Opioid Treatment Agreement - Version 2

1. Doctor and patient: I agree that Dr. Mike Peterson will be the only doctor who will prescribe me opioid medication. I understand that opioids are drugs such as tramadol/tramacet/Bu-Trans/Suboxone/oxycodone/percocet/oxycocet/hydromorphone/Dilaudid/fentanyl/Duragesic/morphine/Kadian/codeine,Tylenol #1/2/3/4. I will not obtain opioid medication from another doctor. If this happens in an emergency situation or if Dr. Peterson is unavailable, I will call Dr. Peterson's office within 24 hours to inform him that this occurred.

2. Treatment expectations and goals: This medication is being used to decrease the severity of my chronic pain and improve my ability to function physically, emotionally, socially and at work. Opioid medications are not expected to completely stop my pain. Because of the limit to which it will decrease my pain, the best evidence of success from this medication is how well it improves my function. My goals for increasing my function are:

   _____

3. I understand that if the opioid treatment does not improve my pain control or my ability to function then it will be reduced or stopped.

4. Take as prescribed: I will take the medication at the dose and frequency ordered by my doctor, following what is written on the label that comes on the medication packaging. I will not increase the dose of my opioid medication on my own and am aware that doing so may lead to this treatment being stopped. I agree to record regularly my use of these opioid medications and how they are working.

5. Side effects: I understand that the common side effects of opioid medication include feeling sick (nausea), vomiting, constipation, drowsiness, dry mouth, and itchiness of the skin. With extended use I am likely to become tolerant to these side effects, except for constipation. Constipation is a very common side effect and I may be ordered medication to help with this problem. Other side effects which are rare include muscle jerks or shaking, muscle spasm, feeling weak, confusion, hallucinations, feeling disoriented, chills, changes in vision, difficulty passing urine, headaches, skin rashes, difficulty in thinking clearly, decreased sexual function, swelling of hands or feet, sweating, and decreased immune function.

6. Driving: There is a risk I may become drowsy when starting opioid therapy or when the dose is increased. I agree not to drive a motor vehicle or operate dangerous machinery until I am on a stable dose and do not experience any drowsiness.

7. Use with other medications: I also understand that I may become very drowsy if I take opioid medication at the same time with other medications that cause drowsiness (such as sedatives, sleeping pills) or with alcohol or cannabis. I will not take any of these without talking to my doctor first.

8. Medication complications: I understand that opioids may cause long-term complications, which may include decreased hormones such as testosterone which may cause sexual function problems or growth of breasts in men or reduced bone density which could cause fractures, unexpected increase in pain sensitivity, and changes in breathing patterns while sleeping which may cause daytime sleepiness and motor vehicle collision.

9. Addiction: I am aware that there is a small but real risk that I may become addicted to the prescribed opioids. The risk of addiction is increased with a past or present history of substance or alcohol use disorder, and prescribed opioids are often reported as a cause for relapse in recovering patients. A history of substance use disorder does not preclude the use of opioids but warrants increased caution by doctor and patient. I know that my doctor may order a consultation with a specialist in addiction medicine if there is a concern about addiction.

10. Adherence: I understand that my doctor may ask me for a urine drug screen sample or a count of my pills or patches at any time. This is performed routinely for all patients to improve the overall safety of using opioids. Urine drug monitoring will also look for other substance use that increases the risks associated with using opioids. Further refills/prescriptions will be tied to completion of urine tests. Doctors and clinics are encouraged to consider a policy of random urines and pill counts for all patients on long-term opioid treatment that are not designated palliative or cancer patients.

11. Use of other medications: I will not use non-prescription medications containing codeine, such as Tylenol #1, cough syrup containing codeine, or "222" tablets.

12. Stopping medications and withdrawal symptoms: I understand that suddenly stopping or reducing the amount of opioid that I am taking may lead to withdrawal symptoms. Initial symptoms may include runny nose, sweating, tearing of the eyes, restlessness and/or diarrhea. Later symptoms may include anxiety, irritability, weakness, twitching and muscle spasms, severe backache and abdominal pain, leg pains and cramps, hot and cold flashes, sleeplessness, nausea, vomiting, slight fever, increased heart rate and blood pressure. These symptoms can be minimized by slowly reducing the opioid dose and should only be done under the direction of my doctor. If I am prescribed to take a medication daily and I have stopped taking my opioid medication for 3 days or more for any reason, I will not resume taking it without talking to my doctor, to avoid overdose or death due to loss of tolerance of the opioid.

13. Appointment attendance: I will attend all appointments, treatments and consultations as requested by my doctor.

14. Running out of medication: I will plan and book appointments well in advance (at least 2 weeks before running out of medication, and at least 4 weeks around Christmas as the clinic will be closed around that time). I understand that if my prescription runs out early for any reason (such as if I lose the medication, take more than prescribed or miss an appointment) I will not be prescribed extra medications. I will have to wait until my next prescription is due.

15. Switching to a different opioid: I agree that my doctor may switch me to a different opioid medication in the future. If this happens, I will return the remaining quantity of my opioid medication to my pharmacy for safe disposal. I will continue to follow the terms of this agreement for my new opioid medication.

16. Stockpiling medications: I will not stockpile any medications - if I have any medications at home whether prescribed or over the counter, I will return them now to the pharmacy for safe disposal. This includes any Tylenol 1 or 2 or 3 or 4, but also any other medication.

17. Safe storage and security: I agree to be responsible for the secure storage of my medication at all times, and I will purchase a medication safe and keep my medications in it at all times. I will not leave my medications in a car or a bag or with another person. I agree not to give or sell my prescribed opioid medication to any other person; nor will I accept any opioid medication from anyone else. I will keep the medication in a safe and secure place out of reach of children.

18. One pharmacy: I will fill my prescriptions at one pharmacy of my choice, which will be:

_____

19. Consent to share information: I agree that my doctor has the authority to share prescribing information in my patient file with other health care professionals (including community pharmacists) when medically necessary.

20. Breaking this agreement: If I break any part of this agreement, I understand my doctor has the right to stop prescribing opioid medications for me.

This document was discussed between me and my doctor. I was given the opportunity to ask questions. I confirm my understanding and acceptance of the terms of this agreement by signing this document.

Patient name: _____

Patient signature: _____

Date: _____

Prescriber signature (Dr. Mike Peterson): _____

This Agreement was developed by Dr. Mike Peterson based on recommendations for a treatment agreement of multiple provincial Colleges (ON, AB, BC), Canadian Opioid Guideline, and RxFiles. It may be used or modified as long as it and the original sources are properly cited.

Opioid Tapering- Information for Patients

Why should I taper or decrease my opioid medication?

Taking high doses of opioids may not provide good pain relief over a long period of time. The amount of pain relief from opioids can become less at higher doses because of tolerance. Sometimes, opioids can actually cause your pain to get worse. This is called "opioid induced hyperalgesia".

The many side effects of opioids increase with higher doses. Sometimes people using opioids do not connect certain side effects to the medication. That is why many people who try a gradual taper to lower doses, report less pain, and better mood, function and overall quality of life. Sometimes, it is only after such a taper that patients appreciate how opioids were not helping as much as they thought.

What are the side effects of opioid therapy over the long term?

Some of the adverse effects of opioid therapy over the long term include:

- *Tolerance* – The medication becomes less effective over time with patients needing higher doses of opioid to achieve the same level of pain control. By itself, this does not mean patients are addicted, although in some patients it is part of addiction.
- *Physical dependence* – If you abruptly stop or decrease your opioid dose by a large amount, you may experience unpleasant symptoms called withdrawal. This is an expected response to regular opioid therapy that is not the same as addiction. *One of the early symptoms of withdrawal is an increase in pain, which is temporarily improved by taking more opioid*. *Many people on long-term opioids believe that this proves that the opioid is working, rather than being a symptom of withdrawal that will lessen with time.*
- *Constipation* – leading to nausea and poor appetite and less commonly, bowel blockage.
- *Drowsiness causing falls, broken bones, and motor vehicle accidents*
- *Fatigue, low energy, depression* – This can significantly affect your function and ability to work or do day-to-day activities.
- *Sleep apnea or impaired breathing while sleeping* – This can contribute to daytime fatigue and poor thinking ability. It increases your risk for many health conditions and also increases your risk of having a car accident.
- *Low testosterone hormone levels in men* – This can lead to low sex drive, low energy, depressed mood, slower recovery from muscle injuries and decreased bone density (thinning of the bones).
- *Low estrogen and progesterone hormones in women* – leading to decreased bone density and low energy.
- *Pain can get worse in some people, especially at higher doses (opioid-induced hyperalgesia)*

What can I expect when tapering or decreasing my opioid medication?

1. *Pain* – One of the first symptoms of opioid withdrawal is increased pain. This pain may be the same pain that you are being treated for, as well as total body joint and muscle aches. Some people will complain of a recurrence of pain at the site of an old healed injury, such as a broken bone. Taking a dose of opioid reduces all of the above pains – but only temporarily. The pain associated with withdrawal generally passes in most people within 1-2 weeks and is lessened by tapering doses very slowly. Many people report that the pain that the opioid was originally being taken for does not worsen when opioids are reduced. *In order to manage any withdrawal medicated pain, prior to reducing your opioids, you and your doctor should develop a plan to deal with this pain.* This can include non-drug strategies such as distraction, activity, stretching, meditation, and heat or the use of some non-opioid medications. Treating withdrawal pain with opioids delays the taper process.

2. *Withdrawal symptoms* – Opioid withdrawal symptoms can be very unpleasant but are generally not life threatening. However, they sometimes cause people to seek opioids from non-medical sources, which can be very dangerous. Therefore, it is advisable to talk with your doctor regarding a safe approach to gradual tapering. Withdrawal symptoms are similar to a flu-like illness and can begin 6-36 hours after your last dose of opioid. If you stop most opioids quickly or suddenly, withdrawal is most severe 24-72 hours after the last dose and will diminish over 3-7 days. Some people will feel generally tired and unwell for several weeks and may feel "down" or not quite themselves for several months, particularly if they have been taking very high doses of opioids. If you choose to decrease your dose slowly (over several weeks or months), withdrawal symptoms are usually much less severe. Your doctor may prescribe some non-opioid medications (such as clonidine and others) to help reduce the severity of withdrawal symptoms. You may experience some or all of the following during withdrawal:
    - Sweats, chills, goose flesh
    - Headache, muscle aches, joint pain
    - Abdominal cramps, nausea, vomiting, diarrhea
    - Fatigue, anxiety, trouble sleeping

    These withdrawal symptoms usually resolve with time. A severe increase in your pain that results in a decrease in your daily function that does not reduce over 3-4 weeks is less likely to be due to withdrawal and should be re-evaluated by your doctor.

How do I taper?

Preparation

1. Enlist support from family, friends and all your healthcare team.
2. Make a plan to manage any withdrawal related pain.
3. Make a plan to manage any withdrawal symptoms including anxiety and trouble sleeping.
4. Learn and practice non-drug pain management strategies.
5. There may be times when the withdrawal symptoms have been really severe, and you are not ready to take the next step. Formulate a plan with your doctor and pharmacist for when you may need to pause or slow down a taper. It is OK to take a break, but the key point is to try to move forward with the taper after the pause.
6. Remember that the long-term goal is improved pain control and quality of life while reducing potential harms of treatment.

Reductions in opioids can be carried out in many ways

1. Fast – Simply stopping your opioids immediately or reducing rapidly over a few days or weeks will result in more severe withdrawal symptoms, but the worst will be over in a relatively short period of time. This method is best carried out in a medically supervised withdrawal center. Ask your doctor is such a center exists in your community.
2. Slow – Gradual dose reductions of 5 to 10% of the dose every 2-4 weeks with frequent follow-up with your doctor is the preferred method for most people. If you are taking any short-acting opioids it may be preferable to switch your total dose to long-acting opioids taken on a regular schedule. This may make it easier for you to stick to the withdrawal plan. A pharmacist can help lay out a schedule of dose reductions.
3. Methadone or buprenorphine-naloxone – Another strategy that may result in less severe withdrawal is a switch to methadone or buprenorphine-naloxone and then gradually tapering off. This requires a doctor trained to use these medications but can be an alternative to the "Slow" method noted above.

