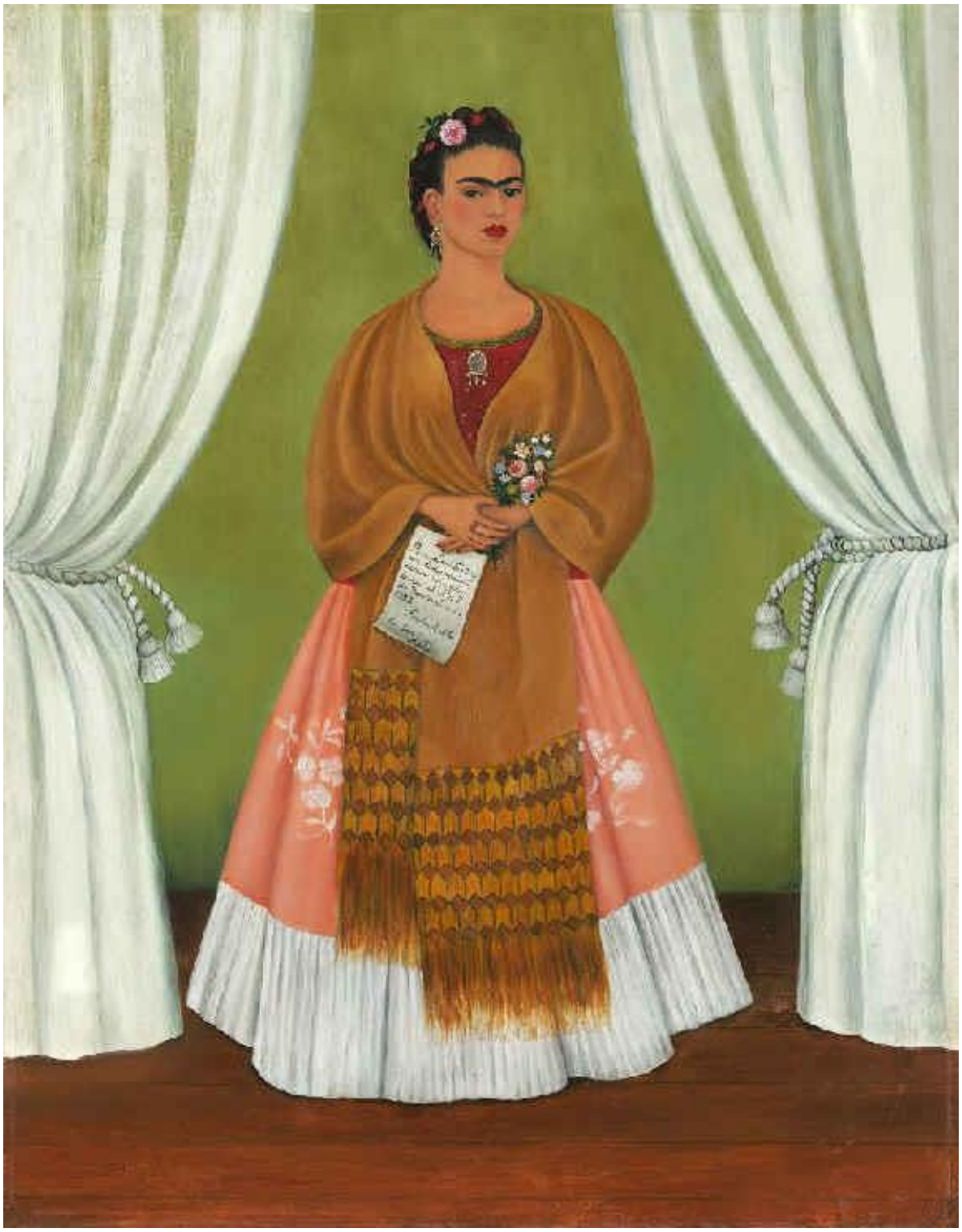
THE NORTHERN HOSPITAL

KETOROLAC



Self Portrait Dedicated to Leon Trotsky (or Between the Curtains), oil on canvas, 1937, Frida Kahlo

"For Leon Trotsky with all love I dedicate this painting on the 7th of November 1937. Frida Kahlo in San Angel, Mexico".

Frida Kahlo, inscription, "Self Portrait Dedicated to Leon Trotsky", 1937.

