This document contains a detailed text of the information for the slides in the Main Course, as a reference and for your convenience.

INTRODUCTION

Slide #1
Welcome to the Indiana State Department of Health Oral Health Program online course: Dentistry and Basic Non-Opioid Prescribing in Pain.

This course consists of three parts, including the:

1. Main Course;
2. Addendum A: Hypothetical Cases with questions, answers, and comments; and
3. Addendum B: Analyzing the Risk of Adverse Events (optional).

This course is being presented by the Indiana State Department of Health and being offered at no charge to the participant.

Slide #2
The goal of this course is to help dentists learn more about the use of non-steroidal anti-inflammatory drugs (commonly referred to as NSAIDs) to alleviate pain in their patients. This course is designed to provide information that can be immediately incorporated into the manner in which dentists practice dentistry.

To help you determine your understanding of this information, we have included various hypothetical cases for your consideration.

We hope you find this course valuable.
Slide #3
Dr. Dmitry Arbuck prepared the Main Course material and helped with the preparation of all other aspects of this online course. Dr. Arbuck is a specialist in the treatment of acute and chronic pain and owns and operates a large multi-disciplinary pain clinic in Carmel, Indiana.

Slide #4
Dr. Arbuck also speaks for, and consults with, many pharmaceutical companies.

Slide #5
The goals of pain management include decreasing pain, increasing function, and utilizing medications that limit unacceptable side effects, including addiction.

Slide #6
The goals of this presentation include gaining knowledge of the appropriate use of acetaminophen and NSAIDs for pain management in dentistry, improving knowledge of the benefits and adverse effects of various NSAIDs, and learning appropriate alternatives to opioid medications for pain management.

Slide #7
This course emphasizes providing information on acetaminophen and NSAIDs; but, some basic information about opioid medications for pain management is also included.

Although, the use of opioids for acute pain in dentistry is appropriate, the long-term use of opioids to manage pain in dentistry is discouraged.

Patients may abuse and divert pain medications. Dentists must do whatever is possible to ensure the best care for patients with pain, and minimize abuse and diversion of pain medications.

In Indiana, dentists are encouraged to use INSPECT to verify the prescription history of patients before prescribing opioids.

Slide #8
Although NSAIDs can be very effective at reducing pain, they are not without risk.

Many studies have demonstrated that deaths can occur among patients taking NSAIDs to manage pain, which include death from GI bleeding and death from cardiovascular problems, such as heart attacks and strokes. The use of NSAIDs is also associated with kidney failure.

Slide #9
The risk of GI bleeding and cardiovascular problems starts almost immediately after a patient begins taking an NSAID medication. That is, this risk is equally high when NSAIDs are used for short-term or long-term treatment.

However, for kidney failure the risk becomes higher the longer an NSAID is taken.
Slide #10
Acetaminophen is used to treat mild to moderate pain and has an efficacy comparable to NSAIDs in some musculoskeletal conditions.
It is commonly combined with other analgesics for increased pain relief. Acetaminophen has few adverse effects, but hepatic toxicity is possible at doses greater than 4 grams per day or with chronic alcohol abuse.
The therapeutic dose of acetaminophen is 4 grams per day in divided doses for acute pain (for up to 2-3 weeks) and 3 grams a day for any longer periods of time.
Lower doses are especially recommended in the elderly, patients with dehydration, liver disease, or substance abuse issues.
Acetaminophen has been found to have a causative relationship with asthma and the current epidemic of asthma in children may be connected to the high utilization rate of acetaminophen in this group.

Slide #11
Acetaminophen has many mechanisms of action. It is a centrally acting analgesic that increases the pain threshold through influence on the brain.
The exact mechanisms of action are not known, but may involve nitric oxide inhibition, NMDA inhibition, substance P inhibition, and COX-II antagonism.
The central action of acetaminophen is linked to COX-III enzyme antagonism in the brain.

Slide #12
NSAIDs are used for three (3) main purposes: analgesia because of their pain relieving property; anti-inflammation due to blocking the arachidonic acid cycle; and antipyresis due to centrally regulated decrease in fever.
This group of medications is used regularly in acute pain.
However, these medications have little to no role in chronic pain management, other than to deal with inflammatory exacerbation of chronic problems.

