THE PATH AHEAD

Commonly Prescribed and Over-the-Counter Drugs as Secondary Causes of Osteoporosis—Part One

Joseph Pizzorno, ND, Editor in Chief; Lara Pizzorno, MA, LMT

Abstract

Prescription and over-the-counter drugs have been effectively used to manage many diseases and to provide symptom relief. Unfortunately, their use may also result in adverse drug reactions and unintended consequences. Proper use of these powerful agents requires understanding both their desired effects and their potential downsides. Fully understanding the unintended consequences can be challenging. Virtually all safety studies are carried out for far shorter periods of time than the actual use of these agents in the real world. Some may take years of use before their sequelae are recognized. This is especially a problem where bone health is concerned since the damage caused by years of minor disruption in function does not show up until compounded by other factors, such as andropause and menopause. This 2-part editorial covers the primary classes of drugs that require bone health monitoring and that may require alternative prescriptions or mitigation strategies. Part One covers aromatase inhibitors, gonadotropin-releasing hormone agonists, anticonvulsants, benzodiazepines, antidepressants, insulin sensitizers, and NSAIDs and acetaminophen. Part Two covers opioids, glucocorticoids, calcineurin inhibitors, H2 blockers, diuretics, anticoagulants, thyroid medications, and contraceptives.

Introduction

A surprising number of prescription and over-the-counter (OTC) drugs promote bone loss. Papers discussing the secondary causes of osteoporosis typically list many of these drugs, but not all of them. The following discusses each of the major classes of drugs that cause bone loss and, where available, alternate medications or mitigation strategies to consider. This discussion is organized to present the following information—*Use:* Conditions the drugs are prescribed to manage; *Commonly prescribed examples*: Trade and brand names of the drugs most often prescribed; *Bone-impairing mechanism(s)*: How and why the drug(s) cause bone loss*; Mitigation strategies, alternative medications to consider*: Where appropriate, recommendations to decrease damage to bone and alternative medications to consider.

Aromatase Inhibitors

Use: Help prevent metastasis in prostate cancer and estrogen receptor–positive breast and ovarian cancer.

Commonly prescribed examples: Exemestane (Aromasin) is an irreversible steroidal inhibitor which forms a permanent bond with the aromatase enzyme, and is deactivating. Anastrozole (Arimidex) and letrozole (Femara) are nonsteroidal inhibitors which inhibit estrogen synthesis by out-competing androgens to bind with aromatase, again inactivating it.

Bone-impairing mechanism: Induce bone loss by inhibiting aromatase, the enzyme that converts androgens (testosterone, DHEA) into estrogens. The complete loss of estrogen that results causes bone loss. Anastrozole and letrozole increase bone turnover, decrease bone mineral density (BMD), and increase the relative risk of vertebral and nonvertebral fractures by 40%, compared with tamoxifen. Bone loss with increased risk of fragility fractures also occurs in women receiving exemestane. Unless proactive bone-building steps are taken, only a partial recovery of BMD is seen following the withdrawal of aromatase inhibitors.[1]

After menopause, women do not stop producing estrogen. The ovaries produce almost no estrogen, but postmenopausal women continue to produce small amounts of estrogen in many other cells and tissues where estrogen plays very important protective roles, including in the cardiovascular system and brain, as well as bones. The estrogen produced in bone becomes more important

after menopause because even these smaller amounts help to inhibit excessive osteoclast activity and increase osteoblast production and activity.

Estrogen plays numerous protective roles in the cardiovascular system, which abounds with estrogen receptors. Cardiomyocytes synthesize estrogen. Estrogen relaxes blood vessels, lessens free radical production, protects against free radical damage, and helps prevent fibrosis.[2]

Estrogen produced in the brain reduces amyloid beta formation and increases its rate of clearance, lowering risk of Alzheimer's disease. In addition, estrogen stimulates the formation of new brain cells in areas of the brain involved in learning and memory.[3]

Aromatase inhibitors prevent the production of *any* estrogen, impacting not just bone but the cardiovascular system as these medications increase risk for elevated levels of VLDL cholesterol, hypertension, and myocardial infarction.[4,5]

In bone, aromatase inhibitors more than double the rate of bone loss normally seen in postmenopausal women and cause fragility fractures. The 3-year risk of vertebral fracture is almost 5-fold greater in women with newly diagnosed breast cancer treated with aromatase inhibitors than in women in the general population.[6]

Obviously, effectively treating breast cancer and preventing its recurrence is top priority, but must women with or recovering from breast cancer take an aromatase inhibitor? Do we have any alternatives? Yes, we do: tamoxifen.

Tamoxifen has long been considered first line therapy for estrogen receptor–positive breast cancers, and its efficacy has been confirmed in recent studies that compared the effectiveness of aromatase inhibitors to that of tamoxifen. In these studies, tamoxifen caused an increase in both BMD and bone quality, while the aromatase inhibitors caused significant losses in both.[7,8]

Tamoxifen has also been shown to be highly effective even when given to breast cancer patients with bone metastasis, although the dose needed was higher. A meta-analysis of 7 trials involving 30,000+ patients found that 5 years of treatment with aromatase inhibitors, *or* 5 years of treatment with tamoxifen alone, *or* tamoxifen used for 2-3 years followed by an aromatase inhibitor for 2-3 years, were all associated with the same 11% reduction in risk for a recurrence of breast cancer.