"I have for long admired the self-portrait by Frida Kahlo de Rivera that hangs on a wall of Trotsky's study. She has painted herself dressed in a robe of wings gilded with butterflies, and it is exactly in this guise, that she draws aside the mental curtain. We are privileged to be present, as in the most glorious days of German Romanticism, at the entry of a young woman endowed with all the gifts of seduction, one accustomed to the society of men of genius".

Andre Breton

For all his years, the Russian's physical appearance was impressive. He carried himself like a hero. His gestures were dynamic, his stride military. Piercing blue eyes behind tortoise shell glasses and a firmly set jaw transmitted intellectual fervour and tenacity, and although he had humour, there was about him a certain commanding severity. He was a man used to getting his way.

He was also a man with a vigorous interest in sex. Around women, Trotsky became especially animated and witty, and though his opportunities were few, his success seems to have been considerable. His was not a romantic or sentimental approach; it was direct and sometimes even crude. He would fondle a woman's knee under the table, or make an unabashedly forthright proposition. At one point his lust for Cristina led him to plan a kind of fire drill, a practice escape over the garden wall at night plus a dash to Cristina's house on Aguayo Street. Only the expressed misgivings of his entourage and possibly Cristina's own fond but firm disinterest finally dissuaded him from the reckless venture.

While his main of white hair, and his even whiter beard made her nickname him "Piochitas" (little goatee) and refer to him as "el viejo" (the old man), Trotsky's reputation as a revolutionary hero, his intellectual brilliance and force of character, strongly attracted Frida. No doubt Rivera's obvious admiration for him fanned the flames: an affair with her husband's friend and political idol would be the perfect retaliation for Rivera's affair with her sister, (Cristina). In any case, Frida employed all her seductive powers to attract Trotsky, enhancing intimacy by speaking to him in English, which Natalia (his wife) did not understand. "Frida did not hesitate to use the word "love"", Jean van Heijenoort recalls. "All my love", were the words she used when she said goodbye to Trotsky".

Frida hardly needed to invent ploys to attract Trotsky. At twenty-nine, she was at that perfect moment when youthful prettiness merges with character to define a more compelling loveliness.....Trotsky began writing letters and slipping them into books he had recommended to Frida. Then, often in the presence of Natalia and Rivera, he would hand Frida the book when she left the house. A few weeks after the end of the Dewey Commission sessions, the coy flirtation had become a full-fledged love affair. The couple met at Cristina's house on Aguayo Street.

Fortunately, Rivera was unaware of the liaison, but by the end of June, Natalia was jealous and deeply depressed. She had been married to Trotsky for thirty five of her fifty five years, and they had left their imprint: her wonderfully warm intelligent face was creased by deep lines. Pathetically, she wrote a note to her husband: "I saw myself in a mirror at Rita's and found I looked much older. Our inner state has an enormous importance in old age: it makes us look younger, it also makes us look older". Trotsky's entourage feared that if the affair was exposed, the scandal would discredit the Russian in the eyes of the world...."

Hayden Herrera, "Frida", 1983.

When the great Russian revolutionary leader Leon Trotsky met Frida Kahlo, at her Blue House in Coyoacan Mexico City in 1937 he was instantly entranced. He pursued her as he did few others. Frida, always enthralled by whom she considered great intellectuals, particularly famous ones at that, was flattered and excited, even though Trotsky was old enough to be her father. For about a half a year she carried on a passionate affair with the charismatic fugitive under the most tensely electric conditions. Circumstances had thrown them together. Trotsky, instigator of the October Revolution, organizer of the Red Army, right hand man of Vladimir Lenin, had lost out in a dramatic power struggle within the Soviet Politburo, to a plodding bureaucrat, by the name of Joseph Stalin. The two were poles apart, Trotsky the brilliant intellectual and idealist visionary who wanted to bring Communism to the world, Stalin the dull party functionary, with a brutal nature, who wanted simply to gain power, hold on to it at all costs, and crush without mercy the slightest opposition. By sheer terror he had come to dominate the politburo, then proceeded to eliminate any he perceived as a threat to his power. Trotsky was number one on his hit-list. The power struggle split not only the Soviets, but the Socialist movement worldwide. Two camps emerged, the "official" Stalinists, who now held supreme power, and the Trotskyists now in exile, who felt that the true ideals of the revolution had been betrayed by power crazed bureaucrats of mediocre abilities.