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Sublingual Buprenorphine Is Effective in the Treatment of Chronic Pain Syndrome

Herbert L. Malinoff,[1]* Robert L. Barkin,[2] and Geoffrey Wilson[1]

Many patients with chronic pain have less than optimal therapeutic outcomes after prolonged treatment with opiate analgesics. Worsening of pain perception, functional capacity, and mood often result. Medical detoxification is often undertaken in this situation. Ninety-five consecutive patients (49 men and 46 women; age range, 26–84) with chronic noncancer pain (maldynia) were referred by local pain clinics for detoxification from long-term opiate analgesic (LTOA) therapy. All patients had failed treatment as manifest by increasing pain levels, worsening functional capacity, and, in 8%, the emergence of opiate addiction. Length of prior LTOA therapy ranged from 1.5 to 27 years (mean, 8.8 years). After a minimum of 12 hours of abstinence from all opiate analgesics, patients were given low doses of sublingual (SL) buprenorphine or buprenorphine/naloxone (Reckitt Benckiser). Maintenance dosing was individualized to treat chronic pain. Daily SL dose of buprenorphine ranged from 4 to 16 mg (mean, 8 mg) in divided doses. Mean duration of treatment is 8.8 months (range, 2.4–16.6 months). At clinic appointments, patients were assessed for pain reports, functional capacity, and mood inventory. Eighty-six percent of patients experienced moderate to substantial relief of pain accompanied by both improved mood and functioning. Patient and family satisfaction was robust. Only 6 patients discontinued therapy secondary to side effects and/or exacerbation of pain. In this open-label study, SL buprenorphine and buprenorphine/naloxone were well tolerated and safe and appeared to be effective in the treatment of chronic pain patients refractory to LTOA.

Keywords: chronic pain, buprenorphine, treatment, detoxification

INTRODUCTION

When chronic pain progresses from a merely bothersome nuisance to becoming a profound affliction, the patient is said to have a chronic pain syndrome (CPS).[1] This is characterized by many of the same features of an addictive illness, including compulsive behaviors, obsessive thoughts, decreased functional capacity, cognitive impairment, and social isolation.[2,3] Growing evidence from functional neuroimaging studies supports the concept that CPS, similar to the phenomena of addiction, results from, and may cause neuroanatomical and neurochemical brain alterations, which may be permanent.[4,5]

CPS consists of long-standing, localized or diffuse complaints of discomfort and pain that have persisted beyond the expected healing time (if resulting from injury) and have resisted more conservative and traditional health care intervention strategies.[6] It is important to differentiate patients with CPS from those who experience chronic pain due to an unresolved or permanent localized injury. The Office of Disabilities of the Social Security Administration[7] uses the following criteria to establish the diagnosis of CPS (patients must meet all the criteria): Any intractable pain of more than 6 months' duration; marked alteration in behavior with depression or anxiety; marked restriction in daily activities; excessive use of medication and frequent use of medical services; no clear relationship to organic disorder; and history of multiple, nonproductive tests,

[1]*Pain/Recovery Solutions, Ypsilanti, Michigan;* [2]*Rush University Medical Center/Rush Pain Center, Chicago Illinois, and Northshore Pain Center, Skokie, Illinois.*
**Address for correspondence: Pain/Recovery Solutions, 4870 Clark Road West, Suite 201, Ypsilanti, MI 48197. E-mail: doctorhlm@aol.com*

treatment, and surgeries. There is a high incidence of CPS in persons with a history of childhood abuse, borderline and narcissistic personality disorders, and lower income.[8,9] Studies suggest that women are up to 4 times more affected than men.[10]

The treatment of CPS is difficult, often inadequate, and associated with high economic and psychological cost.[1,2] The use of opioid analgesics for chronic nonmalignant pain is gaining acceptance but remains controversial.[11] While opiate analgesics are now viewed as appropriate treatment of CPS, a recent review called into question their long-term efficacy.[11] The condition of opioid-induced hyperalgesia[12] may exacerbate the perception of pain in susceptible individuals. The presence of an addictive illness such as opiate or nicotine dependence appears to be a risk factor for failure of chronic opiate analgesic therapy in CPS.[13]

Buprenorphine, a derivative of thebaine, is classified as a partial μ-opioid agonist and κ-antagonist.[14,15] It has a high affinity for the μ-opioid receptor, with slow dissociation, resulting in a long duration of action (6 hours).[15] In lower doses, buprenorphine has an analgesic potency 25 to 40 times more potent than similar milligram doses of morphine.[16] Because it is a partial agonist, its effects plateau at higher doses, and it begins to behave more like an antagonist. This antagonist property in higher doses limits the maximal analgesic effect and respiratory depression. The high-affinity blockade and the partial agonist ceiling confers a high safety profile clinically, a low level of physical dependence, and only mild withdrawal symptoms on cessation after prolonged administration. These qualities make it advantageous for the treatment of opioid dependence.[16]

Buprenorphine has low oral bioavailability (AUC)[17,18] and is thus formulated in a sublingual preparation (Subutex) and in a sublingual formulation with naloxone (Suboxone). Naloxone has very poor sublingual bioavailability and is formulated with buprenorphine to prevent misuse via intravenous injection.

The FDA approved Suboxone/Subutex in 2002 as a treatment of opioid dependence. Sublingual buprenorphine has been successfully used for opioid detoxification and maintenance.[19] It has a better pharmacotherapeutic safety profile than methadone.[20] A regimen of 8 to 12 mg/d sublingually has been used for 5 to 7 days for detoxification from opioids.[20] The slow release of buprenorphine from the μ_1-receptor allows a relatively symptom-free withdrawal.

In the course of using buprenorphine in the detoxification of chronic pain patients from high-dose opiates, we observed significant changes in patient reports of pain and pain perception. We observed many patients on high doses of pure μ-opiod agonists begin to experience significant decrease in pain, improved functional capacity, and improvement in their overall sense of well-being. This commences within days of detoxification from pure μ-agonist therapy. Until recently, there have been few reports in the literature citing or describing buprenorphine as a chronic pain management medicine.[21]

Because of its safety, unique agonist/antagonist activity at the μ_1- and κ-opiod receptors, we began to employ this combination medication as a treatment of CPS patients. Patients referred for detoxification from long-term opiate analgesic (LTOA) therapy were treated with sublingual buprenorphine or buprenorphine/naloxone. Sublingual buprenorphine was with few exceptions associated with significantly lower pain scores, improved functional capacity, and improvement in mood/affect. Patient satisfaction was notable. Patients with comorbid addictive disorders showed stabilization and the same level of improvement as nonchemically dependent patients when both pain and addiction were addressed in a systematic fashion.

Side effects were tolerable and resulted in treatment termination in 6 of 95 patients (6.25%).

Buprenorphine is safe and effective and should be further studied as a treatment of chronic pain disorders.

METHODS

Patient selection

This was a single-center, open-label study in chronic pain patients referred from 3 local pain clinics. All patients had experienced worsening pain despite escalating doses of short- and long-acting opiate analgesics. Most had undergone prior surgeries. Patients were assessed with history/physical examination, blood and urine testing for renal function, liver function, and urine toxicology prior to initiating treatment. Between December 2003 and October 2004, 95 consecutive patients referred to our clinic for detoxification from high doses of opioids were treated with sublingual buprenorphine (see Table 1 for patient demographics).

All patents underwent multidimensional evaluation prior to treatment consisting of history/physical examination with particular attention to co-occurring psychiatric and addictive disorders. Addictive disorders were diagnosed by DSM-IV-TR criteria.[22] All patients gave informed consent for detoxification/substitution with buprenorphine.

Nicotine cessation therapy was offered to all nicotine-dependent patients. Four patients did succeed in becoming abstinent from nicotine during the course of their treatment. The identification of other chemical

Table 1. Patient demographics.

	%	Mean	Range
Male	52		
Female	48		
Age, y		51.3	26–84
Employed	71		
Retired/unemployed	24		
Nicotine dependent	58		
Opiate dependent	8.42		
LTOA use range, y		8.8	1.5–27

dependencies either clinically or with urine toxicology prompted referral to a formal outpatient treatment program, attendance at 12-step meetings, and office-based counseling.

Initially, all patients were detoxified from prescribed opiates using sublingual buprenorphine according to previously published protocols.[23] All detoxification was office based and under the direct observation of the principal investigator (HLM).

Drug administration

All patients were required to discontinue their opiate analgesics at least 12 hours prior to instituting buprenorphine.[23] Patients were given an initial test dose of 1 mg Suboxone (1 mg buprenorphine/0.25 mg naloxone) sublingually and observed for signs of opiate withdrawal. Patients were then given 2 doses of 2 mg Suboxone at 45-minute intervals. Vital signs and symptom scoring were taken at 30-minute intervals. Patients were discharged from the clinic 2 to 2.5 hours after initiating buprenorphine treatment.

Following initial detoxification, patients were treated with varying doses of sublingual buprenorphine for pain. Daily doses ranged from 2 to 20 mg/d in divided doses (Table 2).

Patient assessment

Patients were seen in the clinic 3 to 5 days later and contacted by telephone. Patients were seen at least monthly. Dosing of buprenorphine was changed based on patient reports of opiate abstinence symptoms and pain complaints. A visual analogue scale (VAS) was employed for pain assessment at each clinic visit. This scale has 5 levels of visual discomfort ranging from no pain to severe misery.

Table 2. Buprenorphine dosing.

	Range	Mean
Daily dose (mg)	2–20	8
Duration of treatment (mo)	2.4–16.6	8.8

Data abstraction

All data were abstracted from patients' medical records. To estimate the duration of CPS, we used historical statements from the patient recorded in the initial office evaluation by HLM. The numbers and types of other interventions including current prescriptions were recorded. The most recent opioid prescription was used to define the type and level of LTOA therapy.

Statistical analysis

The data variables are summarized as means ± SD from the mean (SD).

RESULTS

No patient was hospitalized. Side effects including ataxia/lightheadedness, nausea, cephalgia, and diaphoresis were uncommon and resulted in 6 patients (6.25%) discontinuing treatment in the detoxification stage (Table 3). Pain reports as determined by VAS were improved in 86%. Patient and family satisfaction with therapy was robust. Many reported improved mood, diminished sleep disturbance, and improved sense of well-being. Pain relief was secondary to these other psychological improvements.

Tolerance to buprenorphine was not observed. Most patients remain on a stable maintenance dose. Aberrant behavior regarding buprenorphine was limited to 12 patients' self-escalating doses to treat worsening pain. No cases of return to Opiate Analgesics (OA) were identified in the average 8 months of follow-up.

DISCUSSION

We used sublingual buprenorphine (Subutex/Suboxone) in patients with chronic pain. All patients had failed conventional opiate therapy with increasing tolerance to high doses of short and long duration of action opiates, worsening pain perceptions and pain scores, lower functional capacity, and in some instances

Table 3. Responses to treatment with buprenorphine.

	Mean VAS
Before treatment	3.9 ± 0.4
After treatment	2.2 ± 0.5
Patients who reported substantial improvement	86%

Table 4. Adverse effects.

	No. (%)
Ataxia/lightheadedness	12 (12.6)
Nausea	9 (9.5)
Cephalgia	15 (15.8)
Discontinued therapy	6 (6.3)

(8%) the emergence of manifest addiction behaviors. Patients were seen in referral from local pain clinics and referred for opiate detoxification. Buprenorphine was administered to patients after they had discontinued all opioid medications at least 12 hours prior to their clinic visit. All patient were experiencing at least some symptoms of opioid abstinence syndrome prior to initiating sublingual buprenorphine. An initial test dose of 1 or 2 mg was given with physician supervisions. In all cases, this resulted in prompt relief of withdrawal symptoms. An additional dose of 1 or 2 mg was then given, with significant pain relief. Patients were then given an outpatient-specific dosing schedule based on age, prior specific opiate doses, and comorbid conditions. Other medications including neuromodulatory drugs (eg, antidepressants, anticonvulsants) were continued.

Within days to weeks, most patients reported improved pain levels, less distress, improved mood, and increased functional status and capacity. In many cases, patients report significant relief of the depression, anxiety and ''misery'' associated with their chronic pain, prompting us to undertake this study. Therapy with buprenorphine was discontinued in 6 patients due to intolerable side effects including emesis and cephalgia. In most patients, side effects were tolerable and outweighed by the therapeutic effects on pain symptoms. No patient was hospitalized because of adverse events. There were no mortalities in the 95 patients treated.

Table 5. Pharmacokinetics.

Absorption: Readily absorbed 55% (range, 15%–95%) after sublingual administration
Distribution: In rodent models, liver, brain, placenta, GI tract, liver. Parent and metabolite distributed in bile. $V_d \approx 97$ L
Plasma protein binding: 96% protein α and ß globulins, not substantially to albumin
Elimination: Triphasic plasma concentration decline (distribution, redistribution, elimination phases)
$T_{1/2\alpha} = 37$ hours
Metabolism
Hepatic isoenzyme CYP450 3A4 substrate (n-dealkylation to norbuprenorphine-*N*-dealkylbuprenorphine, then phase II metabolism with conjugation to glucuronic acid)
First-pass gut metabolism (mucosal) additionally
Enterohepatic recirculation; parent and metabolites excreted in feces via biliary elimination

Note: Metabolite norbuprenorphine has weak analgesic activity.

Table 6. Buprenorphine/naloxone side effects/adverse reactions.