Slide #13
NSAIDs belong to a number of chemical groups.
Combining NSAIDs from these different groups is generally not indicated and, so far, has not been shown in clinical studies to have a measurable clinical benefit.
However, some clinicians still consider combining medications from different chemical groups to be potentially beneficial in selected cases.

Slide #14
NSAIDs have their primary effect through blocking the action of cyclooxygenase enzymes, specifically COX-I and COX-II enzymes.
NSAIDs have varying degrees of COX-I and COX-II selectivity.
The level of inhibition of these enzymes is dose related.
The degree of such inhibition is associated with a spectrum of both benefits and side effects.

Slide #15
The core mechanism of action of NSAIDs is based on inhibiting arachidonic acid catabolism by interfering with the actions of COX-I and COX-II enzymes.
This slide demonstrates how the COX-I and COX-II enzymes work in various tissues to produce thromboxane, prostaglandins, and prostacyclins, which have the various listed actions.
**COX-I enzyme** serves as a catalyst for the production of *thromboxanes* in platelets, which increases platelet aggregation, to help control bleeding, and produces vasoconstriction.

In the **gastric mucosa**, the COX-I enzyme is a catalyst for the production of *prostaglandins*, which increase gastric mucus production and decrease gastric acid production.

In the **endothelium**, the COX-I enzyme is a catalyst for the production of *prostacyclins*, which decrease platelet production and cause vasodilatation.

**COX-II enzyme** does not serve as a catalyst in platelets or gastric mucosa.

However, like the COX-I enzyme, the COX-II enzyme does serve as a catalyst for the production of prostacyclins in the endothelium.

In the **joints**, the COX-II enzyme is a catalyst for the production of *prostaglandins*, which mediate pain and inflammation.

**Non-selective NSAIDs** block the action of COX-I and COX-II enzymes in platelets, gastric mucosa, endothelium, and joints; thus, preventing the catalysis of arachidonic acid in all of these tissues.

Non-selective NSAIDs produce **therapeutic effects** by blocking the action of the COX-II enzyme, thereby reducing pain and inflammation.

However, because non-selective NSAIDs block the action of both COX-1 and COX-2 enzymes, these drugs also produce potentially **adverse effects**, including a decrease in platelet aggregation and a subsequent prolongation of bleeding time, as well as vasoconstriction.

Notice, **non-selective NSAIDs** can cause BOTH vasoconstriction and vasodilatation, as well as, BOTH a decrease and an increase in the aggregation of platelets, but the **NET EFFECT** is on the side of vasoconstriction, and a decrease in the aggregation of platelets.

**Selective COX-II inhibitors** (*coxibs*) block, primarily, the catalysis of arachidonic acid by the COX-II enzyme in the endothelium and the joints. This is the foundation of the difference in effects and side effects of COX-I and COX-II inhibitors.

COX-II inhibitors have the **therapeutic effects** of reducing pain and inflammation, while avoiding adverse effects in the gastrointestinal system.

However, when a COX-II **inhibitor** blocks the catalysis of arachidonic acid into *prostacyclins* in the endothelium, this blocks the associated vasodilation, **resulting in vasoconstriction**, which can produce **adverse effects**.

This vasoconstriction increases the risk of the **adverse cardiovascular effects** associated with COX-II inhibitors, including myocardial infarction and strokes.

**Slide #16**

Cyclooxygenase-I (or simply COX-I) is a “housekeeping” enzyme responsible for protective cellular functions in the platelets, the stomach, and the kidneys.

The COX-I enzyme facilitates the creation of prostaglandins, which are used for basic protective functions of the body. Normally, COX-I enzyme concentration remains stable at all times in the body.

COX-I inhibitors affect this “housekeeping enzyme” and thus interfere with prostaglandin synthesis.