Because the aromatase inhibitors have toxic effects in the cardiovascular system and brain as well as in the bones, a number of recent papers are suggesting that tamoxifen either be used alone for 5 years or used for 2-3 years followed by the use of an aromatase inhibitor for 2-3 years to lessen the duration of aromatase inhibitor exposure.[9]

The aromatase inhibitors have been proposed to be more effective than tamoxifen because in approximately 8% of women, tamoxifen is not as effective. The reason for this is genetic—specifically, the genetic inheritance of a slow version of the drug-metabolizing enzyme CYP2D6, which converts tamoxifen into its active, cancer-fighting metabolites. The studies that suggested the aromatase inhibitors were more effective did not screen for women with low CYP2D6 activity, so the aromatase inhibitors appeared to be more effective for everyone. They are not, however.[9]

Also, about one-quarter of women who are prescribed tamoxifen are also prescribed a selective serotonin reuptake inhibitor (SSRI) to alleviate symptoms of depression and/or to treat hot flashes. SSRIs make tamoxifen ineffective because they inhibit CYP2D6 to varying degrees, thus preventing the production of tamoxifen's cancer-fighting derivatives. Paroxetine (Paxil) and fluoxetine (Prozac) are the most inhibitory, completely inhibiting CYP2D6. Other SSRIs, such as citalopram (Celexa), escitalopram (Cipralex, Lexapro), sertraline (Zoloft), and fluvoxamine (Luvox), are weaker inhibitors of CYP2D6.[10]

Mitigation strategies, alternative medications to consider: If your patient is currently taking an aromatase inhibitor, consider testing to determine whether tamoxifen could be an effective alternative. Saliva tests can now be easily run to determine if an individual is among the 8% of women whose genetic inheritance includes low CYP2D6 activity that would render her less likely to benefit from tamoxifen. If your patient does have low CYP2D6 activity, all is not lost. You can boost her activity of this enzyme by prescribing boron and instructing her to increase her consumption of cruciferous vegetables. After 4-6 weeks, you can retest to see if she is converting tamoxifen to endoxifen, its most powerful metabolite.[11,12]

Boron does not increase estrogen production, so it is not contraindicated if taking an aromatase inhibitor or tamoxifen. Boron not only boosts the activity of CYP2D6, but has numerous anti-cancer effects as well as bone-building effects, which have been covered in my review of boron.[13]

Gonadotropin-releasing Hormone Agonists

Use: Decrease sex hormone levels in the treatment of hormone-sensitive cancers such as prostate cancer and estrogen receptor–positive breast cancer, certain gynecological disorders like menorrhagia, uterine fibroids and endometriosis, and high testosterone levels in women.

Commonly prescribed examples: Leuprolide (Lupron, Eligard), buserelin (Suprefact, Suprecur), deslorelin (Suprelorin, Ovuplant).

Bone-impairing mechanisms: Suppress secretion of gonadotropin, which is required for FSH (follicle-stimulating hormone) and LH (luteinizing hormone) production. FSH and LH are required for the ovaries' production of estrogen and progesterone in women, and the production of testosterone and its conversion into estrogen (estradiol) in men. Thus, gonadotropin-releasing

hormone (GnRH) agonists suppress estrogen levels, causing bone loss. In women, there is a decrease in BMD of about 6% per year. In men, GnRH agonists are often given along with aromatase inhibitors to maximize androgen deprivation. BMD at hip, wrist, and lumbar spine decreases by 2%-5% after 12 months of androgen deprivation therapy. Relative risk of vertebral and hip fractures increases by 40%-50%. Men also experience a loss of lean body mass, increase in fat mass, and impaired muscular strength, all of which contribute to increased risk of fractures .[1,14] (While these are categorized as agonists, that is only their initial effect. After a few days their continued use results inhibition.)

Anticonvulsants

Use: Manage epilepsy, bipolar disorder, and neuropathic pain.

Commonly prescribed examples: Phenytoin (Dilantin), phenobarbital (Luminal), valproate sodium (Depacon).

Bone-impairing mechanisms: Interfere with vitamin D absorption and metabolism; cause vitamin D and calcium deficiency; may cause deficiency of folate and/or vitamin B6; reduce vitamin K blood levels.[15]

Mitigation strategies, alternative medications to consider: Check your patient's blood levels of vitamin D (25(OH)D and 1,25-D) and vitamin K2—test undercarboxylated osteocalcin (unOC). Increase supplementation if indicated. Also consider supplementing with folate and B6.

Benzodiazepines

Use: Manage epilepsy, anxiety, insomnia, depression, schizophrenia, restless leg syndrome.

Commonly prescribed examples: Diazepam (Valium), triazolam (Halcion), alprazolam (Xanax), chlordiazepoxide (Librium). Full listing available at https://www.drugs.com/drug-class/benzodiazepines.html/.[16]

Bone-impairing mechanism: Bind to and block off dopamine receptors, causing chronic elevation of prolactin and suppressing the activity of the hypothalamic-pituitary-gonadal (HPA) axis. Since HPA axis function is required for the production of estrogen and progesterone in women and testosterone in men, and these hormones play vital roles in maintaining healthy bones, disrupting their production causes bone loss.[17]

Research conducted in Spain assessed risk factors for osteoporosis and fractures in 4960 postmenopausal women aged 50 to 65 years. Its finding: *the 2 top risk factors identified for osteoporosis were low intake of calcium and benzodiazepine use.*[18]

Other papers have reported on benzodiazepines not only causing bone loss, but also increasing risk of falling, further increasing risk for fracture.[19-21]

Mitigation strategies, alternative medications to consider: If your patient is a premenopausal woman or a younger man and remaining on a benzodiazepine is required, then monitor prolactin levels and BMD. Also consider running the DUTCH test (Dried Urine Test for Comprehensive Hormones) or Meridian Valley Lab's 24-Hour Urine Comprehensive Hormone Profile to assess hormone status and discuss bio-identical hormone replacement, if indicated.

