

Emerging Approaches to Opioid-Free Pain Relief: A Review of Suzetrigine's FDA Approval

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Abstract-Opioids are among the most potent analgesics and are commonly prescribed to manage persistent or severe pain. They are often used by individuals with chronic conditions such as headaches and backaches, as well as by patients recovering from surgery or experiencing pain related to cancer, sports injuries, accidents, or other trauma. While effective, opioids carry a high risk of side effects and addiction. In contrast, non-opioid analgesics are typically the first-line treatment for mild to moderate pain due to their safer profile. Recently, on January 30, 2025, the U.S. Food and Drug Administration (FDA) approved a novel non-opioid analgesic, Suzetrigine, marketed under the brand name Journavx™, for the treatment of moderate to severe acute pain. This approval marks a significant advancement in pain management, offering a safer alternative to opioids with a lower risk of addiction and fewer side effects.

Keywords: opioids, non-opioids, FDA, acute sever pain, drug, chronic pain, treatment, Suzetrigine

INTRODUCTION

Pain is a kind of signal which produces by nervous system. It indirectly informs that something may be wrong or abnormal happens in body. Pain is a one type of unpleasant feeling or emotional experience. According to the 'International Association for the Study of Pain' (IASP), Pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage or described in terms of such damage"[1].

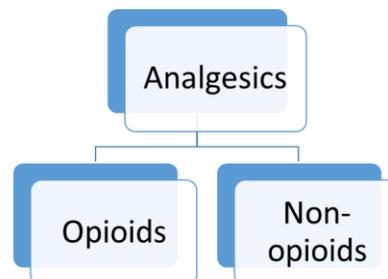
Pain is always a personal experience. Even if the reason for the pain is the same although everyone feels pain differently. Pain may be sharp or dull, mild or severe. It may come and go, or may be feel constant. Pain may feel in one area of body or it may be feels in all over the body.

Pain is a kind of alert for us which says that there is a problem in our body. If we never felt pain, it may

create serious problem for ourself without knowing it, or we might not realize we have a medical problem that needs treatment. Due to facing pain we try to Finding out what's causing that pain and it may help us to determine the best way to manage or treat it.

Pain treatment is tailored to its type, severity, and cause involves, a variety of approaches including medications, physical therapies, heat and cold therapy, acupuncture, psychological interventions, and complementary therapies like massage, meditation, yoga etc. are used.

Multiple kinds of Medications used as a pain reliever. Analgesics are mainly used to treat different types of pain.



Floyd E. Bloom, mentioned that an analgesic drug can be relieve pain selectively without blocking the conduction of nerve impulses, markedly altering sensory perception, or affecting consciousness. Analgesics may be classified into two types, non-opioids (anti-inflammatory drugs) and opioids analgesics. Non-opioid drugs can alleviate pain by reducing local inflammatory responses. They are used for short-term pain relief and for modest pain, such as a headache, muscle strain, bruising, arthritis, etc. While opioids act on the brain. The opioids analgesics were once called narcotic drugs also, because they induce sleep. The opioids analgesics can be used for either short-term or long-term relief of severe pain[2]. Opioids mainly acts on Central nervous system while non opioids on peripheral nervous system. Opioids are more powerful painkiller over non-opioids but it

causes common to sever side effects and there are major risks of addiction of opioids.

DISCUSSION

Pain is a common medical problem and Opioids and non-opioids are two main categories of pain reliving medications. Opioids are the powerful analgesics that act on opioids receptors, while non-opioids work through different mechanisms by targeting inflammation and pain signals.

Opioids are natural or synthetic chemicals which interact with nerve cells that have the potential to reduce moderate to severe pain[3]. Some opioids can be made from the poppy plants directly like, morphine (Dura morph and others). Or others can be made in a laboratory by scientists using same chemical structures for example, fentanyl (Actiq and Fentora). Other opioids those are also very familiar including, codeine, hydrocodone, oxycodone and more[4].

