs has been associated with a higher risk of upper GI complications in comparison with other NSAIDs:

A. Ketorolac***
B. Naproxen
C. Ibuprofen
D. Celecoxib

Correct Answer: A

A meta-analysis of observational studies that summarized relative risks of upper GI complications associated with the use of individual NSAIDs found the highest risk with ketorolac and piroxicam and the lowest risk with ibuprofen and celecoxib.

3. Which one of the following is considered to be an important contributing factor to the development of NSAID-associated GI damage:

A. Direct toxic effect to GI tract after oral ingestion
B. Increased growth of Gram-positive bacteria
C. Prostaglandin deficiency caused by COX inhibition***
4. Which one of the following medications has not been shown to be effective for the prevention of NSAID-associated mucosal injury and ulcer formation:

A. High-dose famotidine
B. Misoprostol
C. Pantoprazole
D. Sucralfate

Correct Answer: D

There are 2 approaches to prevent the development of mucosal injury and ulcer formation for NSAID users. These include (1) adjunctive treatment with a proton pump inhibitor (PPI), high-dose (e.g., double dose) histamine-2-receptor antagonist (H2RA), or misoprostol; and (2) substitution of a traditional NSAID with a COX-2 inhibitor. Gastroprotective strategies that have not been shown to prevent ulceration include use of standard dose H2RAs, sucralfate, or enteric-coated or buffered NSAID formulations.

5. Which one of the following statements about the use of gastroprotective strategies for the prevention of NSAID-associated GI complications is FALSE:

A. Proton pump inhibitors (PPIs) have been shown to be more effective than histamine-2-receptor antagonists (H2RAs) for healing ulcers in patients who are continued on NSAIDs
B. Standard-dose H2RAs have been shown to decrease ulcer formation by more than 40%***
C. The dose of misoprostol found to be effective in clinical trials may limit its use in practice because of poor tolerability
D. When compared with diclofenac plus omeprazole, celecoxib use was associated with a lower incidence of GI toxicity in patients with OA and rheumatoid arthritis (RA)

Correct Answer: B

Gastric acid production can be reduced by 30% to 60% over 24 hours with the use of H2RAs; however, their use at standard doses has not been shown to decrease ulcer formation. Most trials evaluating the efficacy of H2RAs for the prevention of GI complications included ibuprofen and famotidine at double dose (e.g., 40 mg twice daily). A meta-analysis of
randomized, controlled trials studying the use of high-dose H2RAs found that they substantially reduced the incidence of endoscopic ulcers by up to 46%.

6. A woman, 57 years of age, was recently diagnosed with RA. She has been initiated on a disease-modifying antirheumatic drug, but requires more immediate pain relief. Her rheumatologist is recommending that she begin NSAID therapy. She has no other medical conditions and takes only acetaminophen, as needed, for headaches and a daily multivitamin. She is considered to be at low risk for cardiovascular events. Based on the guidelines for the prevention of NSAID-related ulcer complications, which one of the following statements is TRUE:

A. She is considered to be at high risk for GI complications and should be started on celecoxib plus a gastroprotective agent
B. She is considered to be at moderate risk for GI complications and should be started on a traditional NSAID plus a gastroprotective agent
C. She is considered to be at low risk for GI complications and should be started on a traditional NSAID alone***
D. Risk cannot be determined from the information available

Correct Answer: C

The American College of Gastroenterology (ACG) has identified 3 risk categories to assist with decision-making for the initiation of NSAID therapy. Patients at low risk for GI and cardiovascular events, as is the case for this patient, can be initiated on a traditional NSAID alone without the need for gastroprotection.

7. A man, 68 years of age, with hip OA is considered to be at very high risk for NSAID-associated GI complications, but at low risk for cardiovascular events. Which one of the following regimens is MOST appropriate if this patient is started on NSAID therapy:

A. Traditional NSAID plus standard dose H2RA
B. Traditional NSAID plus PPI
C. COX-2 inhibitor alone
D. COX-2 inhibitor plus PPI***

Correct Answer: D

For patients at very high-risk for GI complications, the use of a COX-2 inhibitor alone may not sufficiently provide enough reduction in the risk of GI complications and the addition of a PPI to treatment may be considered.
8. **Which one of the following statements regarding adherence to gastroprotective agents in the setting of NSAID use is TRUE:**

A. Rates of adherence have been found to vary based on the presence of risk factors

B. There is a direct relationship between adherence and the risk for upper GI complications

C. It has been shown that patient adherence to these medications increases within the first year of treatment

D. Assessment of prescriber trends has revealed consistent renewal of therapy, even after 2 years of NSAID use

**Correct Answer: A**

A retrospective, cross-sectional study of United States veterans using NSAIDs found that adherence rates varied based on the presence of risk factors: Those who had less risk factors reported an adherence of 27% and those with at least 3 risk factors reported an adherence of more than 40%. A retrospective, longitudinal observational study of general practitioner prescribing trends in France found that within 2 years after prescribing PPIs for patients on NSAID therapy, about 1/3 of patients did not have their prescriptions renewed by their physician and the risk for upper GI injury was higher among patients with discontinued PPI prescriptions. It has been shown that the number of patients who adhere to gastroprotective agents decreases substantially within the first year of treatment. Adherence to therapy with gastroprotective agents has an inverse relationship to the risk of upper GI events for NSAID users and can be associated with a fourfold increase in the risk of upper GI complications for high-risk patients.

9. **Which one of the following statements about fixed-dose combination therapies is FALSE:**

A. When compared with ibuprofen 800 mg 3 times daily, ibuprofen/famotidine 800/26.6 mg 3 times daily was associated with a statistically significantly lower rate of endoscopic gastric ulcers and upper GI ulcers

B. Naproxen-esomeprazole magnesium and celecoxib had comparable improvements in pain and function from baseline and similar tolerability when studied in patients with symptomatic knee OA

C. When compared with enteric-coated naproxen alone, naproxen-esomeprazole magnesium use was associated with a statistically significantly lower incidence of endoscopic ulceration after 6 months

D. The cost of these formulations is similar to the cost associated with the use of both drugs as separate formulations

**Correct Answer: D**

Fixed-dose formulations have higher costs, but the pharmacoeconomic data that account for all health care-related costs associated with NSAID-associated GI toxicity are unavailable.
10. Which one of the following novel approaches to NSAID therapy may provide enhanced drug absorption and a quicker onset of analgesia:

A. Submicron NSAIDs***
B. Nitric oxide-release NSAIDs
C. Hydrogen sulfide-releasing NSAIDs
D. Phosphatidylcholine-linked NSAIDs

Correct Answer: A

NSAID formulations developed through submicron technologies and nanotechnologies may enhance drug dissolution, thereby improving absorption and bioavailability, which can result in more immediate analgesia. Nitric oxide-releasing NSAIDs may enhance anti-inflammatory and antinociceptive activity, while maintaining the integrity of the mucosal environment. Hydrogen sulfide not only has gastroprotective effects, but can also reverse preexisting ulcers. The noncovalent linking of phosphatidylcholine, an essential phospholipid, to an NSAID may reduce gastric damage and maintain intestinal health, while preserving its analgesic and anti-inflammatory effects.