Common: cephalgia, increased withdrawal symptoms, asthenia, insomnia, miosis, confusion, sedation, nausea, emesis, rigors, constipation, vasodilation
Less common but serious: Respiratory depression, bronchospasm, anaphylaxis, angioedema, hepatotoxicity, orthostatic hypotension
Pregnancy: category C

Our results demonstrate the safety, efficacy, and simplicity of using sublingual buprenorphine to treat chronic nonmalignant pain refractory to LTOA therapy. In all cases, patients had previously failed LTOA therapy as demonstrated by increasing tolerance, worsening pain and mood, decreasing functional capacity, and, in some cases, the emergence of addictive illness. We observed that while pain control independently was often only fair, patients reported better tolerance of their pain, improved mood, and functional capacity. We hypothesize that Suboxone/Subutex effectively blocks the action of spinal dynorphin on κ-opiate receptors. This may result in lessening of perceived discomfort.[25]

Buprenorphine is a partial agonist at the μ-opiate receptor, and an antagonist at the κ receptor. The unique pharmacology of buprenorphine at the μ-opioid receptor (ie, high affinity, low intrinsic activity, and slow dissociation) results in buprenorphine having a good safety profile, low physical dependence, and flexibility in dose scheduling. Buprenorphine as a synthetic opiate partial agonist analgesic has activity that occurs as μ-partial agonist in the central nervous system and peripheral tissues, with κ- and ∂-receptor activity less defined; however, evidence of central κ-receptor antagonist exists with peripheral κ-receptor antagonism.[26,27] Isomeric configuration may provide μ-opioid receptor binding in one configuration and μ-competitive antagonist activity in another configuration. Binding to μ-receptors is slow as is the complementary receptor dissociation accounting for its long duration of action and less physical dependency. Opiate agonist effects appear with up to 1 mg sublingually and doses of more than 1 mg have predominant antagonist activity; therefore, the agonist/antagonist effects are a linear

function of dose. Sublingual buprenorphine produces typical dose-related opiate agonist effects, which are limited by this ceiling effect and maximal at 8 to 16 mg.[23] The duration of analgesia is affected by age and duration and is prolonged in the elderly. Sublingual administration of buprenorphine/naloxone in fixed-dose combination was without naloxone-mediated pharmacologic effects, unlike those predictable effects if given parenterally.

The sublingual preparation approved in the United States, marketed under the brand name Suboxone (Reckitt Benckiser, Berkshire, UK) is available in 2- and 8-mg tablets combined with naloxone at 0.5 and 2 mg, respectively. Naloxone has no effect sublingually because of poor absorption but precipitates withdrawal symptoms if administered parenterally, thereby limiting diversion by opioid-dependent persons.[25,28] The sublingual preparation of buprenorphine alone (Subutex) is also available and is intended for use in the physician-supervised introduction of patients new to the drug to assess the dose effect and potential for withdrawal symptoms. Insurance coverage for Suboxone but not Subutex often dictated which preparation was prescribed for a given patient. Currently, sublingual buprenorphine is not approved by the FDA for the treatment of pain, although the parenteral formulation (Buprenex) has been approved since the 1980s. All patients were made aware of this off-label use of sublingual buprenorphine and gave informed consent.

This was a limited open-label study of nonrandomized patients receiving treatment via a single provider (HLM). As such, it can only suggest an effect of buprenorphine on chronic pain patients. All patients reported here had previously been treated with LTOA therapy with progression in pain symptoms, loss of function, and worsening mood. LTOA therapy is only one factor influencing pain perception in CPS. Emotional state, previous pain experiences, and cultural, environmental, and genetic factors are all known to be consequential.[29–31] Our study did not control for these factors. Responses to buprenorphine were not limited by gender, age, comorbid conditions including addiction, or the use of nonopiate analgesics.

Buprenorphine is subject to control under the Federal Controlled Substance Act of 1970 as a Schedule III drug. Under the Drug Addiction Treatment Act (DATA) of 2000, use of sublingual buprenorphine and buprenorphine/naloxone for treatment of opiate dependence is restricted to physicians who achieve certain qualifying criteria or requirements (Reckitt Benckiser Pharmaceuticals, Inc., information for pharmacists: Suboxone® [buprenorphine hydrochloride sublingual tablets]) and are required to have notified the Secretary of the Department of Health and Human Services of their intention to prescribe these medications.[32]

The use of buprenorphine and buprenorphine/naloxone to treat chronic pain patients refractory to LTOA therapy in this study was safe, effective, and well tolerated by these patients.

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Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients

Danielle Daitch, MD,* Jonathan Daitch, MD,†‡ Daniel Novinson, MPH,§ Michael Frey, MD,†¶ Carol Mitnick, ARNP,†‡ and Joseph Pergolizzi Jr, MD††‡‡**

*Jefferson Medical College, Philadelphia, Pennsylvania; †Advanced Pain Management and Spine Specialists, Fort Myers, Florida; ‡Park Center for Procedures ASC, Fort Myers, Florida; §University of California, San Francisco, California; ¶Virginia Commonwealth University, Richmond, Virginia; **Department of Anesthesiology, Georgetown University Medical School, Washington, DC; ††Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; ‡‡Department of Pharmacology, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

Reprint requests to: Jonathan Daitch, MD, Advanced Pain Management and Spine Specialists, 8255 College Parkway, Suite 200, Fort Myers, FL 33919, USA. Tel: 239-437-8000; Fax: (239) 437-8002; E-mail: jdaitch@ampss.net.

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Abstract

Objective. This study aims to determine the effectiveness of converting patients from high doses of full-opioid agonists to sublingual (SL) buprenorphine.

Design. An observational report of outcomes assessment.

Setting. An interventional pain management practice setting in the United States.

Subjects. Thirty-five chronic pain patients (age 24–66) were previously treated with high-dose opioid-agonist drugs and converted to SL buprenorphine. Patients' daily morphine equivalents ranged from 200 mg to 1,370 mg preconversion, with a mean daily dose of 550 mg.

Methods. A retrospective chart analysis examined numerical pain levels and quality of life scores before and 2 months after conversion to SL buprenorphine.

Results. After continuation of SL buprenorphine therapy for 2 months, the mean pain score decreased from 7.2 to 3.5 ($P < 0.001$), with 34 of the 35 patients examined reporting a decrease in pain. This pain score decrease was robust with regard to initial pain score and preconversion morphine equivalent dosage. Quality of life scores improved from 6.1 to 7.1 ($P = 0.005$).

Conclusion. Average pain scores decreased from 7.2 to 3.5, and quality of life scores increased from 6.1 to 7.1 for 35 patients converted from high-dose full-opioid agonists to SL buprenorphine therapy for more than 60 days. Clinicians should consider buprenorphine SL conversion for all patients on high-dose opioids, particularly patients with severe pain (7–10) unrelieved by their current opioid regimen or patients for whom the clinician does not feel comfortable prescribing high-dose opioids.

Key Words. Buprenorphine; Sublingual Buprenorphine; Opioid Conversion; Opioid-Induced Hyperalgesia; Analgesia; Opioid Tolerance

Introduction

Analgesics that act at several sites along the pain pathway to diminish pain, opioids have been used to treat pain for thousands of years [1–3]. Today, some of the most

commonly prescribed medications for severe pain include opioids, despite their serious side effects and potential for abuse, addiction, and overdose [1,4,5].

Furthermore, prolonged use of opioids may result in physical consequences including opioid tolerance, opioid dependence, and opioid-induced hyperalgesia (OIH) [2–4]. Tolerance occurs when, after repeated use of opioid medication, patients need increased doses to maintain equipotent analgesia [6–8]. Tolerance reduces opioids' efficacy and may be the reason for dose escalation [3,6–8]. Prolonged opioid use may also have hormonal effects resulting in decreased fertility and libido, as well as immunosuppression [2]. Prolonged use of high doses of opioids is more likely to cause toxicity than short-term use of low doses [2].

Chronic pain is defined as pain associated that persists beyond the usual healing course of an injury and adversely affecting the function or well-being of the individual [1,3,9]. The efficacy of opioid therapy, especially high-dose opioid therapy, in treating chronic pain is in debate [1,3,10].

Doses of over 200 mg of morphine equivalents per day are considered high and may be excessive [2,11,12]. Nevertheless, clinicians frequently increase dosage when opioid patients complain of increased pain. Although progressively higher opioid doses may initially improve symptoms in some patients, repeated dose escalations may have limited utility because of adverse effects and other factors [2,12,13]. Clinicians should carefully reassess all patients on chronic opioid therapy who have repeated dose escalations, particularly to greater than 200 mg daily of morphine equivalents. Opioid treatment may require discontinuation or weaning if assessments indicate the presence of intolerable adverse effects, aberrant drug-related behaviors, decreased quality of life, decreased function and physical capacity, or decreased analgesia [2,13,14].

In addition, clinicians should be aware that opioid therapy, especially in high doses, may heighten pain sensitivity and aggravate preexisting pain, indicating OIH [2–4,13–20]. Research has shown certain opioids at high doses can produce allodynia and hyperalgesia, particularly during rapid dose escalation [2,4,13]. Several neuroplastic adaptations may underlie OIH, including: activation of the excitatory neurotransporter N-methyl-D-aspartate through the central glutaminergic system; increased levels of spinal dynorphins that cause the release of pronociceptive neuropeptides; and altered activation of descending pathways, such as the rostral ventromedial medulla, facilitating spinal nociceptive processing [4,6,14,15,18,21,22]. Clinically, OIH will increase the pain of preexisting nociceptive conditions, as well as produce diffuse pain that extends to areas beyond the preexisting nociception. Increasing opioid dose worsens OIH, whereas reducing opioid dose or utilizing alternate medications, such as sublingual (SL) buprenorphine, relieves OIH [8,15].

Buprenorphine, a semi-synthetic phenanthrene derived from thebaine, is a partial μ-agonist and κ-antagonist [3,8,23–26]. Buprenorphine is highly lipophilic and 96% protein-bound in systemic circulation [26,27]. It has a high affinity for the μ-opioid receptor with a slow dissociation, resulting in a long duration of action, and scientific literature supports the high therapeutic index of buprenorphine [25,27].

Buprenorphine's effects plateau at higher doses, limiting the maximal analgesic effect and respiratory depression [24]. The partial agonist ceiling and its high affinity at the μ-opioid receptor confer a high safety profile clinically and a low level of physical dependence [25].

In the 1970s, a parenteral buprenorphine dosage formulation indicated for treatment of pain was brought to the American market [15,25]. Since that time, a sublingual preparation, both alone and in combination with naloxone, has become available as a Schedule III, FDA-approved treatment of opioid dependency [15,25,27]. The Drug Enforcement Administration has acknowledged the legality of off-label of buprenorphine SL to treat pain in chronic pain patients [28]. In July 2010, the FDA approved transdermal buprenorphine for the treatment of moderate to severe chronic pain [29]. Transdermal buprenorphine has been available in Europe for several years, and studies have shown that the transdermal medication is well tolerated and effective in the treatment of chronic cancer and noncancer pain [28–30].

Studies have shown buprenorphine SL is useful for treatment of OIH, though other research has failed to demonstrate buprenorphine's efficacy in treating OIH, such that this proposed finding remains controversial [8,31–33]. A previous retrospective study by the authors demonstrated that conversion from full agonist opiates to buprenorphine SL led to a significant overall decrease in visual analog scale (VAS) of 2.3 points [34]. Significant decreases of pain occurred for all dosage ranges of patients on full agonist opioid medication (0–660 mg). However, the initial study showed lower buprenorphine SL efficacy at levels of >400 mg morphine equivalents, possibly due to a small sample size. Additionally, recent commentaries have questioned the prescription of high-dose opioids, with sublingual buprenorphine viewed as a "safety net" for patients needing to come off of these opioid regimens [35,36].

The purpose of this study was to evaluate the effectiveness of conversion to buprenorphine SL for patients with significant levels of persistent pain on high doses of full agonist opioid medications (200–1,370 mg morphine equivalents). One previous study to examine use of buprenorphine SL for pain management in chronic pain patients on high-dose opioid medication showed a beneficial effect of conversion off high-dose opioid medication onto ibuprofen alone, and even greater benefit after further conversion to buprenorphine SL [8]. This current study differs because of its greater sample size and outpatient setting. Another study found that 67% of patients

hospitalized for buprenorphine conversion reported moderate to dramatic improvements in pain and functional status [37]. This current study differs because of its outpatient setting. A third study showed 88% of patients experienced moderate to substantial pain relief and improved mood and functioning upon conversion to 2–20 mg (mean 8 mg) of buprenorphine SL [38]. This current study differs as patients were converted to significantly higher doses of buprenorphine (28.11 + 5.94 mg), owing to their high opioid doses preconversion.

Methods

Patient Selection

The study was conducted in a private practice setting at an interventional pain management practice in the United States. An electronic medical record system identified chronic pain patients on high-dose full agonist opioids converted to sublingual buprenorphine between July 2010 and April 2011. In order to be included for analysis, patients must have experienced continuous or worsening pain despite the use of opioid analgesics, must have been using at least 200 mg of morphine equivalents, and must have remained on buprenorphine SL after initial conversion for at least 60 days. Researchers obtained approval from an institutional review board that included authorization for a Health Insurance Portability and Accountability Act waiver, as the study was a retrospective chart review. Nonetheless, all patients were provided informed consent.