Antidepressants

Use: Manage symptoms of depression, anxiety disorders, some personality disorders (eg, obsessive compulsive disorder, eating disorders, premature ejaculation). Monoamine oxidase inhibitors (MAOIs) are also used to manage Parkinson disease. Atypical antipsychotics are used to manage schizophrenia, bipolar disorder, and autism.

Commonly prescribed examples: SSRIs, eg, fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil); for a more complete list, see http://en.wikipedia.org/wiki/SSRI#List_of_agents/. MAOIs, eg, selegiline (Emsam, Deprenyl). Atypical antipsychotics, eg, olanzapine (Zyprexa), risperidone (Risperdal), blonanserin (Lonasen); full listing of atypical antipsychotics at http://en.wikipedia.org/wiki/Atypical_antipsychotics#/. Tricyclic antidepressants (TCAs), eg, imipramine (Tofranil), amitriptyline (Elavil). TCAs are less frequently prescribed now but are still in use and have the same adverse effects as SSRIs, and possibly even more detrimental effects on bone (see the discussion of the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE) below).

Bone-impairing mechanism: Inhibit dopamine production and neurotransmission causing chronic elevation of prolactin, disrupting HPA axis activity and the production of sex hormones.[17,22]

Research involving over 27 000 postmenopausal women in Canada found that SSRIs increased risk for osteoporosis by 46%, atypical antipsychotics (aka, 2nd generation antipsychotics) increased risk by 55%, and benzodiazepines increased risk by 17%.[23]

A study conducted in Spain involving more than 63 000 subjects found SSRIs increased risk of osteoporotic fractures by 45%, MAOIs increased risk for osteoporosis 15%, and benzodiazepines increased risk by 10%. A dose-effect relationship was seen with SSRIs and benzodiazepines—the longer any of these drugs were used, the greater the increase in risk for osteoporosis. In contrast, lithium, which is prescribed to manage bipolar disorder, was associated with a 37% lower risk for fracture.[24]

Another study looking into the effects of antidepressants on bone involved 1988 women (aged 57 to 67) participating in the Osteoporosis Risk Factor and Prevention Study (OSTPRE) cohort in Kuopio, Finland. These women were followed for 5 years, during which time bone loss was found to be significantly accelerated in the 319 women who took antidepressants. Those using TCAs lost more than 3 times as much bone as women not taking antidepressants (-3.6 mg/cm^2 vs. -1.1 mg/cm^2).

SSRIs also increased the rate of bone loss, and the higher the dose, the greater the amount of bone lost.[25]

Several studies regarding TCAs were discussed in a paper published in 2020. In one, hip fracture risk in women using TCAs increased 83%. Another showed a 26% increase in fracture risk. In another, TCA use was associated with a standardized incidence ratio of 1.4 for hip fracture. Yet another showed current users of TCAs had an increased risk of sustaining a hip fracture of 1.9—ie, a 90% increase in risk. One study involving 6763 participants showed an odds ratio for fracture (adjusted for multiple potential medication and physical illness confounders) of 1.76 in current users of TCAs. While the precise mechanisms via which TCAs increase risk of fracture have not yet been elucidated, these findings provide sufficient evidence to state that TCAs are not a better option for bones. All antidepressants significantly increase risk of fracture.[26]

The research continues to report very high rates of osteopenia and osteoporosis in people taking any of the long-term psychoactive drugs (eg, anticonvulsants, benzodiazepines, antidepressants), and the higher the dose and longer the drugs were taken, the greater the bone loss. Young Caucasian women have been found to be especially vulnerable to developing hyperprolactinemia, with resulting inhibition of estrogen and progesterone production, and bone loss.[27] Prolactin levels and BMD should be checked in younger women taking any of these drugs and experiencing menstrual problems (an indication that the drug is disrupting normal function of the hypothalamic-pituitary-gonadal axis).

The latest review papers continue to confirm that SSRIs and TCA antidepressants significantly increase fracture risk, and that doctors seriously underestimate the role antidepressants have in increasing fractures.[28,29]

Since 1 in 8 Americans aged 12 and over (NHANES 2011–2014) reported taking antidepressants in the previous month, and one fourth of them have taken antidepressants for ≥ 10 years, the use of antidepressants is a significant contributing factor to osteoporosis and fracture risk.[30]

Mitigation strategies, alternative medications to consider: If your patient is taking an antidepressant, discuss considering a trial of saffron, derived from *Crocus sativus*. More than 12 studies have now found that the spice saffron is just as effective as SSRIs and has fewer or no serious adverse effects.[31-33] The spice's red pigment, crocin, has been shown to significantly decrease symptoms of depression, anxiety, and general psychological distress. Thirty milligrams per day of saffron, which is the amount prescribed in the clinical trials, equals a small pinch of 15-20 threads. There are around 400 saffron threads to a gram, so one gram will last almost a month.[32]

If saffron is not effective, check for alternative antidepressant medications with a lesser antagonizing effect on dopamine receptors in the brain. Antipsychotic drugs cause hyperprolactinemia—and thus osteoporosis—by antagonizing dopamine receptors. Conventional psychoactive drugs all cause hyperprolactinemia, but a few of the so-called "atypical" psychoactive drugs supposedly do not. These include prolactin-sparing antipsychotics: clozapine, aripiprazole, olanzapine. Some of the prolactin-raising antipsychotics include conventional neuroleptics, amisulpride, and risperidone. There are published studies discussing this in the peer-reviewed medical literature that can help you identify the psychoactive drugs with the lowest prolactin-raising profile.[27,34,35]

Insulin Sensitizers

Use: Manage type 2 diabetes.

