Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

NSAIDs (traditional, non-aspirin)

Evidence Summary

Mixed evidence for dementia prevention ranging from benefit to harm. Increased mortality risks from standard pharmacological doses.

Neuroprotective Benefit: Long-term mid-life use in APOE4 carriers might protect the brain, but the data is limited. Some studies report increased risk for dementia with NSAID use.

Aging and related health concerns: Two meta-analyses of RCTs report increased mortality rates with regular-dose traditional non-aspirin NSAIDs and any-dose coxibs. May help reduce cancer risk.

Safety: Regular to high-dose non-aspirin traditional NSAIDs have risks for gastrointestinal events, cardiovascular events, bleeding, and some serious adverse events. Low-doses might avoid those risks but available safety evidence is very limited for chronic use.

What is it? NSAIDs are Non-Steroidal Anti-Inflammatory Drugs, sometimes referred to as NSAIMs (NSAI Medicines) that reduce pain, fever and inflammation. This report focuses on non-aspirin traditional NSAIDs like ibuprofen and naproxen that temporarily inhibit the activity of both cyclooxygenase-1 (COX-1) and COX-2.

An additional class of NSAID drugs are the coxibs that selectively inhibit COX-2. Coxibs were developed with the intent of minimizing gastrointestinal side effects but substantial harms have been noted for many coxibs, including cardiovascular disease, overall mortality, and gastrointestinal harm. This report discusses coxibs periodically but focuses instead on the traditional NSAIDs. Acetaminophen, which does not reduce inflammation, is not considered an NSAID for the purpose of this report.

Neuroprotective Benefit: Long-term mid-life use in APOE4 carriers might protect the brain, but the data is limited. Some studies report increased risk for dementia with NSAID use.

Types of evidence:

- 3 systematic reviews/meta-analyses of observational and/or clinical studies (2003-2008). A meta-analysis from 2015 discounted because of faulty data input/analyses
- 7 prospective cohorts & 1 retrospective database (more studies covered in meta-analyses)
- 1 Cochrane meta-analysis of 6 trials for traditional NSAIDs and 4 trials for Coxibs
- 1 RCT and follow-up analyses (more in meta-analysis)
- 1 conference abstract from 2014

The RCT data shown above suggest no benefit and perhaps harm from NSAID use. For patients with dementia, many randomized trials report that various NSAIDs will not slow disease progression. For example, a 2012 Cochrane review of RCTs observed neither benefit nor harm on cognitive function with the use of traditional NSAIDs (6 trials) or Cox-2 specific inhibitors (4 trials) (2). For prevention, only one trial has been attempted. The ADAPT trial was designed to look at naproxen and celecoxib for prevention of dementia in healthy people over age 70 with Alzheimer's in their family. That trial, designed to treat for 7 years, was stopped after roughly 2 years due to cardiovascular risks observed for both drugs (AlzForum). During the first 3 years of treatment and follow-up, there was a strong trend of *increased* risk of dementia with naproxen (200 mg/d) and celecoxib (200 mg/d) treatment (Breitner 2011 (3)). One follow-up analysis suggested a delayed decreased risk with naproxen and increased risk

with celecoxib but the most recent analysis at 7 years follow-up observed no cumulative effect on dementia risk (4).

It's possible that RCTs have failed to detect the benefit that might be attained from earlier long-term treatment, but the observational data is still mixed between benefit, harm, and null. Benefit from long-term use was suggested from three systematic reviews of observational data (5-7) and a subsequent retrospective database study (8), with overall risk estimates ranging from roughly 0.42 to 0.79 for dementia. However, effect sizes vary considerably with some studies even reporting increased risk (e.g. (6)). Authors of a 4th meta-analysis concluded the beneficial associations were likely an artifact due to bias because of how the relative risks varied based on study design (9). Subsequent prospective studies have been mixed, with increased risk (10, 11), reduced risk (12, 13), no effect (14), and very slight benefits (15, 16) reported on either cognitive decline, dementia risk, or pathology in the brain.