Because of this action, **drugs that inhibit** the COX-I enzyme can influence platelets, the lining of the GI tract, and kidney function, with potentially adverse consequences; such as, increased bleeding time, GI ulcers, and impaired renal function.
Slide #17

The cyclooxygenase-2 (or simply COX-II) enzyme is not normally present in cells and has to be induced into action. This enzyme is built only in special cells (for instance in lung cells) and used for signaling pain and inflammation.

The COX-II enzyme facilitates the production of prostaglandins, which is stimulated only as part of immune response. COX-II production is induced by inflammatory cytokines and growth factors. COX-II inhibitors block the action of the COX-II enzyme. By blocking this enzyme, COX-II inhibitors block the inflammatory response and block mitogen activity. That is, in addition to their widely appreciated anti-inflammatory effect, COX-II inhibitors can also block cell division.

Thus, COX-II inhibitors have therapeutic effects, which include a decrease in pain and inflammation, as well as a decrease in production of new cells.

COX-II inhibitors also produce severe vasoconstriction through its influence on the endothelium, which can be a problem, but which can also have some beneficial effects. One such beneficial effect is the inhibition of angiogenesis, which can help prevent the formation of multiple polyps in the large intestine.

Thus, medications like celecoxib are indicated for treatment of benign familial polyposis due to the significant degree of reducing blood flow to polyps with their subsequent atrophy.

COX-II inhibitors can, however, have major adverse effects, associated with their production of severe vasoconstriction, including heart attacks, strokes, and renal complications, including renal failure.

Many of the adverse effects associated with COX-I inhibitors, such as increased bleeding times and ulcers, are generally not seen with COX-II inhibitors.

Slide #18

Because COX-II inhibitors do not act directly on platelets, one usually does not see the bleeding that can occur with the blocking of platelet aggregation by COX-I inhibitors. However, one needs to remember that in selected patients COX-II inhibitors can have a clinically significant effect on the coagulation of blood.

Also, because COX-II inhibitors do not act on the gastric mucosa, one usually does not see the adverse effects on the gastric mucosa that can occur with COX-I inhibitors.

However, if COX-II inhibitors are combined with even a low dose of aspirin, this protection is reduced and adverse gastric events can occur.

Therefore, the recommendation for patients who take aspirin for cardiac or circulatory problems is to separate the intake of aspirin and other NSAIDs by at least two (2) hours, even with small doses of aspirin; such as those to prevent the recurrence of heart attacks.

Slide #19

The amount of COX-I inhibition varies with different NSAIDs.

For instance, diclofenac provides only 50% inhibition in therapeutic doses and naproxen provides about 95% inhibition, while other NSAIDs fall somewhere between 50% and 95% inhibition.

The higher the level of COX-I inhibition, the higher is the likelihood of adverse effects, such as increased bleeding time, GI ulcers, and impaired renal function.

Matching a particular patient to a particular pain medication, such as an NSAID, can help avoid potential side effects, and reduce the risk of aggravating existing medical conditions.
**Slide #20**
The amount of COX-II inhibition also varies between different NSAIDs.
It is interesting that diclofenac provides higher COX-II inhibition than selective COX-II inhibitors, like celecoxib, in the usual therapeutic doses.
The difference between celecoxib and other NSAIDS is that celecoxib selectively blocks only the COX-II enzyme, while other NSAIDS block both COX-I and COX-II enzymes.
Another point of interest is that meloxicam, ibuprofen, and naproxen all fall within the same range of percentage of COX-II inhibition.

**Slide #21**
In addition to the importance of the amount of inhibition, is the importance of the relative selectivity of inhibition.
Many NSAIDs inhibit both COX-I and COX-II enzymes; but, vary according to which enzyme they inhibit the most; that is, their relative selectivity of inhibition.
Due to the varied degree of COX-I and COX-II inhibition among different NSAIDs, it is noteworthy that:
ketorolac (Toradol) is the most COX-I selective medication; therefore, it has an especially troublesome profile regarding, platelet aggregation, gastric function, and kidney function;
meloxicam (Mobic) is less likely to produce such pronounced effects due to preferential selectivity for COX-II receptors over COX-I receptors.
Also of note:
Even though celecoxib is a selective COX-II inhibitor, it actually has a slightly less amount of COX-II inhibition than meloxicam, which has both COX-I and COX-II inhibition, but is highly selective for the COX-II enzyme.