Commonly prescribed examples: thiazolidinediones (aka, glitazones), eg, rosiglitazone (Avandia), pioglitazone (Actos).

Bone-impairing mechanisms: Mesenchymal stem cells are precursor cells in bone marrow that can develop into osteoblasts, adipocytes, or chrondocytes. The glitazones cause mesenchymal stem cells to become adipocytes. By doing so, these drugs thin bone and increase production of visceral adipose tissue (VAT), which is highly pro-inflammatory. VAT is linked to not only abdominal (apple-shaped) obesity, but also to insulin resistance, type 2 diabetes, and other inflammatory diseases, including osteoporosis.[36]

The glitazones cause bone loss because they are selective agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ). Numerous studies have demonstrated that activation of PPAR-γ in mesenchymal stem cells leads to increased fat cell production and decreased production of osteoblasts. In addition to causing the production of fat instead of bone, the thiazolidinediones decrease the expression of insulin-like growth factor 1 (IGF-1), which promotes bone formation. These 2 actions already secure the thiazolidinediones a top spot on the list of bone-impairing drugs, but the thiazolidinediones also stimulate osteoclast development and activity. So, these drugs both suppress bone formation and increase bone resorption.

Long-term treatment with thiazolidinediones increases the risk of fractures by up to 4-fold in men and postmenopausal women. Risk correlates with the duration of treatment and is significant within 12 to 18 months.1

A recent review discussing the effects of these drugs tells us they increase risk not only for bone fractures (especially rosiglitazone [Avandia]), but also for fluid retention, heart failure, and bladder cancer (pioglitazone [Actos] specifically has been linked to bladder cancer). They also raise levels of LDL cholesterol and VAT, a combination that increases risk of cardiovascular disease.[37]

Mitigation strategies, alternative medications to consider: If your patient has insulin resistance or type 2 diabetes and must take an insulin-sensitizing agent, consider prescribing metformin rather than one of the glitazones. Metformin has a positive effect on osteoblast

differentiation and therefore a neutral or even potentially protective effect on bone.[38]

If your patient does not have insulin resistance or type 2 diabetes, none of the above medications will be needed–and both conditions are reversible. *Many* studies—we've referenced just a handful among dozens of the most recent papers—have now shown that a whole foods Mediterranean-type diet and regular exercise can reverse type 2 diabetes, eliminate excess body fat, boost energy (and an individual's sex life), slow the aging process, and protect bone health. Work with your patient to safely taper down the dose and gradually eliminate the need for these bone-impairing drugs.[39-43]

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen–with the exception of low-dose aspirin

Use: Provide moderate pain relief, reduce swelling and fever (except acetaminophen, which is only analgesic). Low-dose aspirin is also used to lessen the likelihood of excessive blood clot formation.[44]

Commonly prescribed examples: Over-the-counter include acetaminophen (Tylenol), ibuprofen (Advil), naproxen (Aleve), aspirin. Prescription NSAIDs include extra-strength versions of ibuprofen and naproxen, also diclofenac, celecoxib and COX-2 selective inhibitors, such as valdecoxib (Bextra), celecoxib (Celebrex), rofecoxib (Vioxx). Although often referred to collectively, there are 2 categories of OTC pain relievers/fever reducers: acetaminophen and NSAIDs. Acetaminophen is technically not an NSAID because it has virtually no anti-inflammatory activity. It lessens pain by blocking COX-2 in the central nervous system.[45]

Bone-impairing mechanisms: Acetaminophen and NSAIDS, with the exception of aspirin, interfere with the resolution of inflammation and thus, if used frequently, promote bone loss. Chronic inflammation, from any source, signals osteoclasts to work overtime, causing bone loss. Plus, all NSAIDS, including aspirin, significantly decrease kidney function.[46]

The NSAIDs work by inhibiting the activity of the cyclooxygenase enzymes (COX-1 and/or COX-2). The COX enzymes play key roles in the production from the omega-6 and omega-3 fatty acids of not only pro-inflammatory messenger molecules (the series 2 prostaglandins and thromboxanes), but also the anti-inflammatory messenger molecules. These anti-inflammatory molecules include the series 1 and 3 prostaglandins, and even more importantly, recently discovered compounds collectively called the specialized pro-resolving mediators (SPMs), whose job is to resolve the inflammatory process. Not only do all the NSAIDs, except aspirin, interfere with the resolution of inflammation, but in addition these drugs greatly increase risk of (1) upper gastrointestinal tract complications, including peptic ulcer perforation, obstruction, and bleeding, (2) major cardiovascular events, including heart attack and stroke, and (3) liver damage and disease — all of which promote bone loss.[47,48]

It's easy to see how the NSAIDs (except for aspirin) and acetaminophen promote bone loss. NSAIDs keep inflammation going. In addition, they impair gastrointestinal tract, cardiovascular, and liver function—all of which promote bone loss. A well-functioning digestive tract is required both for the effective release from food of the nutrients bones must have to maintain themselves, and for our ability to absorb these nutrients, whether they were released from the food matrix or a supplement. Once nutrients are absorbed from our digestive tract, they travel via the portal vein to the liver and from there are sent out into the bloodstream for delivery through our vasculature (blood vessels and heart) to our bones and the rest of the body. When the vasculature in compromised, so is blood flow, and therefore, so is the ability to deliver both oxygen and nutrients to cells. Insufficient oxygen delivery also increases the production of free radicals, increasing inflammation. Impaired nutrient delivery combined with increased inflammation is a recipe for bone loss.[49,50]

Furthermore, the liver, in addition to running a safety check on portal vein deliveries from the digestive tract and clearing potential toxins, is responsible for converting the vitamin D3 we absorb into 25(OH)D, the primary form in which vitamin D circulates in the bloodstream. 25(OH)D is the precursor for 1,25-D, the hormonal form of vitamin D, the form that enables active absorption of calcium from the intestines. No 25(OH)D means no 1,25-D, and that means only 10-15% of the calcium consumed from food or supplements can be absorbed.