Of concern, a rigorous community-based cohort study in 2009 reported that heavy NSAID use based on pharmacy prescriptions was associated with a *higher* risk of dementia and Alzheimer's disease (adjusted Hazard ratio (HR): 1.66, 95% CI 1.24 to 2.24 for dementia). The higher risk of dementia was seen with both long-term use (5+ years, 1.51 aHR, CI 1.03 to 2.20) and more recent use (1.85 aHR, CI 1.28 to 2.66) (10). The bulk of the NSAID prescriptions in this study were for ibuprofen (46% of the prescriptions, usually at 1200 mg/d), naproxen (14.3%, 500 mg/d), indomethacin (11.3%, 75 mg/d), and sulindac (9.4%, 300 mg/d).

The data may be conflicting because the earlier observational studies that suggested dementia prevention may have been flawed, as suggested by a 2005 meta-analysis that pointed to recall bias, prescription bias, and publication bias (9).

Another explanation is that long-term use in mid-life might protect the brain but use later in the course of dementia might accelerate the damage. Laboratory studies suggest that while neuroinflammation can accelerate disease in early stages by promoting chronic inflammation and related damage, it can also protect against damage by ramping up microglial clearance of toxic proteins and damaged cells. A couple of epidemiology studies support the idea that long-term use could be more protective (6, 15) but most studies have lacked the power to ask this question. However, in an older patient cohort (70+ years), 5+ years of use associated with harm, not benefit. The observed increased risk in this older group may have been due to a delayed onset of dementia, such that these people may have gotten dementia several years earlier if they had not been taking NSAIDs, however, there is no data to support this hypothesis.

A third explanation is that benefit vs harm is dependent on baseline inflammatory status. One 2014 conference abstract suggested that Alzheimer's patients with baseline inflammation may benefit from NSAID treatment while patients without baseline inflammation may experience harm (accelerated cognitive decline) with NSAID treatment.

APOE4 interactions: A fourth explanation is that NSAID efficacy might interact with E4 status, with NSAID use protecting E4 carriers while harming E4 non-carriers. In the Cache county study, less cognitive decline was observed in E4 carriers alone who had started NSAIDs use before age 65 but *faster* cognitive decline was observed in E4 non-carriers who started NSAIDs after age 65 (17). Another prospective cohort reported benefit only in E4 carriers(12). E4 carriers treated with ibuprofen were, based on a posthoc analysis of an RCT, the only Alzheimer's patients that did not show cognitive decline over 1 year (18). However, in the ADAPT trial, there was not even a trend for E4 genotype to modify the relationship between NSAID use (naproxen or celecoxib) and Alzheimer's risk (4).

Summary: Traditional non-ASA NSAIDs might protect the brain from dementia if delivered at the right time and dose to the right subset of people. However, the evidence for that perfect treatment paradigm is weak, and some well-designed studies have observed harm rather than benefit.

Aging and related health concerns: Two meta-analyses of RCTs report increased mortality rates with regular-dose traditional non-aspirin NSAIDs and any-dose coxibs. May help reduce cancer risk.

Types of evidence:

- 2 Meta-analyses on RCTs and mortality + CVD outcomes specifically
- 1 administrative database study
- 4 meta-analyses for cancer
- Various laboratory studies

Although NSAIDs might protect from cancer, there is little evidence to suggest that NSAIDs might slow aging or extend lifespan overall. Instead, clinical studies suggest harm and increased risk of death overall from high-dose traditional NSAIDs or from any dose of coxibs. Low-dose NSAIDs might reduce the risk for these harms but whether such low doses will still protect from cancer is unclear. Laboratory studies are conflicting on harm versus benefit.

