THE NORTHERN HOSPITAL

NAPROXEN

"The Rehearsal on Stage", grisaille monotype, oil on canvas, 1874, Edgar Degas.

On his death in 1917, Edgar Degas had left behind some 1200 paintings and sculptures in his studio. Fully one quarter of all these works related to ballet dancers. He depicted them not on stage performing but rather behind the scenes, at the bar, rehearsals, resting, chatting, sleeping, adjusting costumes, just before curtain rise or just after curtain fall. He also depicted the sheer hard work and exhaustion this dance form entailed. Many of his

works show tired young ballerinas rubbing sore feet or strained backs. Degas' works provide a unique insight into the off-stage world of the Belle Epoch dancers of Paris.

The origins of ballet lay in the Sixteenth century as a formalized dance that emerged in the Royal Courts of France. Performed exclusively by male dancers at first, it was designed to demonstrate and give praise to the glory of the sovereign. Only later on when dancing become a profession, did female dancers begin to appear.

Centuries passed, and by the 1850s, France no longer had a monarchy. The new technique of toe dancing made females far more suited to the sensibilities of a new Romantic age, who applauded fairies, elves and nymphs. The new dance form allowed women to gracefully glide or even seemingly float across the stage. Lightness and grace were the mode and male dancers quickly receded into the background. By the 1870s male dancers had become mere occasional supports to lift and to catch graceful ballerinas. The ballet was no longer played to royalty, but to a middle and increasingly to a rich new bourgeoisie class, in particular a male dominated class. Partly to cater to the new dance style, but also partly to cater to the male dominated audiences, dance costumes became increasingly skimpier. Skirts originally low calf or full length, rose tantalizingly to the knee and even above. Short skirts billowed out when the ballerinas alighted, prolonging the illusion of them gently floating back to earth, all highlighted by blazing gas lights that up-lit the performance at close range. In an age when it was considered immoral for a woman to show her legs, many grand ladies who accompanied their husbands to performances expressed shock and outrage. It need hardly be said however that that very few male patrons ever expressed any outrage.

Edgar Degas in his beautiful paintings captured the apogee of the Belle Epoch dancers, and recorded it for posterity in his unique and haunting Impressionistic style. Every single one of his works depicted female dancers, conforming to contemporary dance taste. It would not be until Tchaikovsky's music again reinvented ballet, that male dancers made a tentative reappearance in the mid 20th century, led by the great Rudolf Nureyev.

In his work "The Rehearsal on Stage", 1874, we see a typical example of a rehearsal scene. Like all of his works Degas made preliminary sketches, which he then later took back to his studio to complete a pastel or painting. The theatre itself has been readily identified as the old Grand Opera in the Rue Le Peletier, which had a capacity of over one thousand seats. The boxes or loges, also known as the "baths" or "draws" can be seen behind the seated gentleman watching the rehearsal from the stage itself. The loges were exclusively reserved for the director of the Opera and for certain rich or well connected influential subscribers, who were more interested in physical proximity to the dancers than any aesthetic experience. They were also ***the*** *place to be seen. Degas did many of his sketches from one of these private boxes. By the time he had completed "The Rehearsal on Stage", the theatre had actually burnt to the ground. Like all contemporary stages of the pre-electric age, it was ablaze with dangerous naked gas-lit lamps, and it is little wonder that it did eventually burn down. In its place would be built the magnificent new Palais Garnier that we know today.*

The ballerinas in Degas' painting are nameless and unknown to us, as is the gentleman who watches them from his chair on the stage. Rose-Marie and Rainer Hagen have

postulated that perhaps he was the Opera director, or the chief choreographer, or simply a VIP friend of one of the dancers. The Hagens go on to explain; "…Degas was less interested in the ballerinas as individual characters than in their movement and gestures. Their faces are usually pale, anonymous. With regard to their gestures what interested him most was what they did more or less subconsciously when they were not playing to the public"

Toe dancing, it need hardly be said, put a great strain onto young bodies, particularly the feet and the lower back. The best and most famous dancers spent many long hours at the rehearsal halls of the Foyer de la Danse of the Palais Garnier. Girls commenced training at a very young age, and could make their stage debuts at the Grand Opera at the age of just 14 years. Most would retire from the stage by about 35 years of age. Little effective muscle ache relief could be offered to dancers in Degas's time, and after the age of 35 in particular modern NSAIDs such as naproxen would have provided some welcome relief!