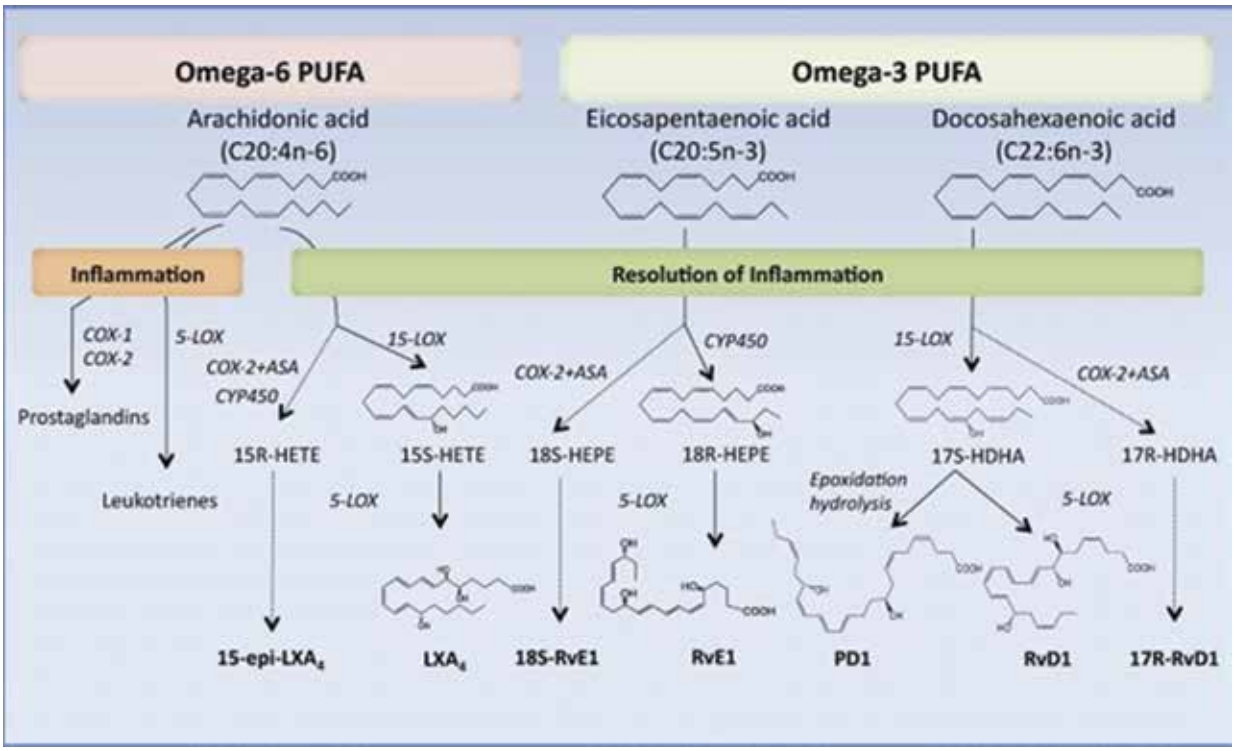
Ibuprofen prevents the formation of the resolvins, the inflammation-ending agents our bodies produce from the essential fatty acids, primarily from the omega-3s EPA and DHA, but also from the omega-6 arachidonic acid when we're not consuming excessive amounts of omega-6.[51]

Acetaminophen rapidly depletes glutathione, which is why this NSAID is so toxic to the liver. And when the liver can't do its job, free radical damage spins out of control, producing more inflammation, which promotes bone loss.[52,53]

Aspirin, in contrast to the other NSAIDs, promotes the resolution of inflammation. Until recently, the resolution of inflammation was thought to be just a passive consequence that occurred as pro-inflammatory signaling slowed and ultimately ceased. We now know that the resolution of inflammation is a highly ordered, active process tightly regulated by a number of mediators derived from EPA, DHA, and arachidonic acid. These SPMs include 3 types of inflammation-ending agents: resolvins, protectins, and maresins.

As the Figure shows, aspirin helps produce 3 kinds of inflammation-ending resolvins: one from EPA, one from DHA, and one from arachidonic acid.

Figure. The omega-6 arachidonic acid is released from phospholipids in cell membranes in the area and metabolized by COX and/or 5-LOX enzymes to form pro-inflammatory mediators, such as prostaglandins and leukotrienes. During the process of resolution of inflammation, the omega-6 fatty acid arachidonic acid is converted by 15-LOX to 15S-HETE, which is rapidly converted to inflammation-resolving lipoxin A4 (LXA4) by 5-LOX. Formation of LXA4 from 15R-HETE can also occur after acetylation of COX-2 by aspirin (ASA).



When aspirin is taken during inflammation, COX-2, the first enzyme involved in the process of producing the resolvins, is acetylated by aspirin and then converts:

- EPA to 18R-HEPE, which is then acted upon by 5-LOX, forming the Resolvins E1 and E2.
- Arachidonic acid to 15S-HETE, which is then converted by 5-LOX into the Resolvin Lipoxin A4.
- DHA to 17R-HDHA, which is then changed by 5-LOX into the Resolvin 17R-RvD1.