A meta-analysis of 31 RCTs (representing 116,429 patients for any health indication except cancer) reported that 7 NSAIDs were linked to a *higher* risk of death from any cause. Ibuprofen was associated with the highest risk of stroke (3.36, 1.00 to 11.60). For ibuprofen, the rate ratio for overall mortality (1.77, range 0.73 to 4.30) was based on limited data - only two RCTs with a high dose (2400 mg/d) and a low number of fatalities. Nevertheless, ibuprofen's mechanism of action overlaps heavily with the other 6 analyzed NSAIDs (naproxen, diclofenac, and 4 coxibs), all of which at least trended towards increased risk of death from any cause (19). A more recent meta-analysis also reported substantial harms from most NSAIDs including high-dose ibuprofen, ranging from heart failure risk, vascular or coronary events, vascular death, and upper gastrointestinal complications. This meta-analysis included 280 trials of NSAIDs vs placebo and 474 trials comparing NSAIDs (20). In people with prior acute myocardial infarction, the risk of death and rehospitalization was higher in people who had used high-dose traditional NSAIDs (e.g. ibuprofen) and by any dose of cox-2 specific inhibitors (coxibs) (21).

These harms are related to normal/high-dose use of traditional NSAIDs or any dose of coxibs. Low doses of traditional NSAIDs, like ibuprofen, might theoretically elicit benefit rather than harm, but there is no strong clinical data to support this claim.

Cancer: Considerable data suggests that long-term use of NSAIDs might reduce the incidence of several cancers. Some studies report lower doses are less effective (22, 23), although some studies report the opposite (e.g. aspirin for ovarian cancer (23)). Notably, some studies report an association between NSAID use and increased cancer risk or mortality. For ibuprofen, increased risk of mortality has been reported from bowel & rectal cancers (reviewed in (22) and from lung cancer mortality (24). For prostate cancer, aspirin has more association with protection than non-aspirin NSAIDs (25) and one observational study reported *increased* risk with non-aspirin NSAID use despite reduced risk from aspirin specifically (26).

Chronic systemic inflammation is thought to be an important driver of aging and related diseases. However, inflammation also serves important roles such as clearing damaged proteins and cells. Laboratory studies are mixed. Some examples: cytokines like TNF alpha are important markers of systemic inflammation but NSAIDs like ibuprofen and celecoxib do not reliably reduce TNF alpha levels and, in some laboratory studies, increased them (27-31). Cox-2 is a major target of traditional NSAIDs and it has been implicated in cellular senescence and neuroinflammation but in cell culture, 2 common COX-2 inhibitors (celecoxib and nimesulide) accelerated senescence while a 3rd (NS-398) inhibited senescence (32). In mice, a lack of Cox-2 counterintuitively exacerbates the damage triggered by an inflammatory insult although a lack of Cox-1 reduces damage (33). In the brain, some activated

microglia exacerbate damage and neuroinflammation while other activated microglia probably slow the disease process (see AlzForum Feb 2015).

Ibuprofen was shown in 2014 to extend the lifespan of yeast, worms, and flies by 17%, 10%, and 10% respectively. This effect could not have been due to COX inhibition because yeast and worm do not express COX (34). Investigators speculated that the effect was due to a mild tryptophan deficiency caused by ibuprofen, although some other researchers were not convinced by this idea (ScienceMag). Ibuprofen extension of lifespan has not been tested in mammals. A related drug not clearly associated with inducing tryptophan deficiency, nitroflurbiprofen, had no effect on lifespan in the Interventions Testing Program (35).

Summary: Drugs that target the right component of inflammation at the right time are probably very protective but whether NSAIDs provide the right type of anti-inflammatory therapy to protect against aging is not clear. Other protective mechanisms of action might occur, but more data is needed.

Safety: Regular to high-dose non-aspirin traditional NSAIDs have risks for gastrointestinal events, cardiovascular events, bleeding, and some serious adverse events. Low-doses might avoid those risks but available safety evidence is very limited for chronic use.

A detailed review of the evidence for harms as of 2007 of regular doses of NSAIDs is here.

- *Cardiovascular and overall mortality risks:* Regular-dose traditional NSAIDs are associated with cardiovascular risks including a higher risk of mortality overall, as described in the Aging section above. People with high blood pressure have an increased risk of fluid retention and edema with NSAID use (Drugs.com).