Patients were assessed initially from their history and physical examination. They were on a variety of full agonist opioids, including predominantly oxycodone (N = 12), hydromorphone (N = 4), oxymorphone (N = 2), fentanyl (N = 6), methadone (N = 5), and morphine (N = 6). Many patients were on combinations of different immediate release and sustained release combinations of opioid medication. Prior to conversion, a nurse practitioner provided patients information about the proper use and initiation of buprenorphine SL, the drug's risks, and its benefits in a 30-minute teaching session. Patients then completed conversions at their homes with phone access to the clinic if needed. The nurse practitioner, with backup from physicians trained in buprenorphine administration, supervised these conversions.

Table 1 shows preinduction morphine equivalent doses [34]. Of the 35 patients analyzed, 21 were male (60%) and 14 were female (40%). Patients averaged 49 years old, with a range of 24–66 years of age. The mean daily preinduction morphine equivalent dose of opioid was 550 mg. At the end of the study, average buprenorphine SL treatment duration was 6 months.

Data

Patients filled out a questionnaire to ascertain their current quality of life, via a validated Quality of Life (QOLS) scale, an 11-point numeral rating scale assessing function for people with pain, with 0 representing nonfunctioning and 10 representing normal quality of life [39]. Patients reported their numerical pain level via an 11-point numerical rating scale (NRS) [40]. Patient levels of withdrawal were evaluated with the Clinical Opiate Withdrawal Scale (COWS) score [41]. All data were abstracted from patient electronic medical records in a standardized manner. Patients were seen at 1-week intervals after home conversion until stable, and then on a monthly basis. For patients with multiple visits pre- and postconversion, this study considered the visit immediately prior to conversion for preconversion scores, and the visit closest to 60 days after conversion for postconversion scores.

Table 1 Equianalgesic dosage morphine equivalent conversion table

Drug	Dose (mg)
Morphine	30
Hydrocodone	30
Oxycodone	20
Oxymorphone	10
Fentanyl patch	12
Methadone	7.5
Hydromorphone	6

Patients' age, sex, diagnosis, medication history, preinduction medication, preinduction COWS, and morphine equivalent dosage were recorded. The most recent opioid prescription was used to define the type and amount of opioid medication. Sustained-release opioid medications were converted to morphine equivalents and added together with any immediate-release opioid medications to obtain a preinduction amount of morphine equivalents for each patient.

Table 1 shows the equianalgesic conversion doses of opioids utilized in the study. As there is no single established set of morphine conversion ratios, two of the authors generated a set of conversion values based upon published values and their clinical experience for a previous study [34]. For the sake of consistency, the same conversion values are used in this article.

The primary outcome evaluated was reduction in self-reported pain after conversion to buprenorphine SL, using a standard 11-point scale (0–10). The secondary outcome analyzed was change in patient QOL scale for patients with chronic pain. A two-tailed, paired Student's *t*-test assessed significance.

Drug Administration

All patients were detoxified from prescribed opioids by using buprenorphine SL in accordance with previously described protocols [34]. Patients received buprenorphine SL after they had discontinued all opioid medications

for at least 24 hours (48–72 hours for methadone and transdermal fentanyl) and had achieved a COWS scale of at least 13. At conversion, patients were given 8 mg of buprenorphine sublingually and told to take an additional 8 mg dose 1 hour later if severe pain or significant withdrawal symptoms continued. Patients were instructed not to exceed 32 mg of buprenorphine SL daily. In addition, oral clonidine was offered during the first week of buprenorphine SL administration as all patients experienced withdrawal symptoms during that time. After 1 week, buprenorphine SL dose was adjusted based on reports of opioid abstinence symptoms, pain complaints, or side effects. Patients were then evaluated at least monthly.

Results

Overall, patients reported a 51% decrease in pain score before and after conversion to buprenorphine SL, from 7.2 to 3.5 points ($P < 0.001$), as shown in Figure 1, with 34 of 35 patients reporting decreased pain. Patients with initial pain ratings of 0–7 (N = 14) had a 54% average pain decrease (2.8 points), whereas patients with initial ratings of 8–10 (N = 21) had a 51% average pain decrease (4.4 points), an insignificant difference.

Patients' QOL scores, also assessed at baseline and after buprenorphine SL conversion, improved from 6.1 to 7.1 ($P = 0.005$). Furthermore, patients converting off higher opioid doses enjoyed a greater average improvement in quality of life score, as patients at or below the median dose (N = 18, range: 200–380 mg) saw average QOL improvement from 6.3 to 6.8 ($P = 0.020$), whereas patients above the median dose (N = 17, range: 405–1,370 mg) saw average QOL improvement from 6.0 to 7.4 ($P = 0.036$).

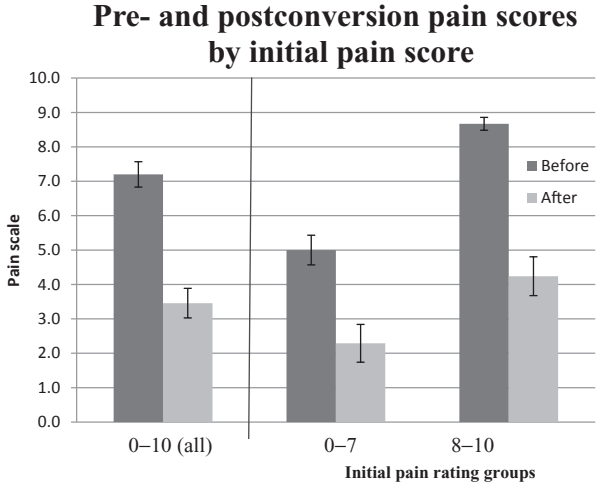

Figure 1 Pre- and postconversion pain scores with standard error for all patients (left) and patients grouped by initial pain ratings (right).

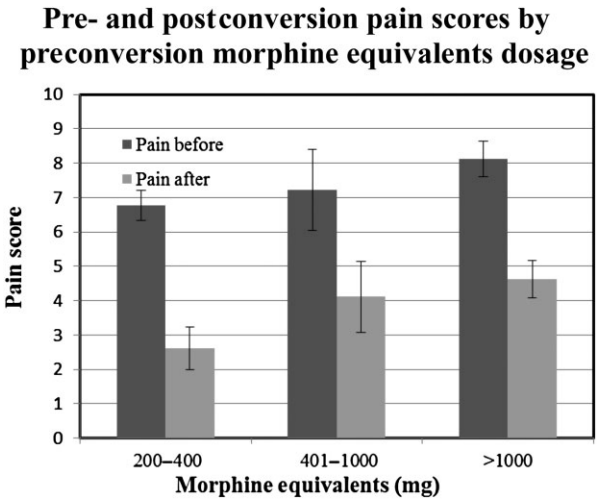

Figure 2 Pre- and postconversion pain scores with standard error for patients grouped by preconversion morphine equivalent dosages.

To assess whether the preinduction morphine equivalents dosage affected the reduction of patients' pain scores, patients were sorted into three groups. All groups showed a statistically significant reduction in pain of at least 40%, as Figure 2 shows. The 200–400 mg morphine equivalents group reported a 61% pain score decrease of 4.2 points from 6.8 to 2.6 ($P < 0.001$, N = 18). The 400–1,000 mg morphine equivalents group reported a 61% pain score decrease of 3.1 points from 7.2 to 4.1 ($P = 0.004$, N = 9). The >1,000 mg morphine equivalents group reported a 61% decrease of 3.5 points from 8.1 to 4.6 ($P < 0.001$, N = 8). Note that as morphine equivalents dosage increases by group, patients' pre- and postconversion pain scores increase as well.

The average dose of buprenorphine SL was 28.11 ± 5.94 mg. Fewer than 30% of patients did not complete the 60-day conversion to qualify for study inclusion.

Discussion

In this retrospective study, after clinicians converted patients taking high-dose opioids greater than 200 mg morphine equivalents onto buprenorphine SL, 34 of 35 patients studied experienced pain reduction. This result suggests that buprenorphine SL tablets can be an effective analgesic for patients who have not attained successful analgesia with traditional high-dose, full agonist opioid medications and that patients without severe pain (NRS 1–7) on high-dose opioid medication may improve analgesia with conversion to buprenorphine.

All the patients in this study underwent withdrawal upon cessation of the opioid medication, indicating physical dependence. This withdrawal, expected in such patients,

included rebound pain and was adequately treated with buprenorphine SL and, if requested, oral clonidine.

Patients with the highest level of morphine equivalents had the highest initial pain score, suggesting tolerance and the presence of OIH [8]. Nonetheless, all groups of patients, regardless of initial morphine equivalent dosages, experienced significant reductions in pain. Furthermore, that patients with initially mild to moderate pain scores of 0–7 showed significant improved analgesia with conversion to buprenorphine suggests that decrease in OIH may not be not the only mechanism by which buprenorphine decreases pain.

This study builds on the authors' previous study, which showed an average decrease in pain of 2.3 points with conversion of 104 patients from 100 to 660 mg of morphine equivalents, but only a mild decrease in pain of 1.1 numerical points in patients taking over 400 mg of morphine equivalents, perhaps owing to a small sample of high-dose patients [34]. In this study, with 35 patients over 200 mg of morphine equivalents, results are more concordant with the hypothesis that OIH was present in patients on high-dose opioids with poor analgesia.

Although different morphine conversion ratios could reasonably have been applied, they would not affect the article's central findings: that after conversion to buprenorphine, patients reported a decrease in pain and quality of life scores. Furthermore, as 34 of the 35 study participants reported decreased pain, the decrease in pain scores would remain robust across preconversion morphine equivalent doses regardless of the exact conversion values used.

Indeed, and unlike in the authors' previous study, this study detected an improvement in QOL scores. An improvement in patient quality of life corresponds with the authors' clinical impressions, and patient reports of improved cognition, function, and pain score postconversion.

This study also shows similar results to the findings of Baron et al., who studied detoxification of 23 patients off high-dose opioid medication [8]. In that study, patients were converted from high-dose opioid medications onto either ibuprofen alone, or ibuprofen and buprenorphine. Both groups showed a highly significant decrease in pain, but the ibuprofen and buprenorphine group showed the greatest decrease in pain. Baron et al. reasoned that the underlying cause for improved pain was the elimination of OIH with detoxification and conversion to buprenorphine. They also believed that the same mechanisms that create OIH may reset after detoxification, thereby reducing pain sensitivity. This study shows similar results in an outpatient setting, which is more relevant to the treatment of chronic pain. Furthermore, this study enjoyed a larger sample than that of Baron et al.

Some patients on high-dose opioid medications attain excellent analgesia. Thus, the authors are not suggesting that all patients on high-dose opioid medication convert to buprenorphine. However, the authors believe that patients who exhibit tolerance and poor analgesia with increasing doses of opioids may be exhibiting OIH; this subset of patients does appear to respond well to detoxification off their high-dose opioid medication via conversion to buprenorphine. Furthermore, this study shows that patients taking high-dose opioids with pain scores in all ranges appear to improve with conversion to buprenorphine. There may be patients on very high doses of opioid medication who are relatively comfortable with NRS pain scores of 7 or less; if the clinician is not comfortable continuing to write for such high dosages, he or she may consider conversion to buprenorphine as well.

Limitations

A potential criticism of this study is that patients are simply switching from one high-dose opioid medication to another. Animal studies suggest that buprenorphine is 25–50 times as potent as morphine [42]. As the average postconversion dose of buprenorphine in this study was 28.11 mg, a direct conversion would imply a morphine dose as high as 700 mg. However, as a partial agonist, buprenorphine has a ceiling effect both on analgesia and side effects, rendering a direct dosage comparison between morphine and buprenorphine unrealistic.

Ultimately, however, due to the QOL improvement and the medication's inherent safety, the authors believe buprenorphine SL is a safer and better choice for analgesia. Furthermore, patients may be able to wean off buprenorphine SL more easily, given the drug's extremely long half-life. Indeed, it has been the authors' clinical impression that many patients can and do begin to decrease their dosage after 4–6 months of buprenorphine therapy.

Another limitation of this study was that it was an observational chart review with no control group. Chart reviews are advantageous in that easily accessible data allows for large sample sizes and are useful in identifying trends that can be examined in subsequent randomized controlled trials. Unfortunately, this study is limited because patient charts may be incomplete, missing, or unrecoverable; there may be difficulty interpreting information in patient charts; verification of past information may be difficult; and causality cannot be established as in a randomized controlled trial. In particular, the authors cannot rule out the possibility of selection bias, as patients who poorly tolerated conversion to buprenorphine may have switched back to opioids within 60 days of conversion and would not be included in this study's results. This issue is somewhat mitigated, as the outpatient clinic refused to switch patients back to opioids; however, some patients may have left the practice to seek high-dose opioids with different providers, potentially skewing results. Similarly, patients may have experienced similar improvement in pain and quality of life from weaning alone, given the high dosage of opioids they were taking. Another limitation is

that this study categorized only patients' total daily doses, leaving unexamined how frequently patients took buprenorphine SL each day and whether that affected analgesia.