Trotsky had been living in Oslo, but the Norwegian government had expelled him in December 1936, under repeated threats from Stalin. In Mexico City, Trotskyist sympathizers were led by the great Mexican Muralist Diego Rivera who lobbied Mexican president Lazaro Cardenas, who was sympathetic to Trotsky. Cardenas agreed to grant political asylum to Trotsky and his wife, Natalia. The two would live with Diego and Frida in Coyoacan for just on two years, guarded night and day by heavily armed police and volunteer militia sympathizers. The strict security was not only to protect Trotsky from Russian Stalinist assassins but also from Mexican Stalinists, who had no sympathy for Rivera whom they accused of painting palaces and pandering to American Captains of Industry. The struggle between Stalinists and Trotskyists was every bit as virulent and violent in Mexico City as it was in the Soviet Union. Indeed fellow Mexican Artist David Alfaro Siqueiros would attempt to assassinate Trotsky by leading a group that machine-gunned the Blue House. Fortunately the attempt was unsuccessful and no one was injured It was upon this tense backdrop being watched by the whole world, that Frida found herself caught up in an incredibly dangerous but for her also breathlessly thrilling because of it, liaison with Leon Trotsky, who had become totally obsessed with her. If the affair was to be discovered it would spell disaster both politically and personally. Trotsky's minders who knew of it did their best to persuade him to call off his pursuit of

Frida Kahlo. The public scandal of discovery could mean that he would lose political support thus rendering him stateless and at the mercy of Stalinist agents.

But perhaps even more dangerous than this, Frida feared the consequences of Diego discovering their affair. He never minded her lesbian liaisons, but he could never really come to terms with her affairs with other men. Frida always believed that Diego, who always carried a gun, was perfectly capable of murder should his jealously be tested too closely. There was also the ever present threat that Trotsky's long suffering wife Natalia would create a public "scene". But for Frida the danger of the affair was not only exhilarating it was also cold revenge for the fact that Diego had had an affair with her own sister, Cristina. But in the end the unendurable anxieties took a heavy emotional toll on both parties and the affair ended abruptly sometime in July. Ella Wolfe, one Frida's close friends, believed that it was Frida and not Trotsky who called off the affair.

Some months after the liaison was over and passions had cooled, on 7th of November, 1937, which also happened to be the anniversary of the Russian Revolution, Frida presented Trotsky with a self portrait for his birthday. It is a most unusual work, in that it runs directly counter to the general evolution of her oeuvre. Gone are the Catholic and Pre-Columbian symbols, as are her, by now rich, array of symbolic motifs. It seems a throwback to her earliest European style. Perhaps this was out of respect to her brief lover whom she still admired as a Revolutionary god. She was never really a Trotskyist or a Stalinist, to her these were just political technicalities. She was in awe of Trotsky for his charisma and his intellect, nothing was more of a turn-on for Frida than a creative and romantic visionary, traits which she also adored in her husband, Diego Rivera. It is as if she is too insecure to show her own creativity, ashamed that she may not "measure up" to expectations. And so she plays it safe. She is dressed to kill (but not to thrill), in old style colonial jewellery. She wears a red ribbon in her hair but it does not go anywhere as her usual symbol of the interconnectedness of life, as in so much of her work from this time - it's just simply a ribbon, nothing more. But it is not entirely a throwback. In her first self-portrait, "Self Portrait in a Velvet Dress", oil on canvas, 1926, her aim was to win back her first boyfriend, who had just jilted her. She is pleading and demure, begging to be forgiven. This is where the similarity ends. Though her dress and setting are conservative and demure, her face is most definitely not. It is the mature face of a woman now in control of her own affairs and her own destiny. We see her hallmark piercing gaze straight back at the viewer that can be unsettling if one tries to hold it for too long. Though expressionless there is the aura of defiance and strength. She is no longer the jilted but rather the jilter; and not just any old jilter, the jilter of one of the most famous men in the world. It is a portrait of paradoxes. There is respect for the man she once worshipped as a god - but her respect now as mature woman is just as strong for herself.

There are only two or three extant faded and very scratchy film records of Frida Kahlo. One, mentioned by her magisterial biographer Hayden Herrera, was taken in 1938 just after she had ended her affair with Trotsky. It features Trotsky, his wife Natalia and Diego amoung some other friends of the time. Herrera describes how she coquettishly snuggles into Diego's lap, cuddling him in such a "kittenish way that one suspects her of trying to excite former lover's jealousy" Her lips are curled into the same secretive smirk, Herrera explains, that she wears in one of her most unsettlingly provocative self-

portraits, where she secretly masturbates while displaying her wounds, in the now lost "Remembrance of an Open Wound", 1938.