- *Gastrointestinal:* Regular dose NSAIDs increase the risk of upper gastrointestinal bleeds and complications (22). Risks are higher in people with a history of peptic ulcer disease, comorbidities like cardiovascular disease (OR 1.84 in one study), old age, concomitant use of anticoagulants, (GI.org)(AAFP)(22), as well as users of SSRI anti-depressants (36, 37). Gastrointestinal bleeding risk can be decreased by concurrent use of protein pump inhibitors, such as lansoprazole.

- *Hepatic:* NSAIDs might have some risk to liver health, particularly in people with impaired liver health or hepatitis C infection, but the risks to the general population are very low (AAFP).

- *Renal*: Complications are possible due to COX-2 inhibition. ACE inhibitors and beta-blockers may increase the risk from NSAID use (AAFP).
- *Hematologic:* Increased risk of bleeding due to antiplatelet effects. Stop use before surgery.
- *Respiratory*: Possible small concern of COX-1 inhibitors and respiratory disease (AAFP). Particular concern in people with asthma, nasal polyps, or recurrent sinusitis.
- *CNS*: reports of rare side effects, more common in elderly, including tinnitus (reversible), psychosis and cognitive changes (esp. with indomethacin), aseptic meningitis (esp. with ibuprofen or naproxen).
- *Drug interactions*: Concomitant use of anticoagulants (AAFP), SSRI or SNRI drugs used for depression and neuropathy (36, 37)(Drugs.com), or alcohol (Drugs.com) may raise the risk of gastrointestinal side effects. Non-aspirin NSAIDs can also raise blood pressure and reduce the effectiveness of all anti-hypertensive drugs except for calcium channel blockers (38). Drugs.com lists many drug interactions for ibuprofen alone (91 major drug interactions, 279 moderate, and 27 minor). Liver microsomes inhibited by NSAIDs include CYP-2C9 (by ibuprofen, ketoprofen, flurbiprofen, indomethacin, diclofenac, and meloxicam) and CYP-2C8/2D6 (celecoxib) (Up-To-Date). Up-To-Date also lists interactions including anticoagulants, antiplatelet agents, anti-hypertensives, calcineurin inhibitors (cyclosporine & tacrolimus), digoxin, diuretics, glucocorticoids, lithium, SSRIs, and methotrexate.

Dosing and Sources:

Some NSAIDs, including ibuprofen, were shown in laboratory studies to lower the levels of A□42 but epidemiology studies have generally found no difference across NSAIDs that do and do not have this property (7, 8, 12, 13). A large retrospective database study in veterans reported that the association of reduced risk was strongest with ibuprofen (8).

Ibuprofen and naproxen are generally considered the safest options, particularly in low doses. Ibuprofen, nabumetone, meloxicam, and etodolac have been reported to have less risk of gastrointestinal complications than sulindac, piroxicam, and ketorolac (Gi.org).

Very little data is available for long-term very low-dose use, either for safety or efficacy. A 2012 systematic review found only one study comparing continuous versus on-demand use of NSAIDs for inflammatory arthritis. In that study, the continuous treatment group had non-significant trends of

higher risks including hypertension (OR 2.79), abdominal pain (1.67), diarrhea (1.35), and depression (3.2) (39).

Cox-1 inhibition may be more protective than Cox-2 inhibition in terms of aging, neurodegeneration, and cardiovascular health, although Cox-2 inhibition can be very effective against pain and acute inflammation. Selective Cox-2 inhibitors (coxibs) were developed to minimize the gastrointestinal side effects of traditional NSAIDs that inhibit both Cox-1 and Cox-2 but in subsequent clinical research, these coxibs have had considerable risks for cardiovascular adverse events and overall mortality and even some gastrointestinal dangers (see Aging section for references). Some researchers have suggested that selective Cox-2 inhibition raises the risk of thrombotic events because it reduces endothelial production of prostacyclin (PGI2) without also reducing platelet production of thromboxane (TxA2, produced by Cox-1) (40, 41).