NAPROXEN

Introduction

Naproxen (trade name in Australia, **Naprosyn**) is a widely used non-steroidal anti-inflammatory drug, (**NSAID).**

It is a non-selective inhibitor of cyclooxygenase.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, are used for their mild to moderate **analgesic** and **anti-inflammatory** effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed classes of drugs and adverse events related to their use are common.

Although the overall risk of a serious gastrointestinal adverse event such as overt bleeding or perforation is relatively low, there are subsets of patients at much higher risk.

The volume of NSAID use results in a substantial burden of morbidity and mortality, and incurs considerable health care costs.

If NSAIDs are needed, it is best to use the *lowest possible dose* of a *shorter-acting* NSAID for as *short a time* as possible

See also separate Document on NSAID overdose.

History

A team led by Claude Winder from Parke-Davis developed mefenamic acid in 1961

In 1971, a U.K. research team, headed by **Professor John Vane**, demonstrated that aspirin-like drugs could inhibit the synthesis of prostaglandins.

The biochemists **Sune K. Bergström, Bengt I. Samuelsson** and **John R. Vane** were jointly awarded the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

Chemistry

Naproxen belongs to the **aryl-propionic acid** group of NSAIDs (which also includes, **ibuprofen** and **ketoprofen**).

Physiology

Cyclo-oxygenase **(or COX)** has 2 forms:

1. COX 1:

- Generation of PGs involved in GIT mucosal protection.
- Generation of thromboxane within platelets.

2. COX 2:

- Generation of PGs involved in the inflammatory process.
- Generation of PGs within the kidney.

NSAIDs may **non-selectively** to inhibit the COX enzyme or may **selectively** inhibit the COX-1 or COX-2 isoforms.

Classification

Accordingly NSAIDS can be classified as:

1. Non-selective COX inhibitors:

These older agents non-selectively inhibit COX 1 and COX 2.

By their COX 1 action they have side effects with respect to GIT ulceration and anti-platelet action.

By their COX 2 action they can have effects on renal function.

Examples include:

- Indomethacin
- Ibuprofen
- Aspirin
- Diclofenac
- Ketoprofen
- Ketorolac
- Mefenamic acid
- **Naproxen**
- Piroxicam
- Sulindac

2. Selective COX 2 inhibitors, (also termed coxibs):

These have fewer side effects as COX 1 is not inhibited to a large extent.

They may still have effects on renal function however.

Examples include:

- Celecoxib
- Meloxicam
- Etoricoxib
- Parecoxib

Note that some selective COX-2 inhibitors (such as meloxicam) are only selective at *low doses.*

Cyclo-oxygenase-2 (COX-2) selective NSAIDs reduce, but do not completely abolish, the risk of ulcer disease and complications.

Concomitant aspirin use negates the effect.

Most benefit occurs in those at least risk, with less risk reduction in those most at risk.

Moreover, COX-2 selective NSAIDs do not cause fewer *dyspeptic symptoms* than nonselective NSAIDs.

Their increased relative risk for adverse vascular events has limited the use of COX-2–selective NSAIDs in patients with cardiovascular risk factors.

The relative cardiovascular and cerebrovascular risk of nonselective NSAIDs is under evaluation. At the time of writing, naproxen appears to confer the least cardiovascular risk.

Preparation

Naproxen as:

Tablets:

- Standard release: 250 mg, 500 mg.
- Extended release: 750 mg, 1000 mg.
- Liquid: 25 mg/ ml.