Although Frida never much cared for Anton Breton's opinion, there is probably no better summary of her life's oeuvre than his famous lines: "There is no art more exclusively feminine, in the sense that, in order to be as seductive as possible, it is only too willing to play alternately in being absolutely pure and at the same time absolutely pernicious. The art of Frida Kahlo is a ribbon about a bomb".

When we prescribe ketorolac in the ED to high risk patients, we play a most dangerous game. This agent is a powerful NSAID and though we much admire it, we must understand it has its limitations. Amoung these limitations is a ceiling effect, and we must resist the thrilling temptation to increase the dosing beyond acceptable limits, as no further benefit will be derived, and only harm will be done. Like Ms. Kahlo, we must show wise judgment, and know when to say enough is enough!

Natalia Sedova and Leon Trotsky are met by Frida Kahlo, Tampico Port, January, 1937.

KETOROLAC

Introduction

Ketorolac (trade name "**Toradol**" amoung others) is a non-steroidal anti-inflammatory agent.

It is available as **oral**, **injectable** and **topical ocular** formulations.

Ketorolac is a **potent** NSAID analgesic and the resulting NSAID related adverse effects can be serious, for example gastrointestinal haemorrhage, surgical haemorrhage and renal impairment.

Despite known "ceiling effects" for the efficacy of non-steroidal analgesia, many deploy enhanced singular doses, seeking better pain control. Increasing the dose of ketorolac however, *beyond the usual recommendations* will not provide better efficacy but will result in increasing risk of developing serious adverse effects. [5]

It should also be noted that a *significant proportion* of patients (up to 25 % in some studies) exhibit little or no response to ketorolac. [5]

See also separate document for NSAID overdose (in Toxicology folder)

History

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

Ketorolac belongs to the **hetero-aryl acetic acid group** of NSIADs (which also include **diclofenac**).

It is a cyclic propionic acid derivative.

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** 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.

Preparations

Ketorolac trometamol as:

Tablets:

- 10 mg.

Ampoules:

- 10 mg in 1 ml ampoule (for IM injection)
- 30 mg in 1 ml ampoule (for IM injection)

Eye Drops:

- 0.5%

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-1** results in **impaired gastric cytoprotection** and **antiplatelet effects**

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

Ketorolac is a **non-selective COX inhibitor.**

Pharmacodynamics

Ketorolac has the following actions:

1. Analgesic:

    - It is a peripherally acting analgesic, via its inhibition of PG synthesis.

      It should also be note that a significant proportion of patients (up to 25 % in some studies) exhibit little or no response to ketorolac. [7]

2. A mild anti-pyretic.

3. Anti-inflammatory

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

The COX 2 inhibitors do not affect platelet activity.

Note **ketorolac** does **not** have:

- Sedative, anxiolytic, opiate or anesthetic effects.
- Any physical dependence effects or withdrawal syndromes.

The onset of analgesic action is: [6]

- Oral: 30 - 60 minutes
- IM / IV: About30 minutes

Peak analgesic effect: [5]

- Oral: 2 - 3 hours
- IM/ IV: ≤ 2 - 3 hours (and so maximal time to pain relief can be **prolonged**).

Duration of analgesic effect is around 4 - 6 hours. [6]

Pharmacokinetics

Absorption:

- Ketorolac is absorbed rapidly and completely via the IM and the oral routes, with 100% bioavailability.

Distribution:

- The Vd of ketorolac is 13 liters
- It is highly protein bound at 99.2%
- It penetrates the BBB poorly.
- Ketorolac can cross the human placenta.
- Ketorolac is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Largely metabolized in the liver.
- Half-life is 5-6 hours.
- Most excretion of ketorolac and its metabolites is via the kidney.

Indications

Short term management of mild to moderately severe pain.

It is **not** recommended in chronic painful inflammatory conditions such as rheumatoid arthritis.

Ocular NSAIDs are used by ophthalmologists as an alternative or adjuvant to ocular corticosteroids

Contra-indications/ 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:

Ketorolac is a category C drug with respect to pregnancy.

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

However, NSAID use has been associated with an increased 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.

Monitoring of the amniotic fluid index (AFI) by ultrasound and the patent ductus arteriosus by fetal echocardiography is recommended in women receiving ketorolac during pregnancy.