Finally, clinical limitations and considerations also exist. Only clinicians with training and experience in working with buprenorphine should convert patients to buprenorphine SL. Untrained clinicians may take courses on utilizing buprenorphine SL but should note that though most courses are directed toward treatment of opioid addiction, a separate entity than buprenorphine conversion for high-dose opioid use. Although legal for clinicians to treat chronic pain patients with buprenorphine without certification, the authors recommend completing at least a standard 9-hour online course in buprenorphine administration. In addition, certain payors are reluctant to cover buprenorphine therapy for such cases, as it is an off-label use from the traditional labeled use of opiate dependence. In general, with preauthorization and discussion with insurance company medical directors, SL buprenorphine can be approved. If not authorized, then alternative formulations exist with generic SL buprenorphine pills, or even generic formulations of buprenorphine in troche gel form.

Conclusion

Patients converting from high-dose full-opioid agonists (200–1,370 mg of morphine equivalents) who continued buprenorphine SL therapy for more than 60 days reported a significant decrease in pain of >50% from 7.2 to 3.5 (3.7 points) and improvement in quality of life from 6.1 to 7.2 (1.1 points). The unique pharmacology of buprenorphine SL as a partial μ-agonist likely results in its therapeutic effects. The use of buprenorphine SL in this study was reasonably safe, effective, and well-tolerated. Buprenorphine SL is an excellent analgesic medication to treat many patients on high doses of opioid medication, and a useful tool for outpatient conversion of high-dose opioid patients within a traditional pain practice.

Based on the results of this study, clinicians should consider buprenorphine SL conversion for patients who initially present on high doses of opioid medication with limited pain control. Similarly, clinicians' own patients, who over time develop tolerance and need escalating doses of opioid medications with limited pain relief, would also likely respond well to conversion to SL buprenorphine. Buprenorphine SL has a better safety profile than traditional high dose opioids and should provide some QOL improvement. A clinician should also consider buprenorphine SL conversion if the clinician does not feel comfortable prescribing high-dose opioids to a given patient. Finally, recent clinical observation of utilizing transdermal buprenorphine demonstrates that transdermal buprenorphine may allow for conversion to SL buprenorphine without withdrawal symptoms, when applied in opioid-dependent pain patients as the initial exposure to buprenorphine [43]. This finding suggests a further simplification in the conversion from high-dose full agonist opioids to SL buprenorphine that may be recommended in the future.

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Canadian Mental Health Association
Mental health for all

Thames Valley
Family Health Team

Buprenorphine/Naloxone Microdosing: The Bernese Method

A Brief Summary for Primary Care Clinicians

Disclaimer:

Microdosing principles are currently not included in any clinical practice guidelines for the management of Opioid Use Disorder, rather it is an off-label practice that has been included in clinical practice amongst addiction specialists. It is therefore important to obtain informed consent prior to initiating it with a patient. Microdosing is frequently used at the London Rapid Access and Addictions Medicine (RAAM) Clinic with good results.

What is Microdosing?

The Bernese Method uses the principle of Microdosing to initiate a patient onto buprenorphine/naloxone (bup/nlx) maintenance therapy. The theoretical background of this method is based on the following hypotheses:

1) Repetitive administration of very small buprenorphine doses with sufficient dosing intervals (e.g. 12 hours) should not precipitate opioid withdrawal
2) Because of the long receptor binding time, buprenorphine will accumulate at the opioid receptor
3) Over time, an increasing amount of a full μ-agonist will be replaced by buprenorphine at the opioid receptor

Therefore, overlapping induction of buprenorphine with ongoing use of opioids, from the unregulated drug market or prescription, including maintenance doses of a full μ-agonist (e.g. methadone or sustained release oral morphine), should be possible without precipitating severe opioid withdrawal. Mild withdrawal symptoms may be experienced during the induction.

Although dosing schedules vary, principles of the Microdsoing method include:

1) Prescriber starts with a low dose of buprenorphine, overlapping with other opioid use
2) Small daily buprenorphine dose increases
3) Abrupt cessation of opioid use at sufficient dose of buprenorphine

Why use it, and who is a good candidate?

Microdosing may have considerable advantages despite taking longer for the overall induction than the traditional protocol. It may be useful for <u>most</u> patients. In more detail:

- It may be helpful for patients fearing withdrawal or experiencing severe symptoms during conventional induction, or who have failed conventional induction due to inability to tolerate withdrawal symptoms

- It may also be beneficial when a switch to buprenorphine is desired for patients maintained on a full μ-agonist such as methadone or slow-release oral morphine (SROM)
- It is no longer necessary to wait for withdrawal before induction, so patients who may not be able to attend daily appointments due to work commitments, etc. are good candidates
- As it negates withdrawal, there may be better treatment retention with buprenorphine/naloxone
- It may have more providers willing to prescribe buprenorphine/naloxone, as the induction is not as complex

Who Should Be Referred to the RAAM Clinic for Induction and Stabilization of Opioid Agonist Therapy (OAT)*?*

- Patients who are on high dose fentanyl patches of 100mcg/hour or greater
- Patients who are using illicit street fentanyl (due to the uncertain risk of precipitated withdrawal)
- Injection drug users
- Methadone conversions

Monitoring Considerations:

If choosing to use Urine Drug Screens (UDS) to assist with monitoring, emphasize that they are being utilized as a patient safety tool. These may be used with each client visit, or as the practitioner deems appropriate.

Reasons to use a UDS are to ensure client safety, augment honesty and accountability, and to inform treatment. It is often the case that clients are unaware of the mixed components of their drug from the unregulated market, or how combining medications, like benzodiazepines, can put them at further risk. UDS can help us assist them in their recovery.

Using the Microdosing method, follow-up appointments may be at a weekly interval, based on individual client's stability. You may choose to have a few days of brief daily follow-up appointments with opioid cessation, to allow for timely titration of buprenorphine/naloxone to a comfortable dose.

How do you prescribe buprenorphine/naloxone via the *Microdosing Method?*

Short-acting Opioid:

Day	Buprenorphine / Naloxone	Opioid
1	0.5 mg daily	Maintain dose
2	1.0 mg daily	Maintain dose
3	1.5 mg daily	Maintain dose
4	2.0 mg daily	Maintain dose
5	2.5 mg daily	Maintain dose
6	3.0 mg daily	Maintain dose
7	4.0 mg daily	Stop short-acting opioid
See the patient on Day 7, after 4mg of Bup/Nlx, and give another 2mg every 1h until comfortable, to a max of 12mg that day. You may instead choose to give an additional 2mg as needed on Day 7, with daily follow-ups thereafter, and increases of 2mg to 4mg/day as needed, until comfortable. Final maximum dose is typically 16mg/day.		

Long-acting Opioid:

Day	Buprenorphine / Naloxone	Opioid
1	0.5 mg daily	Maintain dose
2	1.0 mg daily	Maintain dose
3	1.5 mg daily	Maintain dose
4	2.0 mg daily	Maintain dose
5	2.5 mg daily	Maintain dose
6	3.0 mg daily	Maintain dose
7	4.0 mg daily	Begin taper of long-acting opioid
If long- AND short-acting opioids, stop short-acting opioids here, and begin taper of long-acting opioid		
8	5.0 mg daily	Continue taper
9	6.0 mg daily	Continue taper
10	7.0 mg daily	Continue taper
11	8.0 mg daily	Continue taper
12	10.0 mg daily	Continue taper
13	12.0 mg daily	Continue taper
14	12.0 mg daily	Stop remaining long-acting opioid
Follow-up appointment at Day 7 to outline taper of long-acting opioid. See the patient on Day 14, after 12mg of Bup/Nlx, and give another 2mg every 1h until comfortable, to a max of 16mg that day.		

Low doses of prescribed- Fentanyl/Fentanyl Patch:

Day	Buprenorphine / Naloxone	Opioid
1	0.5 mg	Maintain dose
2	1.0 mg	Maintain dose
3	1.5 mg	Maintain dose
4	2.0 mg	Maintain dose
5	2.5 mg	Maintain dose
6	3.0 mg	Maintain dose
7	4.0 mg	Begin taper of prescription Fentanyl
8	5.0 mg	Continue taper
9	6.0 mg	Continue taper
10	7.0mg	Continue taper
11	8.0 mg	Continue taper
12	10.0mg	Continue taper
13	12.0mg	Continue taper
14	12.0 mg	Stop remaining Fentanyl
Closer follow-up may be needed with Fentanyl conversions. Suggested follow-up appointment at Day 7 to outline taper of Fentanyl. See the patient on Day 14, after 12mg of Bup/Nlx, and give another 2mg every 1h until comfortable, to a max of 16mg that day.		

Community Pharmacy Considerations:

It is advisable to check with the patient's community pharmacy to ensure they have buprenorphine / naloxone to dispense. If you are unsure if the pharmacy has dispensed it using the Microdosing method previously, it is a general courtesy to forward them a copy of the Microdosing Method along with your prescription. They may need a "heads up" that tablets may need to be split to accommodate the smaller doses required in Microdosing.

Carries and Observed Doses for Microdosing:

In general, inductions involve all observed doses at the pharmacy. Daily dispensing will also ensure accuracy and ease of any associated opioid taper.

Missed Dosses During Microdosing Induction:

If one dose is missed during induction, consider repeating the previous day's dose and continue the schedule.

If two doses are missed, consider restarting the schedule.

Withdrawal Management:

Diphenhydramine, loperamide and acetaminophen/ibuprofen may be of benefit for any potential withdrawal.

Local Support for Clinicians:

If you require any assistance or just want to double check your plan, consider contacting the local Rapid Access Addiction Medicine Clinic.

Also consider an e-Consult (https://otnhub.ca/patient-care/) with Addiction Specialist Dr. Ken Lee (ken.lee@sjhc.london.on.ca); or Medical Mentoring for Addictions and Pain (https://ocfp.on.ca/cpd/collaborative-networks/mmap)

Or consultation with Katie Dunham, NP (katie_dunham04@hotmail.com) or call 519-319-4428

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Buprenorphine / Naloxone - The Bernese Method: A Primer for the Clinician. Prepared by the *PHS Health Care Columbia Street Community Clinic and St. Paul's/VGH/RAAC clinicians* (Vancouver, BC).
Dosing schedules adapted from the *Rapid Access Addictions Medicine Clinic / Clinicians London ON.*

Prepared By:
Payal Patel, PharmD, Thames Valley Family Health Team
Katie Dunham, NP, London RAAM Clinic
Ken Lee, MD, London RAAM Clinic

May 2019

Suboxone Taper Instructions for Patient Patient Name:

[This is an example of a customized taper for a patient who followed it and felt his pain drop a lot,and cognition clear when he got rid of his oxycodone. He did super well and had no withdrawal, worsening of pain, or side effects - only improvements of all aspects of his life.]

Copy Provided to Patient Date:

Day	Date	Suboxone Dose	Oxycodone CR Dose
1		0.5 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
2		1.0 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
3		1.5 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
4		2.0 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
5		2.5 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
6		3.0 mg sublingual once in the morning	Maintain current dose (10 mg three times a day)
7		4.0 mg sublingual once in the morning	Begin taper as follows: 10 mg in morning and 10 mg at night See Dr. Peterson this day
8		4.0 mg sublingual once in the morning	10 mg in the morning and 10 mg at night
9		4.0 mg sublingual once in the morning	10 mg in the morning and 10 mg at night
10		4.0 mg sublingual once in the morning	10 mg in the morning
11		4.0 mg sublingual once in the morning	10 mg in the morning
12		4.0 mg sublingual once in the morning	10 mg in the morning
13		4.0 mg sublingual once in the morning	take none - finished Oxycodone CR yesterday
14		4.0 mg sublingual once in the morning	See Dr. Peterson this day. Dr. Peterson will give another 2 mg Suboxone every hour until comfortable, if there is significant withdrawal remaining (there shouldn't be). If there are any side effects, Dr. Peterson may instead reduce the dose.

The purpose of this microdosing schedule is to allow you to very gradually increase your dose of Suboxone, which minimizes or eliminates the withdrawal that normally occurs if Suboxone is started at a higher dose without first stopping your current opioid for at least 24 hours. The taper (gradual reduction in your dose) of your current opioid seen in week 2 of the table above is not essential, but doing this taper in week 2 further reduces the chance that you will experience more than the slightest amount of withdrawal.

Note that some patients require much more than 4 mg of Suboxone to control withdrawal, but that is not common for the doses you are on of your current opioid.

Note that occasionally, a patient will feel that 4 mg is too much for them (they might feel nauseous or sedated or euphoric for example) - if that is the case, stop taking it and contact Dr. Peterson.