The Resolution Of Inflammation

Similarly, the omega-3 fatty acid eicosapentaenoic acid is converted into 18-HEPE by aspirin-acetylated COX-2 or through cytochrome P450 enzymes and subsequently transformed by 5-LOX into 18S- or 18R-resolvin (Rv) E1. DHA is converted into 17S-hydroxy-DHA by 15-LOX, which subsequently is transformed by 5-LOX into RvD1 and then into protectin D1 (PD1). Formation of 17R-RvD1 from 17R-HDHA can also occur after acetylation of COX-2 by aspirin.[54]

Mitigation strategies, alternative medications to consider: If your patient must take acetaminophen or an NSAID to manage chronic pain, take aspirin, at the lowest dose possible, and ensure that intake of EPA and DHA is optimal, which requires consumption of *at least* 2 grams of EPA/DHA daily; however, depending on your patient's diet and other factors, more may be required. A simple blood draw can now be utilized to evaluate omega 6:omega-3 status.[55]

Summary

This first of 2 editorials on commonly prescribed and OTC drugs as secondary causes of osteoporosis clearly demonstrates this is a significant problem. Clinicians reading this journal are likely well versed in the nutritional causes of osteoporosis. However, only addressing nutritional needs may not be adequate if the patient has too many secondary causes of osteoporosis. Effective care requires both supporting the metabolic processes that promote bone building AND removing as many causes of bone function disruption as possible. In Part Two we cover the remainder of the bone-damaging drug classes.

Joseph Pizzorno, ND, Editor in Chief
drpizzorno@innovisionhm.com
http://twitter.com/drpizzorno