Short term use of ketorolac eye drop preparations is unlikely to cause adverse effects, as systemic absorption is expected to be minimal. If ketorolac eye drops is the medicine of choice, to further minimise systemic absorption, apply digital pressure against the inner corner of the eye (over the tear duct) for one to two minutes and blot away excess drops .

Breast feeding:

Small amounts of ketorolac are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

Shorter acting non-steroidal anti-inflammatory agents (NSAID) such as ibuprofen or diclofenac are preferred treatments during breastfeeding.

Women who choose to breastfeed their healthy full-term infant while taking ketorolac should observe the infant for potential adverse effects such as diarrhoea, vomiting, abdominal discomfort and rash.

Short term use of topical preparations, such as eye drops are unlikely to cause adverse effects, as systemic absorption is expected to be minimal.

If ketorolac eye drops is the medicine of choice, to further minimise systemic absorption, apply digital pressure against the inner corner of the eye (over the tear duct) for one to two minutes and blot away excess drops.

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.**

    - 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.

Rarely:

8 Hepatotoxicity

9 Blood dyscracias

Additionally for ketorolac

10. IM injection can cause moderate pain in a small percentage of patients (up to 4 %).

Dosing

Ketorolac is a **potent** NSAID analgesic and the resulting NSAID related adverse effects can be serious, for example gastrointestinal haemorrhage, surgical haemorrhage and renal impairment.

Increasing the dose of ketorolac *beyond the usual recommendations* will not provide better efficacy but will result in increasing risk of developing serious adverse effects.

Note that in the USA and UK ketorolac is licensed for use IV, but it is not in Australia, (even though the formulation is the same).

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

In *general* terms: [2]

Oral:

- Adult, oral dosing is 10 mg every 4 - 6 hours (to a maximum of 40 mg daily).

Parenteral:

- **10 - 30 mg IM 4-6 hourly**

  For IV administration use smaller doses i.e 10 mg IV [5]

Higher IV doses add little or nothing to analgesia, but raise the risk of adverse effects.

The total daily dose should not exceed 90 mg

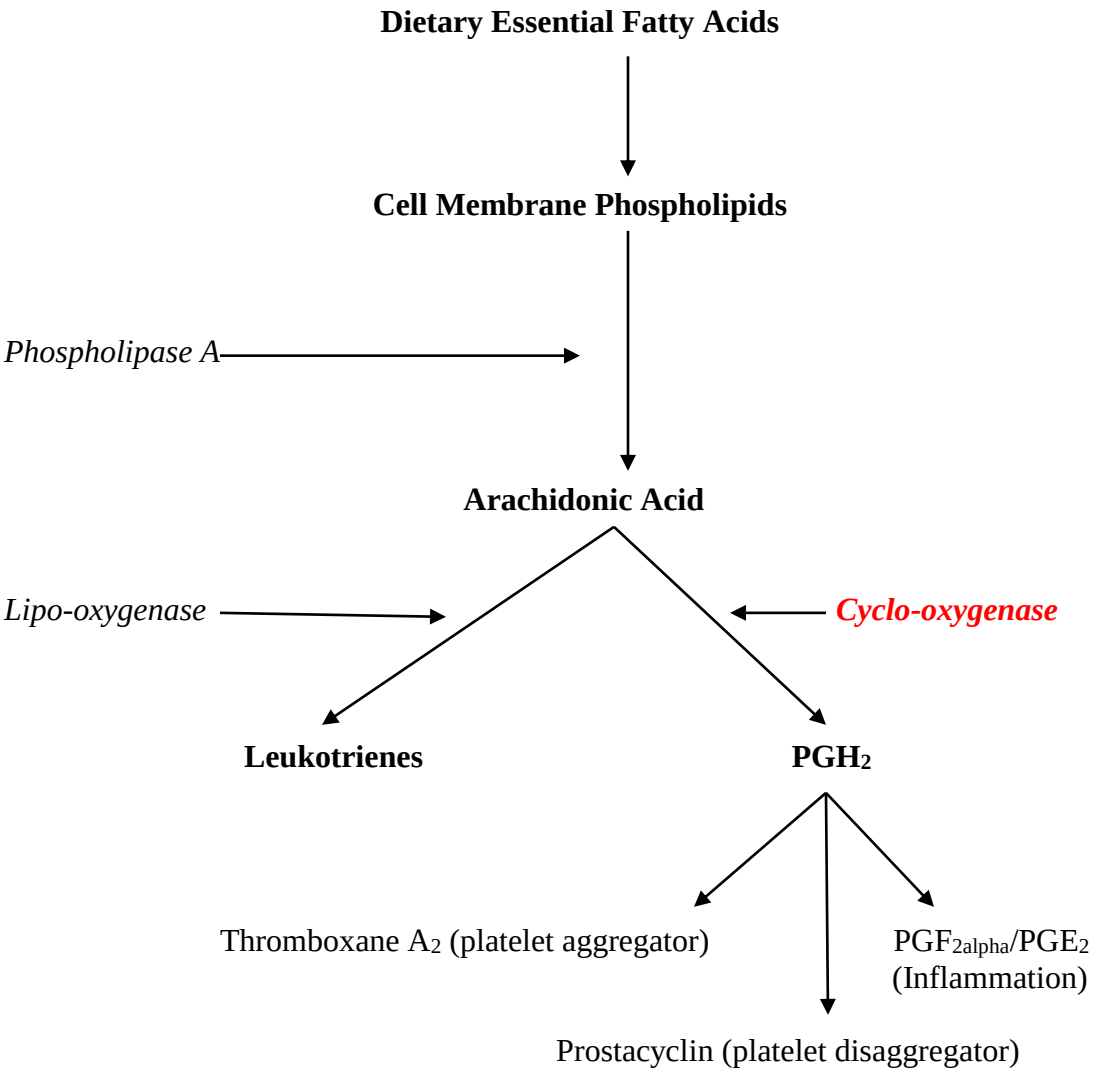
The total duration of ketorolac therapy should not exceed 5 days.