List of opioids and its detailed information:

Table 1 List of opioida

Name of opioids drug	Group of medicines	Brand name	Prescribed for	Dosage forms	Side effects
Oxycodone	Opioid analgesics (narcotic)	Oxycontin, Oxypro, Longtec, Shortec	moderate-to-severe pain.	capsule, tablet	CNS depression, respiratory depression, constipation, causing mental or physical dependence, it may become habit-forming
Oxymorphone	narcotic analgesics	Opana® and Opana ER®	severe & acute pain	tablet, injection	dry mouth, stomach pain or swelling, nausea, vomiting, gas, excessive sweating, fast heartbeat, red eyes, headache, feeling anxious or confused, itching, changes in heartbeat, it may become habit-forming
Hydrocodone	opioid analgesics (narcotic)	Vicodin, Norco, Lortab and Co-Gesic	severe & chronic pain, nonproductive cough	tablets, capsule, syrup	dry mouth, stomach pain, changes in heartbeat, severe respiratory depression, shortness of breath, respiratory tract infection, long term use can lead to dependence and addiction
Codeine	narcotic analgesics	Tuxarin EXR®, Tuzistra XR®	mild to moderate pain, relieve cough caused by the common cold, flu	Tablets, syrups	adrenal gland problems, dizziness, pale or blue lips, pains in the stomach, unusual tiredness or weakness, vomiting, yellow eyes or skin, abdomen unconsciousness, physically addiction, it may become habit-forming, causing mental or physical dependence
Methadone	synthetic opioid analgesic	Dolophine and Methadose	treatment of addicted people to heroin and narcotic, pain medicines, severe pain associated with cancer, neuropathy	tablet, powder, liquid	experience difficulty breathing or shallow breathing, feel lightheaded or faint, experience hives or a rash, swelling of the face, lips, tongue, or throat, chest pain, experience a

					fast or pounding heartbeat, causes addiction
Fentanyl	opioid analgesics	Fentora™, Actiq®, Abstral®, Subsys™, Lazanda®, Duragesic®,	severe pain during and after surgery, used with other medicines just before or during an operation to help the anesthetic (numbing medicine) work better,	tablets, oral drops, sprays, nasal sprays, patches, injection	chest pain or discomfort, difficult or troubled breathing, irregular or shallow breathing, lightheadedness, dizziness, or fainting, pale or blue lips, severe muscle stiffness, slow or irregular heartbeat, unusual tiredness, become mentally and physically dependent
Hydromorphone	narcotic analgesics	Dilaudid® and Exalgo®	severe, acute pain,	tablets	pruritus, sweating, dry mouth, nausea or vomiting, constipation, asthenia, dizziness, headache, somnolence, become dependent
Morphine	narcotic analgesics	Arymo™ ER, Morphabond™ ER, and MS Contin®	severe pain, such as pain caused by a major trauma (for example, an accident) surgery. labor pain in childbirth,	liquid, tablet, capsule	have muscle stiffness, feel dizzy, tired and have low energy – this could be a sign of low blood pressure, nausea or vomiting, become habit-forming, causing mental or physical dependence
Buprenorphine	narcotic analgesics	Subutex, Suboxone, Buprenex, Butrans, Sublocade, Brixadi, and Belbuca	treat acute and chronic pain and opioid dependence, treatment of people with an opioid drug dependence, such as heroin or other opioid medicines	sublingual tablets or film - placed under the tongue, transdermal patches, injection	constipation, feeling or being sick, nausea or vomiting, feeling sleepy or tired, dizzy, vertigo, confusion, headaches, stomach pain, itching or skin rashes, moderate-to-low potential for physical dependence or a high potential for psychological dependence
Tramadol	opiates, or narcotics	Ultram, Ultram ER, Conzip	moderate or moderately severe pain, including pain after surgery or a serious injury,	capsules, tablets	headaches, feeling sleepy, tired, dizzy, feeling or being sick, nausea or vomiting, constipation, dry mouth, sweating, low energy.

Opioids are medications which used in the management and treatment of pain. Opioids are a valuable agent in treating acute and chronic pain. Opioids analgesics can be administered through a variety of dosage forms like oral formulations, including immediate-release or extended-release tablets, syrup formulation with or without antihistamines, rectal formulations. In some cases, it also administrated subcutaneously, intramuscularly or epidurally[5].

Opioids are a broad group of pain-relieving medicines that work with our brain cells. Opioids medicines

travel through the blood stream and bind to opioids receptors in brain cells. It activates that receptor and this active site blocks pain messages and can boost feelings of pleasure[4].

Opioids bind and activate opioids receptors on cells which are located in different organs of the body, especially those involved in feelings of pain and pleasure like, brain, spinal cord, and etc. When opioids attach to these receptors, they block pain signals sent from the brain to the body and release large amounts of dopamine neurotransmitter throughout the body and it relief the pain[6].