Naproxen sodium as:

Tablets:

- Standard release: 275 mg, 550 mg.

Naproxen sodium is used in some formulations. Note that **500 mg naproxen** is equivalent to **550 mg naproxen sodium**.

Mechanism of Action

NSAIDs exert their main effect by inhibition of the enzyme **cyclo-oxygenase (or COX)** with consequent reduction in the synthesis of **pro-inflammatory prostaglandins** derived from **arachidonic acid**, **(see Appendix 1 below).**

Inhibition of **COX−2** results in **anti-inflammatory** and **analgesic action**

Reduction in glomerular filtration rate and renal blood flow occurs with both COX−1 and COX−2 inhibition.

Most NSAIDs are non-selective, inhibiting both COX−1 and COX−2. Although selective COX−2 inhibitors have little or no effect on COX−1 at therapeutic doses, they can still be associated with GI adverse effects.

Aspirin irreversibly inhibits cyclo-oxygenase

Other NSAIDS reversibly inhibit cyclo-oxygenase

Pharmacodynamics

Therapeutic clinical effects of the NSAIDS as a class include:

1. Mild to moderate analgesic
2. Anti-inflammatory action.
3. Mild antipyretic

Note that non-selective NSAIDs can have some mild anti-platelet effects but are *unreliable as a therapeutic agent when compared to aspirin.*

The COX 2 inhibitors do not affect platelet activity.

Pharmacokinetics

Absorption:

- Naproxen is completely absorbed from the GIT after oral administration

Concomitant administration of food can delay the absorption of naproxen but does not affect its extent. After administration of naproxen tablets, peak plasma levels are attained in two to four hours depending on food intake.

Distribution:

- Naproxen has a relatively small volume of distribution which corresponds to about 10 % of the bodyweight in humans.
- At therapeutic levels naproxen is greater than 99 % albumin bound.

Metabolism and excretion:

- Naproxen is metabolised in the liver to 6-ortho-desmethyl naproxen
- The elimination half-life of naproxen is approximately 14 hours.

Indications

Mild to moderate pain

In common with the NSAIDs as a class, indications include:

1. Tension headache
2. Myalgias in general e.g. associated with infections
3. Soft tissue and musculoskeletal traumatic injury
4. Pleuritc pain
5. Inflammatory conditions:
    - Arthritis, arthralgia, tendonitis, fasciitis
6. Osteoarthritis
7. Gout
8. **Dysmenorrhoea**

Note that no single NSAID has been shown to be more effective than any other, but some patients do seem to respond better to one particular agent than to other agents.

Contraindications/ Precautions

Contraindications and precautions of the NSAIDS as a class include:

1. Renal impairment:

   All NSAIDs can cause renal impairment, especially in:

   - The elderly
   - Those who already have renal impairment
   - Those who are taking other nephrotoxic agents.
   - Those who are dehydrated (as prostaglandins are important in maintaining renal blood flow when circulating blood volume is decreased).

2. Elderly, (generally > 65 years):

   - The elderly are at more risk of NSAID adverse effects, particularly renal impairment, heart failure, and GI ulceration..

3. Heart failure

   - Due to the sodium and water retaining properties.

4. Hypertension:

   - Due to the sodium and water retaining properties.

5. Gastritis / oesophagitis/ peptic ulcer disease:

   - The risk of GIT side effects is less with the COX-2 selective agents.

6. Known allergy to NSAIDS.

7. Asthma:

   - NSAIDs in general are a well recognized risk factor for asthma.

     If a person with asthma has taken NSAIDs previously without triggering asthma symptoms, the use of NSAIDs on a future occasion is not contraindicated.

Pregnancy:

Naproxen is a class C drug with respect to pregnancy.

Class C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without

causing malformations. These effects may be reversible. Specialized texts should be consulted for further details.