**Slide #22**
In addition to the well-known influence of NSAIDs on the arachidonic cascade, NSAIDs also work by blocking voltage dependent sodium channels.
NSAIDs also produce positive allosteric modulation of potassium channels, resulting in hyperpolarization, which keeps these potassium channels open.
All of these actions produce peripheral analgesia, similar to that produced by lidocaine.

**Slide #23**
The adverse effects of NSAIDs were mentioned above.
This slide demonstrates that gastrointestinal and cardiovascular adverse effects may occur almost immediately, within the first two weeks of treatment, and remain elevated throughout the course of treatment, as indicated by the odds ratios in the slide.
Therefore, the treating provider needs to understand that it does not take months or years for NSAIDs to cause upper GI or cardiovascular effects. Risk is evident shortly after NSAIDS are initiated and remains elevated throughout the course of treatment.
The risk of renal problems associated with NSAIDs also occurs almost immediately after the initiation of treatment. However, the risk of renal problems actually increases the longer a patient is taking an NSAID.

**Slide #24**
Odds ratios were used in the previous slide to indicate the risks of having various adverse events with NSAIDs, over time
These odds ratios provide estimates of relative risks of adverse events with NSAIDs.
**Relative risk** is the RATIO obtained by dividing the risk of an adverse event among those taking a medication by the risk of an adverse event among those not taking a medication.

Understanding the concepts of **risk**, **relative risk**, and **excess risk**, form the foundation for understanding adverse effects associated with NSAIDs. **Addendum B** contains more information about these concepts, for those that are interested. From the standpoint of this course, this extra material is optional.

**Slide #25**
The adverse effects for NSAIDs have straightforward time considerations. The risk of gastrointestinal and cardiovascular events remains about the same over time, while the risk of renal events increases over time.

**Slide #26**
This slide indicates that there is a positive association between dose and GI complications, for most NSAIDs.

**Note:**
The relative risks associated with low doses are seen in blue. The relative risks associated with high doses are seen in orange. There is a positive relationship between dose and relative risk for all but one of the listed NSAIDs. The exception is celecoxib, where the relative risk for GI complications is inversely related to dose; that is, a low dose produces a larger relative risk than a high dose. To reiterate, for most NSAIDs as the dose increases the relative risk for a severe GI adverse event increases.

**Slide #27**
As indicated previously, the risk of a GI adverse event generally increases as the dose increases. This is also true for cardiovascular adverse effects. Myocardial infarction is one of the several cardiovascular effects described. On this slide, odds ratios (ORs) are used to measure the overall association between NSAIDS and GI events, and between NSAIDs and myocardial infarction. As previously stated, the odds ratio is an estimate of the relative risk.

**With respect to adverse upper GI events:**
Patients taking a low to medium dose of an NSAID were 2.4 times as likely to have an adverse upper GI event as those not taking an NSAID; while Patients taking a high dose were 4.5 times as likely to have an adverse upper GI event as those not taking an NSAID.

**With respect to myocardial infarction:**
Patients taking a low dose of an NSAID were 1.2 times as likely to have a MI as those not taking an NSAID; while Patients taking a high dose of an NSAID were 1.6 times as likely to have an MI as those not taking an NSAID.

**Slide #28**
In addition to the influence of dose on GI and cardiovascular adverse events, it is important to be aware of influence of dose on renal adverse events. This slide illustrates that NSAID use is associated with acute renal failure, and this association becomes stronger as the dose increases.
This study evaluated almost 400,000 participants from the General Practice Research Database of the United Kingdom.

Patients were aged 50-84; free of known cancer, renal disease, liver cirrhosis, or systemic connective tissue disease.

The study focused on the occurrence of pre-renal failure or renal failure that was believed to be associated with inhibition of renal prostaglandins.

As you can see in the slide, the risk of NSAID-associated acute renal failure was found to increase with NSAID dose.

Patients prescribed a low to medium dose had an elevated risk of renal failure (RR=2.5), compared to non-users.