References

1. Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. *Am J Med*. 2010 Oct;123(10):877-884. doi: 10.1016/j.amjmed.2010.02.028 PMID: 20920685
2. Dworatzek E, Mahmoodzadeh S. Targeted basic research to highlight the role of estrogen and estrogen receptors in the cardiovascular system. *Pharmacol Res*. 2017 May;119:27-35. doi: 10.1016/j.phrs.2017.01.019 PMID: 28119050
3. Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. *Trends Mol Med*. 2013 Mar;19(3):197-209. doi: 10.1016/j.molmed.2012.12.007 PMID: 23348042
4. Foglietta J, Inno A, de Iuliis F, et al. Cardiotoxicity of Aromatase Inhibitors in Breast Cancer Patients. *Clin Breast Cancer*. 2017;17(1):11-17. https://doi.org/10.1016/j.clbc.2016.07.003
5. Abdel-Qadir H, Amir E, Fischer HD, et al. The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. *Eur J Cancer*. 2016 Nov;68:11-21. doi: 10.1016/j.ejca.2016.08.022 PMID: 27693889
6. Hong AR, Kim JH, Lee KH, et al. Long-term effect of aromatase inhibitors on bone microarchitecture and macroarchitecture in non-osteoporotic postmenopausal women with breast cancer. *Osteoporos Int*. 2017 Apr;28(4):1413-1422. doi: 10.1007/s00198-016-3899-6 PMID: 28083668
7. Kalder M, Hans D, Kyvernitakis I, Lamy O, Bauer M, Hadji P. Effects of Exemestane and Tamoxifen treatment on bone texture analysis assessed by TBS in comparison with bone mineral density assessed by DXA in women with breast cancer. *J Clin Densitom*. 2014 Jan-Mar;17(1):66-71. doi: 10.1016/j.jocd.2013.03.003 PMID: 23562130
8. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011 Sep 7;103(17):1299-309. doi: 10.1093/jnci/djr242 PMID: 21743022
9. Yu Z, Guo X, Jiang Y, et al. Adjuvant endocrine monotherapy for postmenopausal early breast cancer patients with hormone-receptor positive: a systemic review and network meta-analysis. *Breast Cancer*. 2018;25(1):8-1‹6. doi: 10.1007/s12282-017-0794-8
10. Cronin-Fenton DP, Damkier P. Tamoxifen and CYP2D6: A Controversy in Pharmacogenetics. *Adv Pharmacol*. 2018;83:65-91. doi: 10.1016/bs.apha.2018.03.001 PMID: 29801584
11. Pawlik A, Słomińska-Wojewódzka M, Herman-Antosiewicz A. Sensitization of estrogen receptor-positive breast cancer cell lines to 4-hydroxytamoxifen by isothiocyanates present in cruciferous plants. *Eur J Nutr*. 2016 Apr;55(3):1165-1180. doi: 10.1007/s00394-015-0930-1 Epub 2015 May 27. PMID: 26014809; PMCID: PMC4819954.term=26014809
12. de Vries Schultink AHM, Huitema ADR, Beijnen JH. Therapeutic Drug Monitoring of endoxifen as an alternative for CYP2D6 genotyping in individualizing tamoxifen therapy. *Breast*. 2018 Dec;42:38-40. doi: 10.1016/j.breast.2018.08.100. Epub 2018 Aug 22. PMID: 30153552.
13. Pizzorno L. Nothing Boring About Boron. *Integr Med (Encinitas)*. 2015 Aug;14(4):35-48. PMID: 26770156 PMCID: PMC4712861
14. Ziaran S, Goncalves FM, Sn JB. Complex metabolic and skeletal changes in men taking long-term androgen deprivation therapy. *Clin Genitourin Cancer*. 2013 Mar;11(1):33-8. doi: 10.1016/j.clgc.2012.08.005. Epub 2012 Sep 19. PMID: 23000203
15. Beerhorst K, van der Kruijs SJ, Verschuure P, Tan IY, Aldenkamp AP. Bone disease during chronic antiepileptic drug therapy: general versus specific risk factors. *J Neurol Sci*. 2013 Aug 15;331(1-2):19-25. doi: 10.1016/j.jns.2013.05.005. Epub 2013 May 21. PMID: 23706474
16. Benzodiazepines. Drugs.com. Updated February 5, 2019. Accessed March 4, 2021. https://www.drugs.com/drug-class/benzodiazepines.html.
17. Damsa C, Bumb A, Bianchi-Demicheli F, et al. "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. [In eng]. *J Clin Psychiatry*. 2004;65(8):1064-1068. PMID:15323590
18. Luz Rentero M, Carbonell C, Casillas M, González Béjar M, Berenguer R. Risk factors for osteoporosis and fractures in postmenopausal women between 50 and 65 years of age in a primary care setting in Spain: a questionnaire. *Open Rheumatol J*. 2008;2:58-63. PMID: 19088873
19. Pinheiro MdeM, Ciconelli RM, Martini LA, Ferraz MB. Risk factors for recurrent falls among Brazilian women and men: the Brazilian Osteoporosis Study (BRAZOS). *Cad Saude Publica*. 2010 Jan;26(1):89-96. PMID: 20209213
20. Williams LJ, Pasco JA, Stuart AL, et al. Psychiatric disorders, psychotropic medication use and falls among women: an observational study. *BMC Psychiatry*. 2015 Apr 8;15:75. doi: 10.1186/s12888-015-0439-4. PMID: 25884941
21. Requena G, Huerta C, Gardarsdottir H, et al. Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies across databases from the PROTECT-EU project. *Pharmacoepidemiol Drug Saf*. 2016 Mar;25 Suppl 1:66-78. doi: 10.1002/pds.3816. Epub 2015 Jun 23. PMID: 26100105
22. Bushe C, Shaw M. Prevalence of hyperprolactinaemia in a naturalistic cohort of schizophrenia and bipolar outpatients during treatment with typical and atypical antipsychotics. *J Psychopharmacol*. 2007 Sep;21(7):768-773. Epub 2007 Jul 2. PMID: 17606473
23. Bolton JM, Targownik LE, Leung S, Sareen J, Leslie WD. Risk of low bone mineral density associated with psychotropic medications and mental disorders in postmenopausal women. [In eng]. *J Clin Psychopharmacol*. 2011;31(1):56–60. PMID: 21192144
24. Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol*. 2008 Aug;28(4):384-91. PMID: 18626264
25. Rauma PH, Honkanen RJ, Williams LJ, Tuppurainen MT, Kröger HP, Koivumaa-Honkanen H. Effects of antidepressants on postmenopausal bone loss - A 5-year longitudinal study from the OSTPRE cohort. *Bone*. 2016 Aug;89:25-31. doi: 10.1016/j.bone.2016.05.003. Epub 2016 May 11. PMID: 27179631
26. Power C, Duffy R, Mahon J, McCarroll K, Lawlor BA. Bones of Contention: A Comprehensive Literature Review of Non-SSRI Antidepressant Use and Bone Health. *J Geriatr Psychiatry Neurol*. 2020 Nov;33(6):340-352. doi: 10.1177/0891988719882091 PMID: 31665962
27. O'Keane V. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. *J Psychopharmacol*. 2008 Mar;22(2 Suppl):70-75. PMID: 18477623
28. Wu, Q. Depression and antidepressant medications: both are linked to increased fracture risk. *Osteoporos Int*. 2019;30(3):695-696. https://doi.org/10.1007/s00198-018-4785-1 PMID:30488276
29. van de Ven LI, Klop C, Overbeek JA, de Vries F, Burden AM, Janssen PK. Association between use of antidepressants or benzodiazepines and the risk of subsequent fracture among those aged 65+ in the Netherlands. *Osteoporos Int*. 2018 Nov;29(11):2477-2485. doi: 10.1007/s00198-018-4632-4. Epub 2018 Aug 15. PMID: 30112636 PMCID: PMC6208956 DOI: 10.1007/s00198-018-4632-4
30. Donzelli A, Schivalocchi A, Giudicatti G. The underestimation of antidepressants role in risk of fractures: clinical and public health implications. *Osteoporos Int* 2019 Feb;30(2):533-534. doi: 10.1007/s00198-018-4681-8. Epub 2018 Nov 30.
31. Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol* 2014 Nov;29(6):517-27. doi: 10.1002/hup.2434. Epub 2014 Sep 22. PMID: 25384672
32. Barbara Tóth B, Hegyi P, Lantos T, et al. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. *Review Planta Med*. 2019 Jan;85(1):24-31. doi: 10.1055/a-0660-9565. Epub 2018 Jul 23. PMID: 30036891
33. Dai L, Chen L, Wang W. Safety and Efficacy of Saffron (Crocus sativus L.) for Treating Mild to Moderate Depression: A Systematic Review and Meta-analysis. J Nerv Ment Dis. 2020;208(4):269-276. doi:10.1097/NMD.0000000000001118
34. O'Keane V, Meaney AM. Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia? *J Clin Psychopharmacol*. 2005 Feb;25(1):26-31. PMID: 15643097
35. Besnard I, Auclair V, Callery G, Gabriel-Bordenave C, Roberge C. [Antipsychotic-drug-induced hyperprolactinemia: physiopathology, clinical features and guidance]. [Article in French] *Encephale*. 2014 Feb;40(1):86-94. doi: 10.1016/j.encep.2012.03.002. Epub 2013 Aug 5. PMID: 23928066
36. Antonopoulou M, Bahtiyar G, Banerji MA, Sacerdote AS. Diabetes and bone health. *Maturitas*. 2013 Nov;76(3):253-9. doi: 10.1016/j.maturitas.2013.04.004. Epub 2013 Apr 28. PMID: 23628280
37. Alemán-González-Duhart D, Tamay-Cach F, Álvarez-Almazán S, Mendieta-Wejebe JE. Current Advances in the Biochemical and Physiological Aspects of the Treatment of Type 2 Diabetes Mellitus with Thiazolidinediones. *PPAR Res*. 2016;2016:7614270. doi: 10.1155/2016/7614270. Epub 2016 May 23. PMID: 27313601
38. Meier C, Schwartz AV, Egger A, Lecka-Czernik B. Effects of diabetes drugs on the skeleton. *Bone*. 2016 Jan;82:93-100. doi: 10.1016/j.bone.2015.04.026. Epub 2015 Apr 23. PMID: 25913633
39. Maiorino MI, Bellastella G, Chiodini P, et al. Primary Prevention of Sexual Dysfunction With Mediterranean Diet in Type 2 Diabetes: The MÈDITA Randomized Trial. *Diabetes Care*. 2016;39(9):e143-e144. PMID:27352954
40. Salas-Salvadó J, Guasch-Ferré M, Lee CH, Estruch R, Clish CB, Ros E. Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. *J Nutr*. 2015;146(4):920S-927S. doi: 10.3945/jn.115.218487. PMID: 26962178; PMCID: PMC4807638
41. Cespedes EM, Hu FB, Tinker L, et al. Multiple Healthful Dietary Patterns and Type 2 Diabetes in the Women's Health Initiative. *Am J Epidemiol*. 2016 Apr 1;183(7):622-33. doi: 10.1093/aje/kwv241. Epub 2016 Mar 2. PMID: 26940115
42. Álvarez-Pérez J, Sánchez-Villegas A, Díaz-Benítez EM, et al. Influence of a Mediterranean Dietary Pattern on Body Fat Distribution: Results of the PREDIMED-Canarias Intervention Randomized Trial. *J Am Coll Nutr*. 2016;35(6):568-580. [Epub ahead of print] PMID: 27314172