Tyler S. Oesterle, M.D., M.P.H. says opioids medicines are very effective for treating pain but somewhere they are dangerous also. At lower doses, opioids may make you feel sleepy. But higher doses of opioids can slow down your breathing system and heart rate, sometime which can lead to death[4].

American society of anesthesiologist states that "While opioids can effectively relieve pain, it also carries some risks and can be highly addictive". Opioids can induce some side effects like, Sleepiness, Constipation, and Nausea etc. Opioids can also cause more serious side effects that can be life-threatening. In addition, if you suddenly stop taking opioids, you can sometimes experience symptoms such as jittery nerves or insomnia. The risk of addiction is especially high when opioids are used to manage chronic pain over a long period of time. Opioids can make brain and body belief that this drug is necessary for survival. As you learn to tolerate the dose you've been prescribed, you may feel that you need even more medication to relieve the pain and it sometimes resulting in

addiction. More than 2 million Americans misuse opioids and every day more than 90 Americans die by opioids overdose according to the National Institute on Drug Abuse[7].

National Institute on Drug Abuse mentioned that opioids use during pregnancy can harm the health of both a pregnant person and their baby. Babies exposed to opioids before birth have a higher risk of health problems that include premature birth and low birth weight. They also may experience some symptoms after birth, such as irritability, crying, tremors, or poor feeding. This is known as neonatal opioids withdrawal syndrome (NOWS)[8].

Anti-inflammatory drugs also known as non-steroidal anti-inflammatory drugs (NSAIDs) which are a type of non-opioids analgesic. They are used to relieve pain and reduce inflammation without being classified as opioids. Many non-opioids drugs including aspirin, ibuprofen, diclofenac etc. are used to treat moderate pain.

List of non-opioids and its detailed information:

Table 2 List of Non opioids

Name of non-opioids drug	Group of medicines	Brand name	Prescribed for	Administratio n form	Side effects
Ibuprofen	NSAIDs	Advil, Motrin, Nurofen, Brufen, Genpril, Ibu-Tab, Ibuprom, Ibutab 200, Midol	fever and to relieve minor aches and headaches, muscle aches, arthritis, menstrual periods, the common cold, toothaches, and backaches	Tablet, capsule, liquid, gel, cream, spray	headache, dizziness. drowsines s, diarrhea, fatigue, restless sleep, nausea, feeling sick, vomiting, constipation, abdominal pain, inflammation of the stomach, stomach ulcer, raised blood pressure, allergic reactions, worsening of asthma symptoms, kidney failure, black poo and blood in vomit

Aspirin	nonsteroidal anti-inflammatory drug (NSAID)	Ascriptin, Aspergum, Aspirin, Bayer, Easprin, Ecotrin, Enterocote, Halfprin, Ninoprin, Norwich Aspirin	mild to moderate pain, inflammation or arthritis, lowers the risk of heart attack, stroke or blood clot, to treat aches and pains such as headache, toothache and period pain	Tablet, Chewable capsule,	ringing in your ears, confusion, rapid breathing, severe nausea, vomiting, bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds, fever lasting longer than 3 days, swelling, or pain lasting longer than 10 days, upset stomach, heartburn, mild headache.
Acetaminophen	analgesics and antipyretics (fever reducers)	TYLENOL®, Comtrex®, Drixoral®, Excedrin Migraine®, Midol®, Sinutab®, Theraflu®, Vanquish®	mild to moderate pain of headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, reactions to vaccinations (shots), and fever	tablet, capsule, syrup, suspension, injection	skin rash, hypersensitivity reactions, nephrotoxicity characterized by elevations in blood urea nitrogen (BUN) and creatinine, and hematological abnormalities such as anemia, leukopenia, neutropenia, and pancytopenia
Meloxicam	nonsteroidal anti-inflammatory drugs (NSAIDs)	Mobic and Vivlodex	relieve the pain, tenderness, swelling, stiffness caused by juvenile rheumatoid arthritis	Tablet, capsule, oral suspension	severe stomach pain, black tarry stools, vomiting of blood or material that looks like coffee grounds, skin rash, swelling of the face, fingers, feet, or lower legs
Piroxicam	nonsteroidal anti-inflammatory drug (NSAID)	Feldene, Alti-Piroxicam	Treatment of pain and help relieve symptoms of arthritis (osteoarthritis, rheumatoid arthritis), inflammation, swelling, stiffness, and joint pain	Capsule	frequent urge to urinate, cold sweats, diarrhea, dry mouth, high fever, irregular, fast or slow breathing, swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, light-colored stools, pain or discomfort in the arms, jaw, back, or neck, red skin, feeling things that are not there, severe headache, stomach pain, suddenly sweating, armpit, trouble sleeping
Celecoxib	NSAIDs	Celebrex®, Elyxyb®	pain, tenderness, swelling and stiffness	capsule	unexplained weight gain, difficulty breathing, swelling of the abdomen, feet, ankles, or lower legs, face, throat, tongue,