If there are any side effects from Suboxone (for example, feeling weak, euphoric, or in significant withdrawal), contact Dr. Peterson by phone before taking any more Suboxone or your current opioid.

As with any opioid, call 911 if you have shallow breathing, confusion, slurred speech, or are not responsive to those around you (though there is much less risk for these opioid overdose symptoms on Suboxone compared to the risk from your existing opioid). Advise loved ones in your home that you are starting a new opioid and while it is unlikely that you will have a problem, they should know the signs of opioid overdose (shallow breathing, confusion, slurred speech, or not responding well when you talk to them) and know what to do (call 911) - again, by switching you to Suboxone, the risk of opioid overdose will be much smaller than on your current opioid, which has a much higher risk of opioid overdose than Suboxone. Note that the risk of opioid overdose is much higher if you are also taking sedative drugs like lorazepam or clonazepam or alcohol, so you should normally avoid taking these drugs while on any opioid.

Our clinic staff have been notified that if patient has side effects, I will speak to them on a same day basis rather than requiring them to drive into clinic. In the extremely unlikely event that Dr. Peterson is not available during this taper, please ask to be booked with another pain physician at our clinic. An additional backup plan during the taper (or at any time when you are on Suboxone), is to go to the CMHA Suboxone Clinic at 648 Huron Street, which again is highly unlikely to be necessary.

Dr. M Peterson

Neuropsychopharmacology. 2016 Aug;41(9):2344-51. doi: 10.1038/npp.2016.38. Epub 2016 Mar 16.

Antidepressant-like Effects of Buprenorphine are Mediated by Kappa Opioid Receptors.

Falcon E[1], Browne CA[1], Leon RM[1], Fleites VC[1], Sweeney R[1], Kirby LG[2], Lucki I[1,3].

Questions about BUPRENORPHINE - NALOXONE and the Answers that may SURPRISE YOU

A booklet for people taking opioids for CHRONIC PAIN

Rx FILES

What is buprenorphine–naloxone (bup-nal)?

Brand name = **SUBOXONE®** (other equivalent brands are available)

It is two medications combined into one tablet.

buprenorphine (bup) = opioid	**naloxone (nal)** = opioid blocker
Used for pain management (off-label). Off-label means that use for pain is not an official Health Canada approved use even though it has been found to be useful.	Has no effect when dissolved under the tongue (like in bup-nal tablets) as the body quickly breaks it down.
Also used to treat opioid cravings and withdrawal.	Included to discourage misuse, such as injecting or snorting. When naloxone enters the body through the bloodstream or nose, it blocks opioids from working. This is why naloxone (like in a take home kit) is the treatment for an opioid overdose.

How are bup-nal tablets taken?

They must be placed under the tongue and fully dissolved.

Why must bup-nal tablets be taken under the tongue?

Bup is absorbed through the tissue under the tongue into the bloodstream. If the tablet is swallowed, it will not work. That would be like skipping your dose and could lead to an increase in pain.

What can I do if my bup-nal tablet does not dissolve or I do not like the taste?

It can take up to 10 minutes for the tablet to fully dissolve and it is important not to drink, eat, or talk during this time.

Try having a cool drink to wet your mouth BEFORE your dose.

If you have any trouble, talk to your pharmacist about changing brands of bup-nal. Some brands may dissolve better and/or you may like the taste better.

Can you tell which of these are FACTS, and which are MYTHS?

1. Bup-nal is only for people who misuse drugs.
2. The naloxone in bup-nal tablets will cause opioid withdrawal.
3. Bup-nal is safer than other opioids.
4. Bup-nal is the pill form of methadone.

1. Bup-nal is only for people who misuse drugs.

This is a myth.

Many medications have more than one use (for example some blood pressure medications can also be used for migraine prevention). Bup-nal can be used to treat chronic pain and it can be used to treat opioid cravings and withdrawal related to opioid use.

2. The naloxone in bup-nal tablets will cause opioid withdrawal.

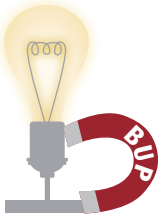
This is a myth.

The naloxone in bup-nal will only cause opioid withdrawal if the tablets are taken differently than prescribed, such as being snorted or injected.

3. Bup-nal is safer than other opioids.

This is a fact.

Bup-nal is safer than fully active opioids (see light bulb example on page 6-7) because it has less risk of opioid side effects like mood changes, overdose, and death.



4. Bup-nal is the pill form of methadone.

This is a myth.

Bup-nal is a different medication than methadone and it has unique effects in the body. See the next two pages for what makes bup-nal so different.

What are the side effects of bup-nal?

- Bup-nal has a lower risk of side effects compared to other opioids but can cause headache, nausea, stomach upset, and constipation.
- Usually these side effects lessen or disappear with time.
- Contact your prescriber or pharmacist if you are experiencing these side effects for longer than one week while on bup-nal.

Will I have to go to the pharmacy every day to get my dose?

When bup-nal is first started you may need to go to the pharmacy daily. Once you are on a stable dose your prescriber may be able to prescribe take home doses so you do not have to go the pharmacy every day.

How many times a day will I need to take bup-nal for pain?

When used for pain, bup-nal may be taken 1 to 4 times a day. It depends on the person. For some, pain will be well controlled with only one dose a day. Others have good pain control after their dose, but then experience an increase in pain later in the day. If this happens to you, talk to your prescriber.

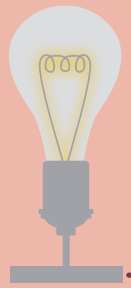
Will bup-nal work for me?

Pain treatment requires many approaches to find the best fit for an individual. Talk to your care team if:

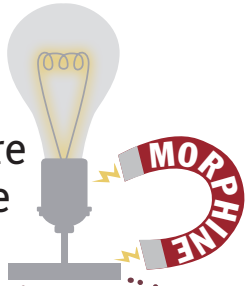
- After reading this booklet, it sounds as though bup-nal might be a good fit for you.
- You are taking bup-nal and your pain worsens or you are experiencing side effects.

WHAT MAKES BUP-NAL UNIQUE?

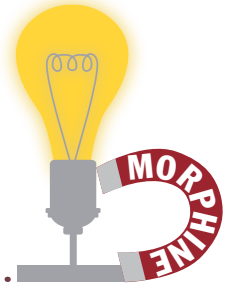
This light is like the opioid receptor in your brain.



Opioids, like morphine, are magnets that are attracted to the receptor/light.



These opioids turn the light fully on.



Examples:

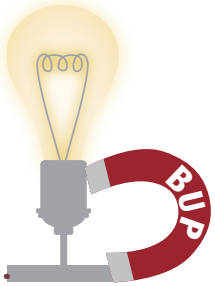
hydromorphone (Dilaudid®, Hydromorph Contin®)

morphine (Kadian®, Statex®)

oxycodone (OxyNEO®)

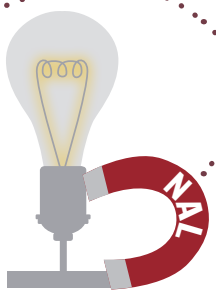
methadone (Metadol®, Methadose®)

fentanyl (Duragesic®)



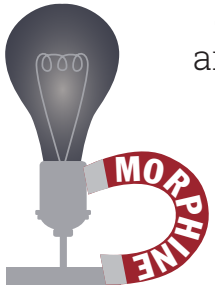
Buprenorphine (bup) turns the receptor only partly on. You can see that the light is not as bright, like a light bulb on a dimmer switch.

Naloxone (nal) doesn't turn the light on at all.



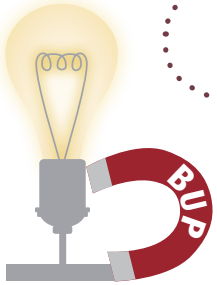
HOW COULD BUP-NAL HELP ME?

Sometimes keeping a light bulb too bright ends up burning it out.



Sometimes when opioids are used at high doses and for a long time, they stop working for pain. This is like a light bulb that has been burning really bright and hot, and now has burned out. Using bup can give your opioid receptors a rest, and this means less pain in some people.

It may seem hard to believe, but turning on the opioid receptor only part way actually has a lot of benefits.



Turning the receptor only partly on also means:

- ☑ *less risk of overdose*
- ☑ *less constipation*
- ☑ *less sexual problems*

Continue reading to learn about:

- other possible benefits of bup-nal
- the story of Sarah* – a Saskatchewan resident who was treated with many opioids for chronic pain. The opioids caused her more harm than benefit and it wasn't until she was changed to bup-nal that she felt she was able to get her life back.

* Sarah's story has been used with permission. Her name has been changed to protect her privacy.

Why should I consider switching to bup-nal from other opioids?

I'm on opioids and...	Switching to bup-nal may help because...
My pain is a bit better but my mood and/or energy is low.	Bup not only provides pain relief but also has unique effects within the brain that can **improve mood and energy.**
Opioids helped with my pain at first, but now my pain is worse, even though my dose went up.	Sometimes opioids can actually increase pain especially if they are used at high doses and/or for long periods of time. The unique effects of bup may help to **reduce the pain** caused by other opioids.
I tried tapering off opioids, but I had bad withdrawal and/or my pain seemed to get worse.	Bup is a useful option for people trying to taper down their opioids because it has a slower and more gradual wearing off effect in the brain and has **less risk of withdrawal.**
Opioids help with my pain but I am usually constipated.	Bup has a **lower risk of constipation** compared to other opioids.
I worry about accidentally overdosing on opioids.	Bup has a much **lower risk of overdose** compared to other opioids (see light bulb example earlier).
I am experiencing sexual problems and/or my hormone levels are low.	Long-term use of opioids can cause reduced hormone levels (like testosterone & estrogen) and interfere with sexual function. Bup has a **lower risk of these side effects** compared to other opioids.

Sarah's Story: Bup-nal Gave Me My Life Back!

"I was diagnosed with fibromyalgia when I was 18 years old. The pain was so bad, and it just seemed to be getting worse and worse. I took Tylenol #1s, then Tylenol #3s and then I was prescribed fentanyl and hydromorphone.

My perfect life became a total mess when I started taking opioids. I was on opioids for 15 years. I was a real-life zombie. I was also severely depressed because of the opioids. I was in a deep dark hole I couldn't get out of. My life fell apart. I lost everything and anything that ever meant something to me. And I mean everything! Everyone had written me off. No one wanted to help me. I was treated awfully and shamed.

My life changed when I met my new, amazing medical team. I was told I should be dead from the high doses of opioids I was taking, but I was blind to it. My medical team is so wonderful. They supported me through this journey of mine when I had no other support at all. They helped me switch from the other opioids to Suboxone (bup-nal).

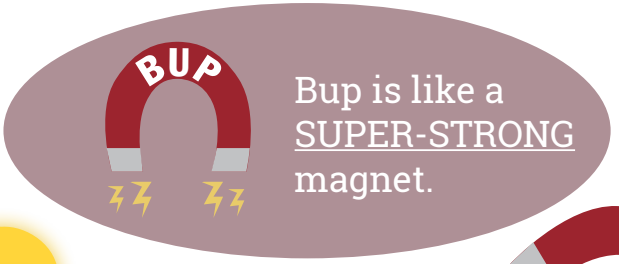
Once on Suboxone I felt like I had come out of a coma. Suboxone really helped me. I could see again. The nightmare was over. I started feeling like myself again. I started singing and dancing. My family and friends started to come around after they realized the old me was back. I am so happy now. I'm so grateful for everything I have. Truly. I have my mind and body back and it's amazing!

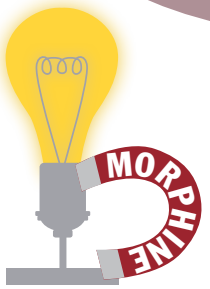
I'm eternally grateful to my medical team for saving my life. It's been a year now and my life has changed for the better immensely! I've done a 360 with my life and I'm really happy. I enjoy everything again. It's so wonderful and so worth it! Your life will change! **I felt like a human again.** It's so worth it. Every day is a blessing. It really is. This is what I learned through my journey."

Not everyone's experience will be like Sarah's but her story does provide a window into how bup-nal can help.
See page 11 for more tips from Sarah!

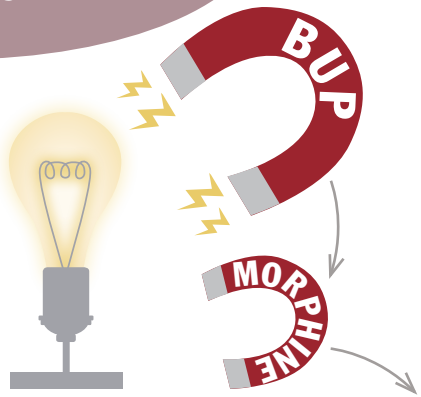
WHAT METHODS ARE AVAILABLE ...FOR STARTING BUP-NAL?

What happens if you take both bup and another opioid together?





If there is already an opioid in your body ...



Bup will push it off.