43. Joseph JJ, Echouffo-Tcheugui JB, Golden SH, et al. Physical activity, sedentary behaviors and the incidence of type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). *BMJ Open Diabetes Res Care*. 2016 Jun 23;4(1):e000185. doi: 10.1136/bmjdrc-2015-000185 PMID: 27403323
44. Safe Use of Over-the-Counter Pain Relievers and Fever Reducers. U.S. Food and Drug Administration. https://www.fda.gov/drugs/understanding-over-counter-medicines/safe-use-over-counter-pain-relievers-and-fever-reducers. Published 2021. Accessed March 4, 2021.
45. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J*. 2008 Feb;22(2):383-90. Epub 2007 Sep 20. PMID: 17884974
46. Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW, Murphy MJ. Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. *Kidney Int*. 2013 Jul;84(1):174-8. doi: 10.1038/ki.2013.76. Epub 2013 Mar 13. PMID: 23486517
47. Pelletier JP, Martel-Pelletier J, Rannou F, Cooper C. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys. *Semin Arthritis Rheum*. 2016 Feb;45(4)(suppl):S22-S27. doi: 10.1016/j.semarthrit.2015.11.009. Epub 2015 Dec 2. PMID: 26806184
48. Bruyère O, Cooper C, Pelletier JP, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis-From evidence-based medicine to the real-life setting. *Semin Arthritis Rheum*. 2016 Feb;45(4)(suppl):S3-S11. doi: 10.1016/j.semarthrit.2015.11.010. Epub 2015 Dec 2. PMID: 26806188
49. Tankó LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *J Bone Miner Res*. 2005 Nov;20(11):1912-20. Epub 2005 Jul 18. PMID: 16234963
50. Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascul Pharmacol*. 2015 Aug;71:40-56. doi: 10.1016/j.vph.2015.03.005. Epub 2015 Apr 11. PMID: 25869516
51. Chiang N, Serhan CN. Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. *Mol Aspects Med*. 2017 Dec;58:114-129. doi: 10.1016/j.mam.2017.03.005. Epub 2017 Mar 31. PMID: 28336292
52. Guañabens N, Parés A. Osteoporosis in chronic liver disease. *Liver Int*. 2018;38(5):776-785. doi: 10.1111/liv.13730. [Epub ahead of print] PMID: 29479832
53. Patel SJ, Luther J, Bohr S, et al. A Novel Resolvin-Based Strategy for Limiting Acetaminophen Hepatotoxicity. *Clin Transl Gastroenterol*. 2016 Mar 17;7:e153. doi: 10.1038/ctg.2016.13. PMID: 26986653
54. Titos E, Clària J. Omega-3-derived mediators counteract obesity-induced adipose tissue inflammation. *Prostaglandins Other Lipid Mediat*. 2013 Dec;107:77-84. doi: 10.1016/j.prostaglandins.2013.05.003. Epub 2013 May 21. PMID: 23707933
55. Omega-3 and -6 Fatty Acids. Quest Diagnostics. Testdirectory.questdiagnostics.com. https://testdirectory.questdiagnostics.com/test/test-detail/91001/omega-3-and--6-fatty-acids?cc=MASTER. Published 2021. Accessed March 4, 2021.