			caused by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, juvenile rheumatoid arthritis, painful menstrual periods, short-term pain including pain caused by injuries, surgery and other medical or dental procedures		lips, eyes, or hands. diarrhea, nausea, excessive tiredness, itching, loss of appetite, pain in the upper right part of the stomach, yellowing of the skin or eyes, flu-like symptoms, fever, rash
Naproxen	nonsteroidal anti-inflammatory drug (NSAIDs)	Accord, Aleve, Anaprox, Apranax, Ultra, Flanax, Maxidol, Naprosyn, Narocin, Pronaxen, Soproxen, Xenifar	fever and to mild pain, headaches, muscle aches, arthritis, menstrual periods, the common cold, toothaches, backaches	Tablet, liquid	confusion, headache, ringing in the ears, changes in vision, tiredness, drowsiness, dizziness and rashes
Cannabinoids	anti-emetics and anti-epileptic	Marinol, Cesamet, Acomplia	treating various conditions, including pain, anxiety, epilepsy, and nausea,	Tablet, liquid, spray	dry mouth, increased heart rate, impaired judgment, and potential for anxiety or paranoia
Nefopam	non-opioid or non-narcotic painkiller	Acupan	moderate pain, after an operation or a serious injury, dental pain, joint pain and muscle pain, or pain from cancer	Tablet	feeling sick, nausea, dizzy, lightheaded, nervous, confused or shaky, dry mouth, difficulty peeing, numbness or tingling in your hands and feet

Daniel E Becker and James C Phero says that, non-opioids provide excellent analgesia for mild to moderate pain. They are particularly useful in the initial management of pain that has an inflammatory

component. This includes pain associated with musculoskeletal trauma and dentistry[9].

You can have some of these drugs in different ways including as a liquid, tablet, capsule or caplet, granules

that dissolve in water and also by an injection and suppositories. Some of them are also come as a gel or spray which can apply on skin.

Non-opioids have analgesic, anti-inflammatory, and ant platelet effects. They inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins[10].

Dr. W. Michael Hooten, says that Opioids are often used to combat pain because they can be very effective at relieving pain for a short period of time. Taking opioids poses significant risks, including addiction and overdose. Alternatives to opioids are available, and it's wise for people who need pain relief to seriously consider using non-opioids options when possible. Overdosing on opioids triggers low blood pressure, a slow rate of breathing and the potential for breathing to stop, as well as the possibility of a coma. Opioids overdose has a significant risk of death. Non-opioid approaches to managing chronic pain not only eliminate the risks of addiction and overdose, in many cases, they also offer more effective pain relief that lasts longer and allows people to maintain a higher quality of life than is possible with ongoing opioids use[4].

All over studies says that current pain relief treatments include several analgesics and central nervous system (CNS) agents, nonsteroidal anti-inflammatory drugs, local anesthetics, antidepressants, anticonvulsants, and opioids. These agents act via mechanisms that are not specific to pain sensation, signal transmission, or perception and often have side effects because they affect multiple targets and organs. mainly opioids are efficacious and widely used analgesics for sever pain

but it has carried a risk of addiction due to their effects on the CNS. Due to these liabilities, new classes of non-opioid analgesics are needed so that it can specifically inhibit moderate to acute pain without addictive potential and to provide safety.

From the long time the FDA has supported to the development of non-opioids pain treatment. As part of the FDA Overdose Prevention Framework, the agency has issued draft guidance aimed at encouraging development of non-opioid analgesics for acute pain and awarded cooperative grants to support the development and dissemination of clinical practice guidelines for the management of acute pain conditions[11].