The use of non-steroidal anti-inflammatory agents (NSAID) during the first trimester has not been associated with an increased risk of congenital malformations.

However, use of NSAID may increase risk of spontaneous abortion, but this has not been conclusively confirmed.

Maternal use of NSAID in late pregnancy has been associated with an increased risk of premature closure of the ductus arteriosus, persistent pulmonary hypertension of the newborn, nephrotoxicity and oligohydramnios.

Therefore, the use of all oral and topical NSAID preparations (except for low dose aspirin) is not recommended during pregnancy. [4]

Breastfeeding

Is generally considered safe, however, if an NSAID is required in a breastfeeding patient, **diclofenac** or **ibuprofen** is preferred. [1]

Adverse Effects

Adverse effects of the NSAIDS as a class include:

1. Exacerbation of CCF

2. Exacerbation of hypertension

3. CVS events:

    - There is some evidence that cardiovascular harm (**stroke/ ACS**) is a general adverse effect of NSAIDs **other than aspirin. This risk is greatest with the selective COX 2 inhibitors, (see also Appendix 3 below).**

    - Low-dose aspirin may reduce the increased cardiovascular risk associated with NSAIDs, but it will increase gastrointestinal adverse effects.

4. GIT upset:

    - Nausea/ dyspepsia

    - Inflammation/ erosions/ ulceration:

      With the secondary complications of dyspepsia, GIT bleeding or perforation.

Upper abdominal pain or discomfort has been reported in up to a half of NSAID users, but symptom analysis cannot reliably distinguish between NSAID-related dyspepsia and pain due to peptic ulceration.

About 15% to 30% of NSAID users have ulcers visible at endoscopy, but many of them are asymptomatic until complications such as anaemia, bleeding or perforation occur

Over-the-counter NSAIDs may also cause dyspeptic symptoms, but their risk of causing ulcer and bleeding appears to be lower than for **prescribed** NSAIDs, because of their lower dose, shorter half-life and generally shorter duration of use. [2]

The **Patient Risk factors** for NSAID-induced upper gastrointestinal bleeding or perforation are as follows, (in order of risk):

- ♥ **Older age**
- ♥ Past history of upper gastrointestinal bleeding
- ♥ Past history of peptic ulcer disease
- ♥ *Helicobacter pylori* infection
- ♥ Concomitant drugs, including (in order of risk) anticoagulants, antiplatelet drugs, SSRIs and corticosteroids
- ♥ Significant co-morbidity
- ♥ Smoking
- ♥ Excessive alcohol intake

Specific **NSAID risk factors** include:

- ♥ Higher doses
- ♥ Long duration of use:
    - ♥♥ The risk of ulcer is higher with longer-acting NSAIDs such as piroxicam and ketoprofen, than with shorter-acting agents such as **ibuprofen** and **diclofenac.**

5. Renal impairment:

Especially in:

- Elderly

- Those with pre-existing renal impairment

- Dehydration

NSAIDs, in general have been associated with acute interstitial nephritis with haematuria, proteinuria and, occasionally, nephrotic syndrome.

6. Allergic reactions.

- **Allergic type reactions are relatively common with the NSAIDs as a class.**

  NSAIDs, in general can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal and may occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use.

7. Bleeding:

- **Aspirin** produces the strongest effect in this regard via its irreversible effect on COX.

  All other **non-selective** NSAIDs may *slightly* increase risk of bleeding via an antiplatelet effect mediated by reversible COX 1 inhibition.

  The COX 2 inhibitors do not affect platelet activity.

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Rarely:

8 Hepatotoxicity

9 Blood dyscracias

Dosing

Exact dosing regimens can depend on the condition being treated as well as its severity.

In general terms:

Naproxen (standard release):

- 250 - 500 mg twice daily.