Patients prescribed a high-dose had a more than three-fold greater risk of developing acute renal failure (RR=3.4), compared to non-users.

**Slide #29**

NSAIDs are, to varying degrees, associated with hypertension.

Usually, aspirin and sulindac do not affect blood pressure.

Celecoxib causes mild elevation.

Ibuprofen is associated with intermediate elevation.

Medications like indomethacin, piroxicam, and naproxen are associated with significant blood pressure changes.

**Slide #30**

With respect to GI adverse effects,

It is of paramount importance to remember that gastrointestinal adverse effects are usually silent and undetected in 60-80% of people.

For these people, anemia and life-threatening blood loss develop without being noticed.

With respect to cardiovascular adverse effects,

NSAIDs have a FDA class warning that includes a risk for cardiovascular adverse effects.

Among NSAIDs, naproxen is generally considered the safest NSAID for patients at risk for cardiovascular adverse events.

**Slide #31**

Additional adverse effects which are less known but noticed in clinical practice include adverse effects in the mental arena and include irritability, anxiety, and sometimes psychotic reactions.

Menstrual disturbance and hemolytic anemia are also observed.

The hemolytic anemia is based on induction of antibodies to Rh antigen by NSAIDs.

**Slide #32**

There are several adverse effects associated with NSAIDs that are common, but are often overlooked.

These include: fluid retention and edema; exfoliative dermatitis; Stevens-Johnson Syndrome; epidermal necrolysis; headache; dizziness; hot flashes; and syncope.

**Slide #33**

It is well known, and must be remembered, that the use of NSAIDs during pregnancy is always of some danger, and may rise to the level of unacceptable danger.

NSAIDs are categorized as Category C in the first and second trimesters.

This means that fetal problems are found in mice but not in humans.
As such, these medications need to be used with caution and discretion during the 1\textsuperscript{st} and 2\textsuperscript{nd} trimesters, dictated by the patient’s choice and the physician’s judgment. NSAIDs are categorized as \textbf{Category D} in the \textbf{third trimester}, and are \textbf{contraindicated}. This is due to their potential for causing premature closure of the ductus arteriosus in the fetus.

**Slide #34**

NSAIDs can interact with other medications to produce adverse reactions. The most common adverse reactions of various medications, in combination with NSAIDs, include:

- **Angiotensin Converting Enzyme inhibitors (or ACE inhibitors)** such as \textit{lisinopril} (common trade name Zestril) which may cause an increase in the likelihood of acute kidney failure and interfere with blood pressure control;
- **Anticoagulants** may cause an increase in bleeding time;
- **Angiotensin Receptor Blockers (or ARBs)** such as \textit{valsartan} (common trade name Diovan) and \textit{losartan} (common trade name Cozaar) may cause an increase in the likelihood of acute kidney failure and interfere with blood pressure control;
- **Beta-blockers** such as \textit{propranolol} (common trade name Inderal) and \textit{metoprolol} (common trade name Toprol) may fail to control blood pressure;
- **Lithium** may cause acute lithium blood level elevation, which can produce lithium toxicity, with the potential for seizures and death;
- **Loop diuretics** such as \textit{furosemide} (common trade name Lasix), \textit{torsemide} (common trade name Demadex), and \textit{bumetadine} (common trade name Bumex) may cause an increase in the likelihood of kidney failure; and
- **SSRIs** may cause an increase in bleeding.

**Slide #35**

Historically, multiple approaches were used to decrease the risk of adverse effects associated with NSAIDs. These approaches included the introduction of \textit{enteric coating} to decrease upper GI events or using \textit{pro-drugs}, which decrease direct influence of NSAIDS. Unfortunately, all of these approaches relate only to \textit{upper GI tract} adverse effects. Another approach that reduces the risk of upper GI adverse effects is combining NSAIDs with \textbf{gastro-protective agents}. Unfortunately, this approach also does not reduce the risk of lower GI adverse effects.

One can select COX-\textit{II} inhibitors to reduce the risk of adverse effects throughout the GI tract, but these drugs potentially increase cardiovascular and renal risks.