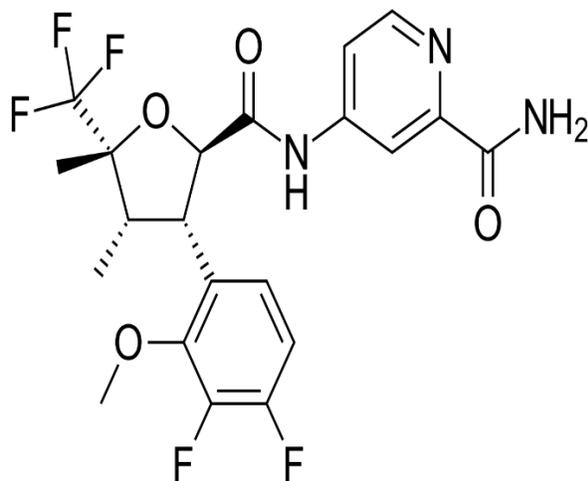
Recently on January 30, 2025 U.S. Food and Drug Administration approved Journavx (suzetrigine) 50 milligram oral tablets, a first-in-class non-opioid analgesic, to treat moderate to severe acute pain in adults. Jacqueline Corrigan-Curay, J.D., M.D. said that “An approval for a new non-opioids analgesic therapeutic class for acute pain offers an opportunity to mitigate certain risks associated with using an opioid for pain and provides patients with another treatment option. This action and the agency’s designations to expedite the drug’s development and review underscore FDA’s commitment to approving safe and effective alternatives to opioids for pain management”[12].

Suzetrigine is the first drug to be approved in this new class of pain management medicines which is used for the treatment of moderate to severe pain. it is sold under the brand name Journavx[12].

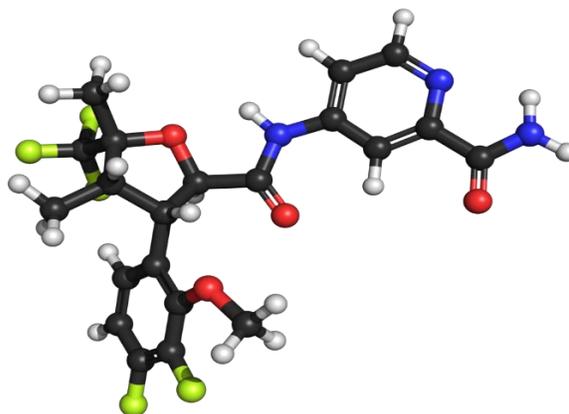
Detailed information about Suzetrigine:

Name of non-opioids drug	Suzetrigine
Belongs to the group of medicines	First-in-class of non-opioid analgesic
Brand name	Journavx
	Suppresses pain at the same level as an opioid, but without the risks of addiction, sedation, or overdose, helpful in treating moderate-to-severe acute (short-term) pain
Administration form	Tablet
Side effects	Itching, rash, muscle spasms, and increased levels of creatine kinase

Structure of Suzetrigine:



Suzetrigine 2D structure



Suzetrigine 3D structure

Figure 1 Structure of Suzetrigine

Voltage-gated sodium channel 1.8 (Nav1.8) is a genetically and pharmacologically validated pain target that is selectively expressed in peripheral pain-sensing neurons and not in the central nervous system. Suzetrigine is a non-opioid analgesic that works on peripheral nervous system. It acts as a selective inhibitor of Nav1.8 dependent pain-signaling pathways in the peripheral nervous system including lack of addictive potential[13].

One study mentioned that VX-548 (suzetrigine) is a potent and selective inhibitor of Nav1.8 currents relative to other Nav channels in human dorsal-root ganglion neurons in vitro. In two phase 2 clinical trials of postoperative pain, as compared with placebo, the highest dose, but not lower doses, of VX-548 reduced pain over a 48-hour period with produce some side effects such as a Headache and constipation[14].

One research reported that, the high selectivity of suzetrigine for Nav1.8 and its mechanism of action translated to a well-tolerated profile in vivo, with no evidence of addictive potential. Their data of study says that suzetrigine had no serious neurological, behavioral, or cardiovascular effects[15].

FDA mentioned that the most common adverse reactions in study participants who received suzetrigine (Journavx) were itching, muscle spasms, increased blood level of creatine phosphokinase, and rash. Additionally, FDA advise patients to avoid food or drinks containing grapefruit when taking Journavx[12].

CONCLUSION

A new class of non-opioids are the best option against highly addiction potent opioids to treat moderate to severe pain. Suzetrigine represents a new class of non-opioid analgesics that are selective Nav1.8 pain signal inhibitors, which acts on peripheral nervous system only without affecting Central nervous system. By working on the peripheral nervous system to safely treat severe pain without addictive potential, selective pain signal inhibitors like suzetrigine could alter the paradigm of pain management.

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