Future research:

- Ongoing studies are testing if subpopulations of people are more likely to benefit from NSAID treatment, such as baseline inflammatory state by Sid O'Bryant's group. The long-term effects of NSAID may also depend on *APOE4* status or on mid-life vs late-life treatment. Most longitudinal cohorts lack sufficient power to address these questions but perhaps could be pooled.

- Clinical studies are testing other strategies to reduce systemic inflammation. Etanercept, a TNF alpha inhibitor, may have slowed cognitive decline in a small recent Alzheimer's trial (AlzForum). An additional etanercept trial funded by the EU (below) is scheduled to begin soon.

- The EU has recently invested in a large collaborative project on neuroinflammation called INMiND – Imaging Neuroinflammation in Neurodegenerative Diseases. Key components: a clinical trial on etanercept in MCI patients, the development of imaging tools to measure neuroinflammation, and differentiating good vs bad microglial phenotypes (42).

Search process –Searches in drugs.com, Up-to-date, and google for clinical reviews. Done simultaneously with the ASA analysis.

PubMed -

- Nsaids, cognitive
- ADAPT

- NSAIDs, Alzheimer
- low-dose ibuprofen, mortality
- cellular senescence, NSAID, cox
- prostacyclin, thromboxane, lifespan
- prostacyclin, thromboxane, filtered for meta-analyses & systematic reviews
- cox, telomere
- nsaid, telomere
- dyspepsia, NSAID
- TNFalpha, ibuprofen
- TNFalpha NSAIDs
- Cytokines NSAIDs
- PPIs, NSAID (google search)
- Aspirin & cognitive or dementia or Alzheimer or mortality (separate searches)
- Also searches in drugs.com, Up-to-date, and google for clinical reviews

References:

1. Sommer, I.E., et al., *Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis.* J Clin Psychiatry, 2012. 73(4): p. 414-9.http://www.ncbi.nlm.nih.gov/pubmed/22225599

2. Jaturapatporn, D., et al., *Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease.* Cochrane.Database.Syst.Rev., 2012. 2:CD006378.: p. CD006378.http://www.ncbi.nlm.nih.gov/pubmed/22336816

3. Breitner, J.C., et al., *Extended results of the Alzheimer's disease anti-inflammatory prevention trial.* Alzheimers.Dement., 2011. 7(4): p. 402-411.http://www.ncbi.nlm.nih.gov/pubmed/?term=21784351

4. Alzheimer's Disease Anti-inflammatory Prevention Trial Research, G., *Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT).* Alzheimers Dement, 2013. 9(6): p. 714-23.http://www.ncbi.nlm.nih.gov/pubmed/23562431

5. Szekely, C.A., et al., *Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review.* Neuroepidemiology., 2004. 23(4): p. 159-169.http://www.ncbi.nlm.nih.gov/pubmed/15279021

6. Etminan, M., S. Gill, and A. Samii, *Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies.* BMJ., 2003. %19;327(7407): p. 128.http://www.ncbi.nlm.nih.gov/pubmed/12869452

7. Szekely, C.A., et al., *No advantage of A beta 42-lowering NSAIDs for prevention of Alzheimer dementia in six pooled cohort studies.* Neurology., 2008. 70(24): p. 2291-2298.http://www.ncbi.nlm.nih.gov/pubmed/18509093

8. Vlad, S.C., et al., *Protective effects of NSAIDs on the development of Alzheimer disease.* Neurology., 2008. 70(19): p. 1672-1677.http://www.ncbi.nlm.nih.gov/pubmed/18458226

9. de Craen, A.J., et al., *Meta-analysis of nonsteroidal antiinflammatory drug use and risk of dementia.* Am.J.Epidemiol., 2005. 161(2): p. 114-120.http://www.ncbi.nlm.nih.gov/pubmed/15632261

10. Breitner, J.C., et al., *Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort.* Neurology., 2009. 72(22): p. 1899-1905.http://www.ncbi.nlm.nih.gov/pubmed/?term=19386997