One possible approach to reduce systemic risk would be to use topical NSAIDs, where applicable. Unfortunately, no NSAID formulations presently exist that assist with reducing the risk of cardiovascular and renal problems.

The only solid and proven way to decrease the risks associated with NSAIDs is to: \textbf{decrease the dose} administered; and \textbf{shorten the patient’s exposure} to the medication.

**Slide #36**

Another way of decreasing adverse effects is to:

Avoid using NSAIDs in \textbf{high-risk populations}, such as elderly people with congestive heart problems, patients with coronary artery disease, hypertension, or renal or liver problems. Also, \textbf{dehydrated patients} need to have proper hydration before NSAIDs are used.
**Slide #37**

IC$_{50}$ is the concentration of an inhibitor, such as an NSAID, where the activity of the targeted enzyme, or enzymes, is reduced by half.*

For NSAIDs, only 50 to 80% of the activity of the targeted enzyme, or enzymes, has to be inhibited before there is a clinical effect.

Inhibiting 99% may cause more adverse effects without gain in efficacy; so, lower doses may be safer.


**Slide #38**

It is known that shorter half-life NSAIDs are, in general, safer than longer half-life NSAIDs, because organs and tissues have more time to recover.

Short half-life medications include diclofenac, ketorolac, and ibuprofen.

Long half-life medications include naproxen, meloxicam, and piroxicam.

**Note:**

The risk associated with a particular NSAID can be influenced by its dosage, half-life, duration of use, and its relative selectivity.

**Slide #39**

To reiterate, it is important to be careful when combining NSAIDs with other medications.

Remember, combining NSAIDs with aspirin significantly increases gastrointestinal risk. Therefore, a two (2) hour break between taking aspirin and an NSAID is indicated.

As mentioned previously, other medications also interact with NSAIDs. A clinician needs to take a good patient history in order to know which medications a patient is taking, and thus avoid unwanted interactions.

**Slide #40**

Recently, the FDA strengthened the drug labels for NSAIDs, including over the counter medications such as Motrin, Advil, and Aleve.

These medications can cause many adverse effects, some of which are now known to be life-threatening.

In the past, pharmaceutical companies were instructed to inform patients that NSAIDs “MAY CAUSE” strokes and heart attacks.

Presently, this language has been strengthened to “CAUSE” strokes and heart attacks.

People who have cardiovascular disease are at the greatest risk, particularly people who recently had myocardial infarction or cardiac bypass surgery.

**Note:** Among patients with cardiovascular disease, naproxen is considered the safest NSAID.

In summary, NSAIDs are effective and safe if used appropriately.

The following guidelines, in general, increase the safety of NSAIDs when prescribed to patients:

1. The lowest therapeutic dose is always the safest;
2. The prolonged use of medications should be avoided, whenever possible;
3. Combination of medications should be assessed carefully; and
4. Different patient populations should be assessed carefully.

**Slide #41**
The *last four slides in this presentation* summarize what medications a dentist might consider when prescribing NSAIDs for pain in patients with certain pre-existing medical conditions.

The preferred non-opioids for patients with High Blood Pressure are Sulindac and Celecoxib.

These patients should avoid Naproxen, Ibuprofen, Indomethacin, and Piroxicam.

**Slide #42**
The preferred non-opioid for patients Vascular Risks (MI, strokes) is Naproxen.

These patients should avoid Ibuprofen, Diclofenac, and Celecoxib.

**Slide #43**
The preferred non-opioid for patients with GI, kidney, and bleeding problems are Meloxicam, Diclofenac, and Celecoxib.

These patients should avoid Ketorolac, Indomethacin, Ibuprofen, Naproxen, Ketoprofen, and Piroxicam.

**Slide #44**
Pregnant women should *never* use NSAID’s in the third trimester.

Patients on aspirin, including 81 mg, should take them at a 2 hour interval before or after taking an NSAID.

Thank you for your participation in the Indiana State Department of Health Oral Health Program online Continuing Education Course covering Dentistry and Basic Non-Opioid Prescribing in Pain.

Please proceed to **Addendum A: Hypothetical Cases**.