If you go from a fully bright light bulb to a partially bright light bulb too fast, you may feel withdrawal. This means bup has to be started carefully.

SUPPORT:

Switching to bup-nal can be much easier to do with support. During the transition some people describe no new symptoms but some develop very uncomfortable symptoms like nausea, headache, muscle aches and pains, and trouble sleeping.

THE GOOD NEWS IS:

- these symptoms should only last a few days at most
- there are non-opioid medications like clonidine that can help – ask your prescriber or pharmacist
- once on a stable dose of bup-nal withdrawal symptoms should disappear

There are two methods for starting bup-nal. Discuss with your care team which way may be best for you.

OPTION 1
Traditional/Conventional Induction Method

- You have to be in opioid withdrawal.
- This means stopping your opioid for 12-72 hours before starting bup-nal.
- Once you start bup-nal, the withdrawal will gradually go away.
- You can also take medications to reduce withdrawal symptoms.

OPTION 2
Micro-dosing Method off-label dosing

- You can keep using your previous opioid until bup-nal has kicked in.
- The bup-nal is started at a very low dose and slowly increased.
- You probably won't have withdrawal, but it will take longer for the bup-nal to kick in.
- Not all health care workers have experience with this method.

Sarah's Thoughts on Changing to Bup-Nal:

You'll need help and support.
If you make goals, you can reach them.

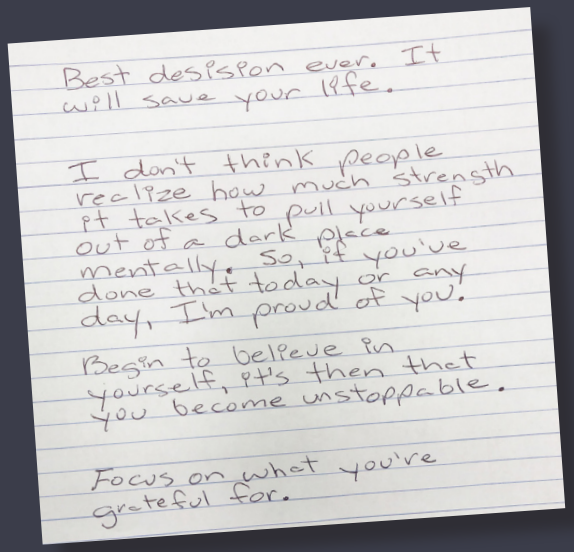
Find something that motivates you - my biggest motivation is my son. You must focus. Believe in yourself!

Willpower is important. Stay determined.
You WILL get there!

Medications are helpful - for me it was clonidine for a few days to manage withdrawals.

Sarah is a Saskatchewan resident with chronic pain. Over a period of 15 years, she was prescribed many different opioids to treat her pain. Unfortunately, they caused her more suffering than relief. It wasn't until she was switched to buprenorphine-naloxone that she felt she got her life back.

Here are some of Sarah's thoughts on bup-nal use for chronic pain:



See page 9 of this booklet for Sarah's complete story.

Funding for the creation and printing of this booklet was supported by Health Canada's *Substance Use and Addictions Program*.
This booklet represents the views of RxFiles Academic Detailing, and not necessarily the views of Health Canada.

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College of Pharmacy and Nutrition
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I strongly recommend incorporating buprenorphine to your practice for the following reasons:

1. Lack of respiratory depression (so it's super safe compared to other opioids, other than rare cases of sedation, but that is quite rare). There are case reports but it's exceedingly rare unless taken with large amounts of benzos or alcohol at the same time. There is a ceiling effect on respiratory depression so if patients take more and more buprenorphine (or inject it or take more than prescribed) they are unlikely to die, whereas from all other opioids there is no such effect and they will die if they take too much. I have seen 1 case of respiratory depression but it was an unusual patient and I can't say for sure it was actually from the Suboxone (it was much higher doses than the patch); none of my 4 Suboxone mentors who are addiction MDs who do this full time have ever seen respiratory depression in tens if not hundreds of thousands of patients. I can tell you many times I have seen nodding off from other opioids, and we all know of patients who have had problems with them.
2. You really can't get "high" from Suboxone as the opioid receptors are activated but only up to a ceiling level.
3. Higher doses of buprenorphine (the doses used in Suboxone or Sublocade) will block other opioids, so in addition to little to no risk of overdose from this drug, they are unlikely to die of an overdose if they use too much of another opioid. This is why Suboxone/Sublocade is preferable for treating opioid addiction because it will prevent heroin/fentanyl/oxycodone/hydromorphone overdose quite handily.
4. Buprenorphine acts on kappa receptors, which have a mild antidepressant effect, wheras all other opioids are depressants/"downers".
5. Tolerance is usually not significant, so there won't be treatment failure with time, and it won't cause opioid hyperalgesia with time (central sensitization to pain, which often happens when other opioids are used long-term).
6. When used in the patch form, the doses are in micrograms which is very little compared to Suboxone or Sublocade. The patch lasts a week. You can really control your patient's dose of their opioid (in contrast to pills where you have to give large numbers and often multiple are used a day and patients can easily run out early or use too much). So, patients have a very safe treatment and it's unlikely they can do anything to hurt themselves with it if they use too much, but it's still an opioid and the risks and responsibilities to use it only as prescribed remain important.

The main downsides to buprenorphine are:
1. Bu-Trans is not covered on ODB (Suboxone is)
2. In rare cases the patch will cause severe itch or blistering, so patients should be advised to remove the patch if this occurs. This can usually be resolved by spraying flovent a couple puffs on the skin from 2 inches away, allowing to dry, before initially applying the patch.
3. If patients start too quickly they can get precipitated withdrawal. However, that only applies to Suboxone/Sublocade doses and will not occur at patch doses.
4. A lot of people get nausea and vomiting. Patients needs to be warned about this, and starting doses kept low. It usually starts mildly when it happens, and worsens as the dose is titrated so be prepared to lower the dose or tell pts to do that if it happens. Many patients get no nausea at all, and they are great candidates for buprenorphine.

Sedation/nodding off is extremely rare on buprenorphine. For the patch, I have only seen that less than 5 times in probably 500 people I have put on it and it's usually mild and the patient can remove the patch. I can't say I remember seeing it on Suboxone or Sublocade, and I've put hundreds of people on Suboxone. Always give driving advice when starting new meds, it's not just opioids can can cause sedation, that can happen with most pain meds - don't drive until you know you are not sleepy or groggy from the medication.

I am happy to discuss further.

OPIOID MANAGER SWITCHING OPIOIDS

University Health Network | Centre for Effective Practice

- Opioid withdrawal symptoms are unpleasant, but not life-threatening. What is life-threatening with opioids is overdose. So remember, it is safer to underdose. Be careful during pregnancy, because severe acute withdrawal has been associated with premature labour and spontanous abortion.
- After switching, it is important to warn the patient (and relative or friends) about signs of overdose: slurred or drawling speech, emotional lability, ataxia, "nodding off" during conversation or activity.
- Consider a 3-day "tolerance check:" contact the patient 3 days after starting the new opioid to check for signs of over-sedation and to ensure that pain relief is at least comparable to the pre-switch treatment.
- Patients at higher risk of overdose include: elderly, on benzodiazepines, renal or hepatic impairment, COPD, sleep apnea, sleep disorders and cognitive impaired.
- These doses are approximations due to inter-individual variation.

The form below is designed to guide the provider in switching from one opioid to another using the table of morphine equivalent suggested by the guideline. A copy of the completed form may be given to the patient and should be sent to the pharmacist.

Morphine Equivalence Table

Opioid (Oral Dose)	Equivalent Doses (mg)	Conversion to MEQ
Morphine	30	1
Codeine	200	0.15
Oxycodone	20	1.5
Hydromorphone	6	5
Meperidine	300	0.1
Methadone & Tramadol	Dose Equivalents unreliable	
Transdermal fentanyl	60 – 134 mg morphine = 25 mcg/h 135 – 179 mg = 37 mcg/h 180 – 224 mg = 50 mcg/h 225 – 269 mg = 62 mcg/h 270 – 314 mg = 75 mcg/h 315 – 359 mg = 87 mcg/h 360 – 404 mg = 100 mcg/h	

Switching Opioids:	
If previous opioid dose was:	**Then, SUGGESTED new opioid dose is:**
High	50% or less of previous opioid (converted to morphine equivalent)
Moderate or low	60-75% of the previous opioid (converted to morphine equivalent)

Switching Opioid Form

Patient name:…… Today's date: ……/ ……../ ……..

Switching from ……..…….…… to ……..…….

Start switching on Monday: ……/ ……../ …….. (mm/dd/yy)

Current opioid(s) regimen:

- Opioid name, dose and frequency: ……
- Opioid name, dose and frequency: ……
- Opioid name, dose and frequency: ……

Current total daily dose of opioid: …… / day

Switching from current opioid to morphine equivalent:

Morphine to morphine:	multiply by 1
Oxycodone to morphine:	multiply by 1.5
Hydromorphone to morphine:	multiply by 5

Current **morphine** equivalence dose: …… / day

Proportion of the initial daily dose that will be switched to the new opioid: ( ) 50% ( ) 60% ( ) 75% ( ) other: ……

Total morphine equivalents that will be switched to the new regimen: ……/day

Switching from morphine equivalent to the new opioid:

Morphine equivalent to morphine:	multiply by 1
Morphine equivalent to oxycodone:	multiply by 0.667
Morphine equivalent to hydromorphone:	multiply by 0.2

From morphine equivalent to the new opioid: The total daily dose of the new opioid is: …… /day

New opioid regimen:

- Opioid name, dose and frequency: ……
- Opioid name, dose and frequency: ……
- Opioid name, dose and frequency: ……

Comments:

……

……

For questions, please call Dr. ……..…… Phone number: (……) ……..…- ……..……

To access the Canadian Guideline for Safe and Effective Use of Opioids for Non Chronic Cancer Pain and to download the Opioid Manager visit **http://nationalpaincentre.mcmaster.ca/opioid/**

EXHIBIT 2.13. DSM-5 Criteria for OUD[72]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance.
10. Tolerance,* as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    b. A markedly diminished effect with continued use of the same amount of an opioid
11. Withdrawal,* as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome
    b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms

* This criterion is not met for individuals taking opioids solely under appropriate medical supervision.

Severity: mild = 2–3 symptoms; moderate = 4–5 symptoms; severe = 6 or more symptoms

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TABLE 1. URINE BROAD SPECTRUM TOX SCREEN (DRUG MENU AND REPORTING CUT OFFS)

OPIOIDS	Reporting Cut-off (ug/L)	OPIOIDS (cont'd)	Reporting Cut-off (ug/L)	AMPHETAMINES	Reporting Cut-off (ug/L)	BENZODIAZEPINES	Reporting Cut-off (ug/L)
Acetylcodeine	25	Norbuprenorphine (buprenorphine metab.)	15	Amphetamine (methamphetamine metab.)	50	Aminoflunitrazepam (flunitrazepam metab.)	25
Acetylmorphine (heroin metab.)	5	Norcarfentanil* (Carfentanil metab.)	1	Butylone#	15	Aminonitrazepam (nitrazepam metab.)	25
Acetylfentanyl*	5	Norfentanyl (fentanyl metab.)	15	DiMeMethcathinone# (dimethylmethcathinone)	50	Aminoclonazepam (clonazepam metab.)	25
Acetylnorfentanyl* (acetylfentanyl metab.)	50	Norhydrocodone (hydrocodone metab.)	50	Ethylone#	15	Bromazepam	25
Alfentanil*	5	Normeperidine (meperidine metab.)	50	MBDB	25	Desalkylflurazepam (flurazepam metab.)	25
Buprenorphine	15	Noroxycodone (oxycodone metab.)	25	MDA	50	Desmethylclobazam (clobazam metab.)	25
Butorphanol	50	Norpropoxyphene (propoxyphene metab.)	50	MDEA	50	**Etizolam****	**2**
Codeine	75	Nortilidine (tilidine metab.)	50	MDMA ("Ecstasy")	50	**Flualprazolam****	**2**
Codeine-6Glc (codeine metab.)	150	O-Desmethyltramadol (tramadol metab.)	25	MDPV#	15	**Flubromazolam****	**2**
Desmethyltapentadol (tapentadol metab.)	100	Oxycodone	25	Mephedrone#	15	HO-Alprazolam (alprazolam metab.)	25
Dextromethorphan	50	Oxymorphone	25	Methcathinone#	25	**HO-Etizolam** (Etizolam metab.)**	**5**
Dextrorphan	50	Pentazocine	50	Methamphetamine	50	**HO-Flualprazolam** (Flualprazolam metab.)**	**2**
EDDP (methadone metab.)	100	Sufentanil*	5	Methedrone#	15	HO-Midazolam (midazolam metab.)	25
Fentanyl	5	Tapentadol	100	Methedrone_NPE# (methedrone metab.)	50	HO-Triazolam (trizolam metab.)	25
Hydrocodone	25	Tilidine	50	Methylone#	15	Lorazepam	25
Hydromorphone	25	Tramadol	50	Methylphenidate	50	Nordiazepam (diazepam metab.)	25
Meperidine	50			Pentedrone_NE# (pentedrone metab.)	50	Oxazepam (nordiazepam, temazepam metab.)	50
Methadone	100			PMA (para-methoxy-amphetamine)	50	Temazepam	25
Mitragynine (“Kratom”)	25			alpha-PVP#	15		
Morphine (heroin, codeine metab.)	50			Ritalinic_acid (methylphenidate metab.)	25		
Nalbuphine	50			TFMPP (3-Trifluoromethyl-phenylpiperazine)	25		
Nalorphine	50						
Naloxone	25						
Naltrexol	25						
Naltrexone	25	*Fentanyl analogues		#Substituted Cathinones “Bath Salts"		** Designer Benzodiazepines	