11. Sonnen, J.A., et al., *Nonsteroidal anti-inflammatory drugs are associated with increased neuritic plaques.* Neurology, 2010. 75(13): p. 1203-10.http://www.ncbi.nlm.nih.gov/pubmed/20811000

12. Szekely, C.A., et al., *NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type.* Neurology., 2008. 70(1): p. 17-24.http://www.ncbi.nlm.nih.gov/pubmed/18003940

13. Cote, S., et al., *Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease.* Alzheimers.Dement., 2012. 8(3): p. 219-226.http://www.ncbi.nlm.nih.gov/pubmed/22546354

14. Arvanitakis, Z., et al., *Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology.* Neurology., 2008. 70(23): p. 2219-2225.http://www.ncbi.nlm.nih.gov/pubmed/18519870

15. Grodstein, F., et al., *Anti-inflammatory agents and cognitive decline in a bi-racial population.* Neuroepidemiology., 2008. 30(1): p. 45-50.http://www.ncbi.nlm.nih.gov/pubmed/18259082

16. Waldstein, S.R., et al., *Nonsteroidal anti-inflammatory drugs, aspirin, and cognitive function in the Baltimore longitudinal study of aging.* J.Am.Geriatr.Soc., 2010. 58(1): p. 38-43.http://www.ncbi.nlm.nih.gov/pubmed/?term=20122039

17. Hayden, K.M., et al., *Does NSAID use modify cognitive trajectories in the elderly? The Cache County study.* Neurology., 2007. 69(3): p. 275-282.http://www.ncbi.nlm.nih.gov/pubmed/17636065

18. Pasqualetti, P., et al., *A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease.* Aging Clin.Exp.Res., 2009. 21(2): p. 102-110.http://www.ncbi.nlm.nih.gov/pubmed/19448381

19. Trelle, S., et al., *Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis.* BMJ., 2011. 342:c7086. doi: 10.1136/bmj.c7086.: p. c7086.http://www.ncbi.nlm.nih.gov/pubmed/?term=21224324

20. Coxib, et al., *Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.* Lancet, 2013. 382(9894): p. 769-79.http://www.ncbi.nlm.nih.gov/pubmed/23726390

21. Gislason, G.H., et al., *Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction.* Circulation., 2006. 113(25): p. 2906-2913.http://www.ncbi.nlm.nih.gov/pubmed/16785336

22. Rostom, A., C. Dube, and G. Lewin, in *Use of Aspirin and NSAIDs to Prevent Colorectal Cancer*. 2007: Rockville (MD). http://www.ncbi.nlm.nih.gov/pubmed/20722142

23. Trabert, B., et al., *Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium.* J Natl Cancer Inst, 2014. 106(2): p. djt431.http://www.ncbi.nlm.nih.gov/pubmed/24503200

24. Brasky, T.M., et al., *Prediagnostic nonsteroidal anti-inflammatory drug use and lung cancer survival in the VITAL study.* J Thorac Oncol, 2012. 7(10): p. 1503-12.http://www.ncbi.nlm.nih.gov/pubmed/22982651

25. Liu, Y., et al., *Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review and meta-analysis.* BMC Med, 2014. 12: p. 55.http://www.ncbi.nlm.nih.gov/pubmed/24678716

26. Veitonmaki, T., et al., *Use of aspirin, but not other non-steroidal anti-inflammatory drugs is associated with decreased prostate cancer risk at the population level.* Eur J Cancer, 2013. 49(4): p. 938-45.http://www.ncbi.nlm.nih.gov/pubmed/23079475

27. Ehsani, M., et al., *The role of prophylactic ibuprofen and N-acetylcysteine on the level of cytokines in periapical exudates and the post-treatment pain.* Daru, 2012. 20(1): p. 30.http://www.ncbi.nlm.nih.gov/pubmed/23351387