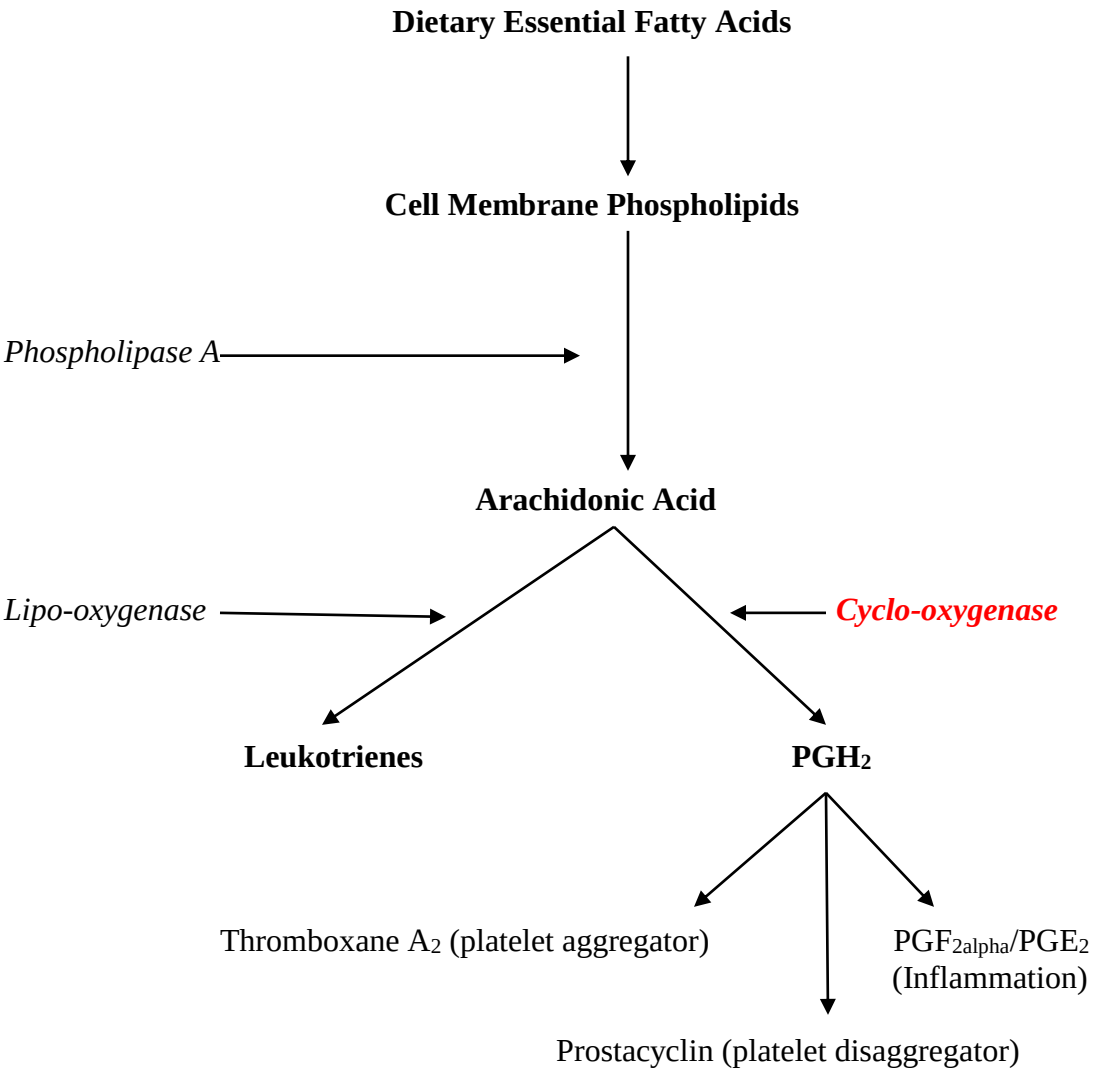
Naproxen (extended release):

- 750 - 1000 mg once daily.