Use reduced doses for > 65 years, or < 50 kg, or mild renal impairment:

- **Oral**, 10 mg every 6 - 8 hours (maximum 30 - 40 mg daily).
- **IM**, initially 10 mg, followed by 10 - 15 mg every 4 - 6 hours (maximum 60 mg daily). Stop or change to oral route as soon as possible.

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

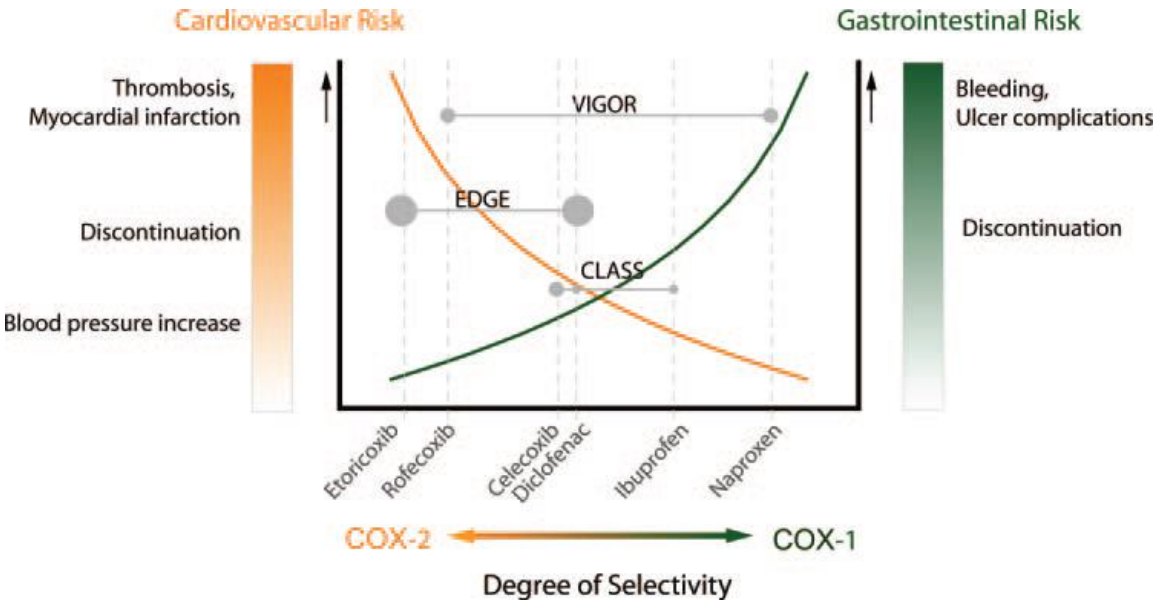
Appendix 2

Considerations in prescribing NSAIDs:

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

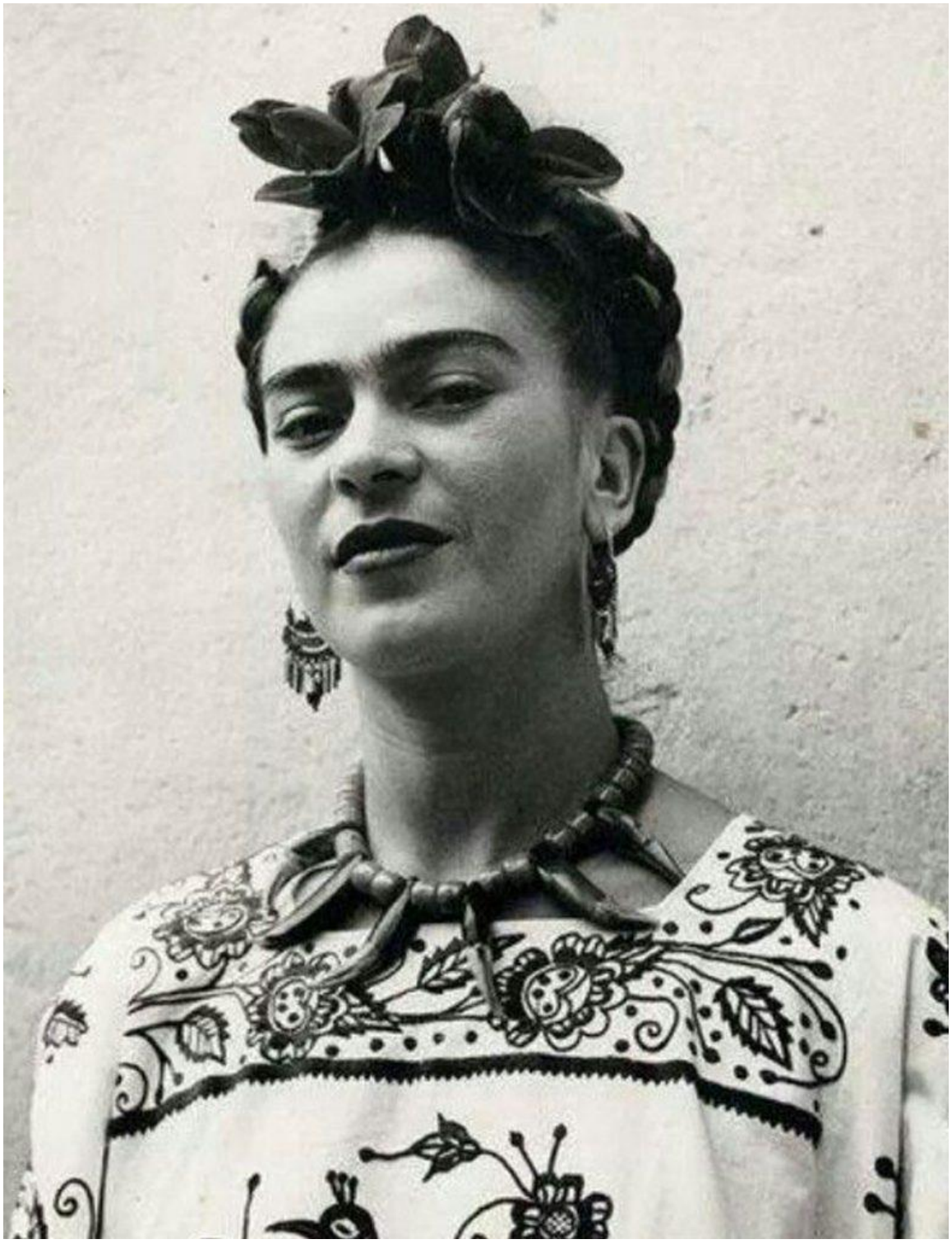
- Consider nonpharmacological treatment if appropriate.
- Consider the harm- benefit profile for NSAIDs in each patient and encourage patients to address modifiable cardiovascular risk factors.
- Use the minimal effective dose for the shortest time possible.
- Consider using alternatives such as fish 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).

Frida Kahlo accompanies Leon Trotsky, amidst a heavy police and militia security guard presence, 1937.



".....On her lips is the provocative half smile she wears in "Remembrance of an Open Wound"

Hayden Herrera

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