28. Matsiegui, P.B., et al., *Ibuprofen does not affect levels of tumor necrosis factor alpha and soluble tumor necrosis factor receptor types I and II in Gabonese children with uncomplicated Plasmodium falciparum malaria.* Eur Cytokine Netw, 2007. 18(4): p. 201-5.http://www.ncbi.nlm.nih.gov/pubmed/17964975

29. Page, T.H., et al., *Nonsteroidal anti-inflammatory drugs increase TNF production in rheumatoid synovial membrane cultures and whole blood.* J Immunol, 2010. 185(6): p. 3694-701.http://www.ncbi.nlm.nih.gov/pubmed/20713883

30. Sacco, S., et al., *Nonsteroidal anti-inflammatory drugs increase tumor necrosis factor production in the periphery but not in the central nervous system in mice and rats.* J Neurochem, 1998. 71(5): p. 2063-70.http://www.ncbi.nlm.nih.gov/pubmed/9798931

31. Shahriari, S., et al., *Effect of Ibuprofen on IL-1beta, TNF-alpha and PGE2 levels in periapical exudates: a double blinded clinical trial.* Iran J Immunol, 2011. 8(3): p. 176-82.http://www.ncbi.nlm.nih.gov/pubmed/21931204

32. Kim, S.R., et al., *Selective COX-2 inhibitors modulate cellular senescence in human dermal fibroblasts in a catalytic activity-independent manner.* Mech Ageing Dev, 2008. 129(12): p. 706-13.http://www.ncbi.nlm.nih.gov/pubmed/18848576

33. Aid, S., R. Langenbach, and F. Bosetti, *Neuroinflammatory response to lipopolysaccharide is exacerbated in mice genetically deficient in cyclooxygenase-2.* J Neuroinflammation, 2008. 5: p. 17.http://www.ncbi.nlm.nih.gov/pubmed/18489773

34. He, C., et al., *Enhanced longevity by ibuprofen, conserved in multiple species, occurs in yeast through inhibition of tryptophan import.* PLoS Genet, 2014. 10(12): p. e1004860.http://www.ncbi.nlm.nih.gov/pubmed/25521617

35. Miller, R.A., et al., *An Aging Interventions Testing Program: study design and interim report.* Aging Cell, 2007. 6(4): p. 565-75.http://www.ncbi.nlm.nih.gov/pubmed/17578509

36. Anglin, R., et al., *Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis.* Am J Gastroenterol, 2014. 109(6): p. 811-9.http://www.ncbi.nlm.nih.gov/pubmed/24777151

37. Oka, Y., et al., *Meta-analysis of the risk of upper gastrointestinal hemorrhage with combination therapy of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs.* Biol Pharm Bull, 2014. 37(6): p. 947-53.http://www.ncbi.nlm.nih.gov/pubmed/24681541

38. White, W.B., *Cardiovascular effects of the cyclooxygenase inhibitors.* Hypertension, 2007. 49(3): p. 408-18.http://www.ncbi.nlm.nih.gov/pubmed/17261646

39. Adams, K., C. Bombardier, and D. van der Heijde, *Safety and efficacy of on-demand versus continuous use of nonsteroidal antiinflammatory drugs in patients with inflammatory arthritis: a systematic literature review.* J Rheumatol Suppl, 2012. 90: p. 56-8.http://www.ncbi.nlm.nih.gov/pubmed/22942330

40. Curiel, R.V. and J.D. Katz, *Mitigating the cardiovascular and renal effects of NSAIDs.* Pain Med, 2013. 14 Suppl 1: p. S23-8.http://www.ncbi.nlm.nih.gov/pubmed/24255997

41. Konstam, M.A. and M.R. Weir, *Current perspective on the cardiovascular effects of coxibs.* Cleve Clin J Med, 2002. 69 Suppl 1: p. SI47-52.http://www.ncbi.nlm.nih.gov/pubmed/12086293

42. Mohammadi, D., *INMiND: getting to the bottom of neuroinflammation.* Lancet Neurol, 2013. 12(12): p. 1135-6.http://www.ncbi.nlm.nih.gov/pubmed/24229613

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