Maximum, daily dose is 1250 mg

Appendix 1

NSAID Action



Platelet aggregation will depend on the ratio:

Prostacyclin
Thromboxane A_2

Aspirin irreversibly inhibits cyclo-oxygenase.

Other NSAIDS reversibly inhibit cyclo-oxygenase

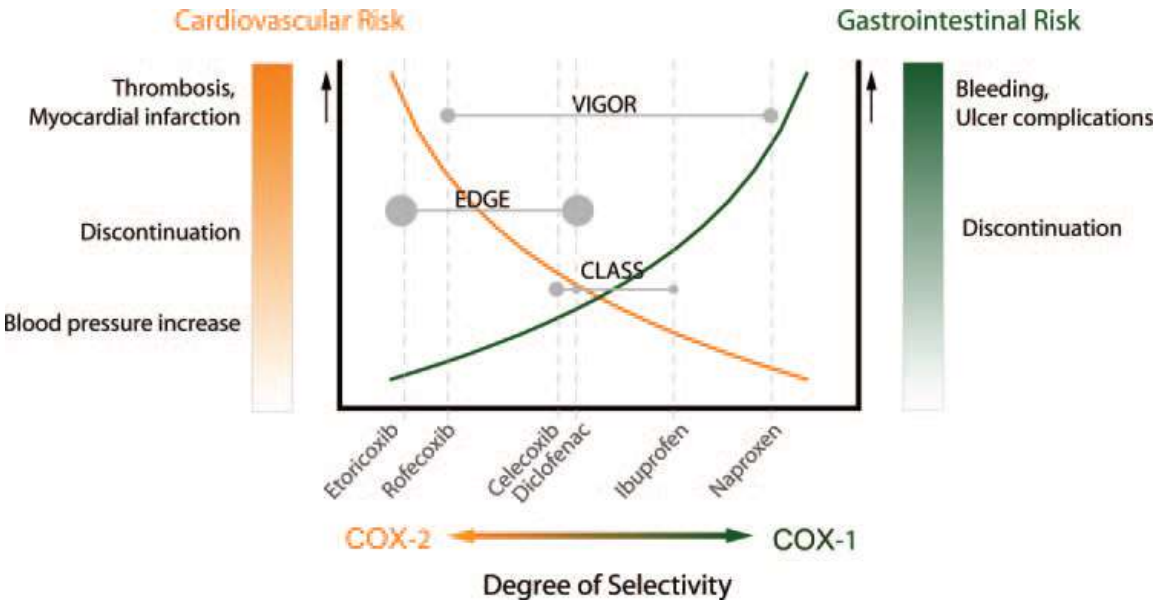
Appendix 2

Considerations in prescribing NSAIDs:

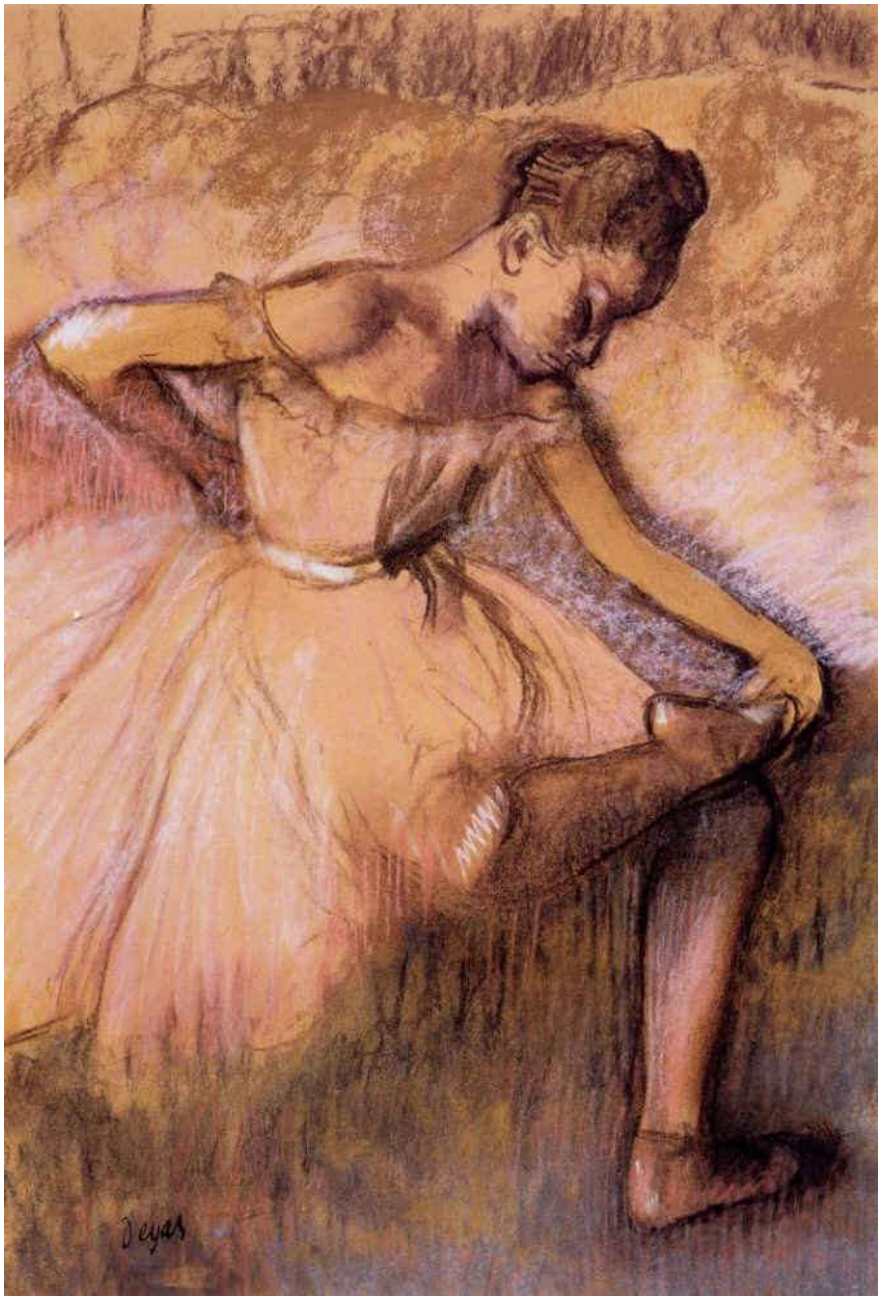
Important points to consider when prescribing Nonsteroidal anti-inflammatory drugs (NSAIDs) include: [2]

- Consider nonpharmacological treatment if appropriate.
- Consider the harm- benefit profile for NSAIDs in each patient and encourage patients to address modifiable cardiovascular risk factors.
- Use the minimal effective dose for the shortest time possible.
- Consider using alternatives such as fish oils or paracetamol to reduce the need for NSAIDs.
- Consider testing for *Helicobacter pylori* infection and treat if present.
- Choose an NSAID with a short half-life for use in the older patient and in patients with renal impairment.
- Use topical NSAIDs where appropriate.
- Use NSAIDs with low risk of gastrointestinal complications (eg ibuprofen, diclofenac).
- Use only one non-aspirin NSAID at a time.
- Monitor by assessing both adverse effects and the need for NSAID use.
- Co-prescription of a **proton pump inhibitor.**

Appendix 3



Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented GI risk, (From Elliott M. Antman et al. Use of Nonsteroidal Anti-inflammatory Drugs, An Update for Clinicians, A Scientific Statement From the American Heart Association. Circulation. 2007;115:1634-1642).(Vigor, Edge, Class refer to various clinical trials).



“The Pink Dancer”, pastel on paper, 1900, Edgar Degas.

References

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4. RWH Pregnancy & Breastfeeding Guidelines, 25 February 2015.

Dr J. Hayes
Reviewed April 2017.