Note: Updated information appears in bold type

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TABLE 1. URINE BROAD SPECTRUM TOX SCREEN (DRUG MENU AND REPORTING CUT OFFS)

ANTI-DEPRESSANTS	Reporting Cut-off (ug/L)
Amoxapine	25
Bupropion	25
Citalopram	50
Clomipramine	25
Desipramine	25
Desmethylcitalopram (citalopram metab.)	50
Desmethyldoxepin (doxepin metab.)	25
Desmethyltrimipramine (imipramine metab.)	25
Doxepin	25
Duloxetine	25
Fluoxetine	25
HO-Bupropion (bupropion metab.)	25
Imipramine	25
mCPP (trazodone metab.)	25
Mirtazapine	25
N-Desmethylclomipramine (clomipramine metab.)	25
N-Desmethylmirtazapine (mirtazepine metab.)	25
Norfluoxetine (fluoxetine metab.)	50
Nortriptyline (amitriptyline metab.)	25
O-Desmethylvenlafaxine (venlafaxine metab.)	50
Paroxetine	25
Sertraline	25
Trazodone	25
Trimipramine	25
Venlafaxine	50

ANTI-PSYCHOTICS	Reporting Cut-off (ug/L)
Aripiprazole	50
Asenapine	50
Chlorpromazine	50
Clozapine	50
Dehydroaripiprazole (aripiprazole metab.)	50
Fluphenazine	50
Haloperidol	50
HO-Quetiapine (quetiapine metab.)	50
HO-Risperidone (risperidone metab.)	50
Lurasidone	50
N-Desmethylclozapine (clozapine metab.)	50
N-Desmethylolanzapine (olanzapine metab.)	50
Norquetiapine (quetiapine metab.)	50
Olanzapine	50
Quetiapine	50
Risperidone	50

CANNABINOIDS	Reporting Cut-off (ug/L)
THCA (cannabis metab.)	25
JWH-018_4-OH‡ (JWH-018 metab.)	25
JWH-019_5-OH‡ (JWH-019 metab.)	25
JWH-073_3-OH‡ (JWH-073 metab.)	25
UR-144_5-OH‡ (UR-144 metab.)	25
XLR-11_4-OH‡ (XLR-11 metab.)	25
‡Synthetic cannabinoids "Spice"	

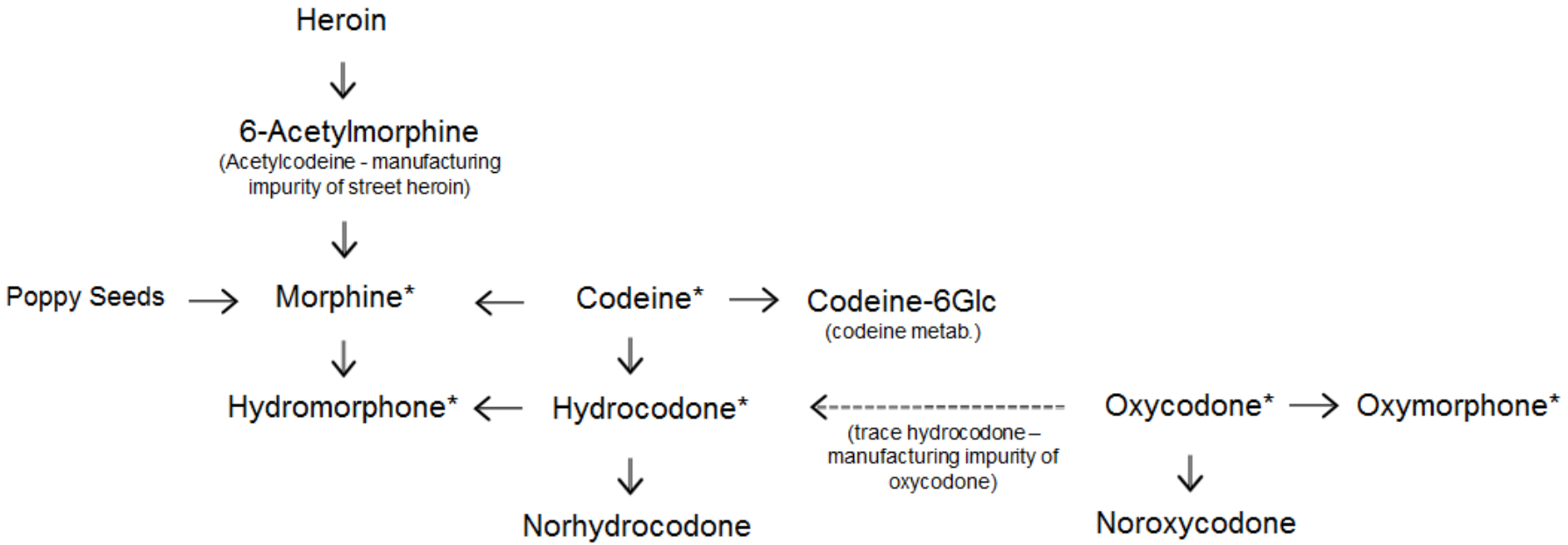
OTHER	Reporting Cut-off (ug/L)
Benzoylecgonine (cocaine metab.)	50
Brompheniramine	50
Buspirone	50
Carbamazepine	50
Carbamazepine_EPX (carbamazepine metab.)	50
Carisoprodol	50
Chlorpheniramine	50
Cocaethylene (ethanol/cocaine metab.)	25
Cyclobenzaprine	50
Dehydronorketamine (ketamine metab.)	50
Desmethylzopiclone† (zopiclone metab.)	5
Diphenhydramine	50
Ephedrine	150
Gabapentin	500
Ketamine	50
Levamisole (cocaine cutting agent)	5
Lidocaine	50
Meprobamate (carisoprodol metab.)	50
Methaqualone	50
Methoxetamine	50
N-Desmethylcyclobenzaprine (cyclobenzaprine metab.)	50
Norketamine (ketamine metab.)	50
Phencyclidine (PCP)	50
Pregabalin	50
Pseudoephedrine	150

OTHER (CONT.)	Reporting Cut-off (ug/L)
Promethazine	50
Zolpidem-PCA† (zolpidem metab.)	25
Zopiclone†	5
†Z-drugs	

Note: Updated information appears in bold type

DRUGS OF ABUSE METABOLIC PATHWAYS - REFERENCE DOCUMENT

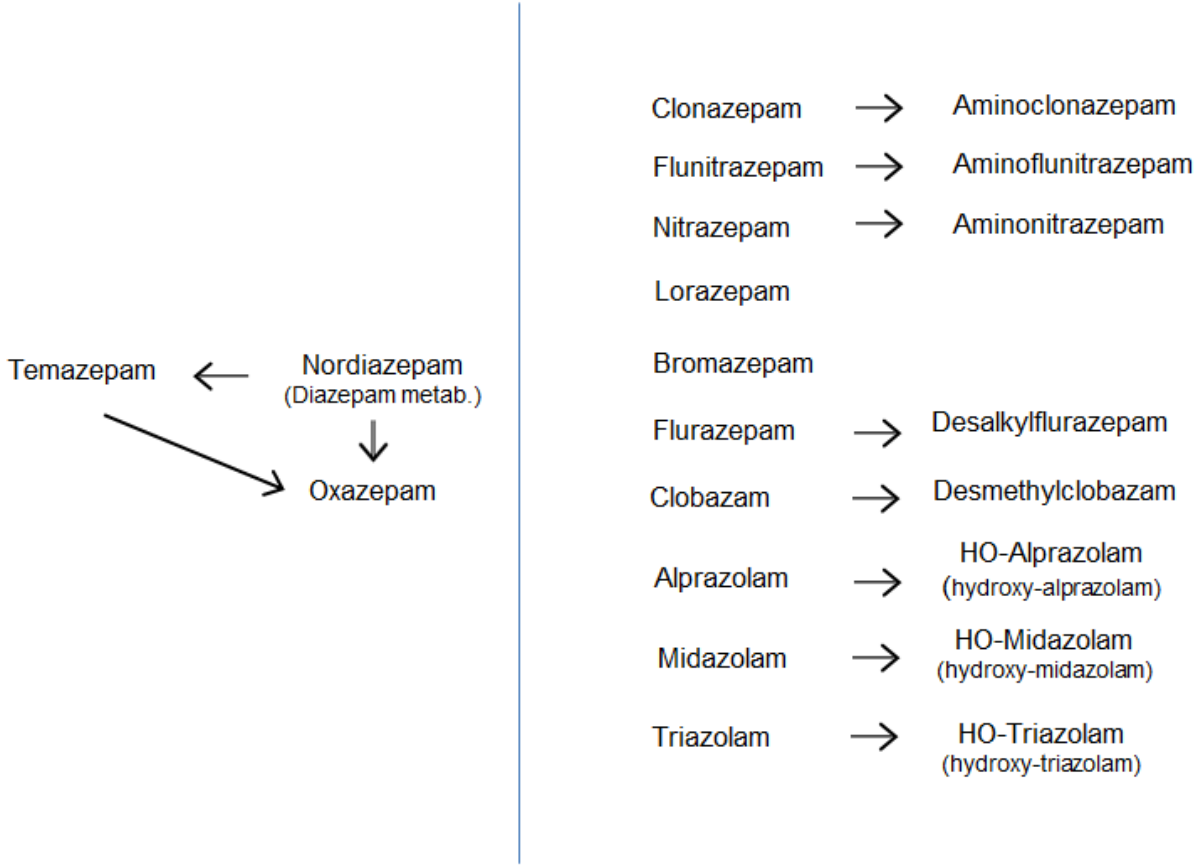
Figure 1. Principal Opiate Metabolic Pathways



*a compound could be a parent drug or metabolite

NOTE: This diagram includes opiates that can be detected by urine Broad Spectrum Toxicology Screen (BST) offered by LifeLabs ON

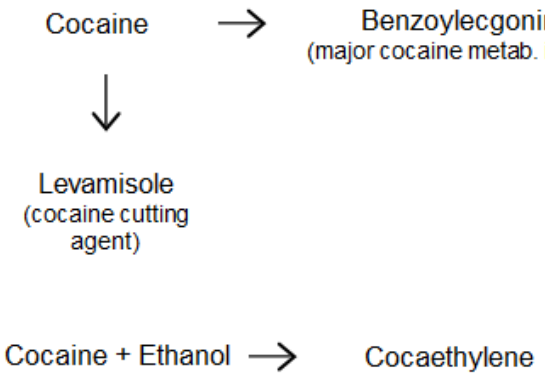
Figure 2. Principal Benzodiazepine Metabolic Pathways



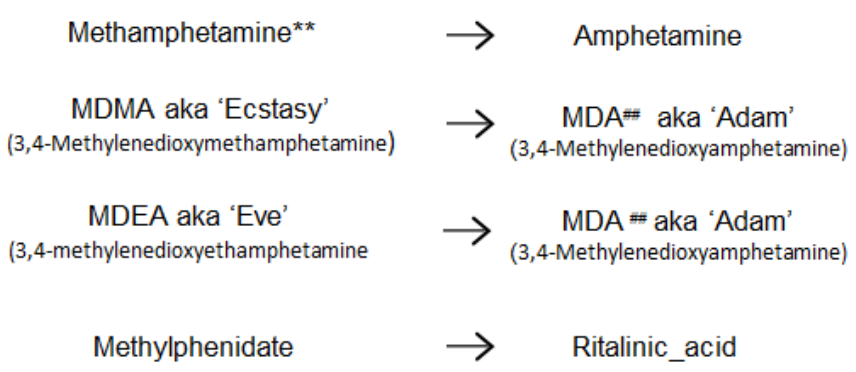
NOTE: This diagram includes benzodiazepines that can be detected by urine Broad Spectrum Toxicology Screen (BST) offered by LifeLabs ON

Figure 3. Drugs of Abuse Metabolic Pathways

a) Included in the 'Other' category of Broad Spectrum Tox Screen



b) Included in the 'Amphetamines' category of Broad Spectrum Tox Screen



** Methamphetamine reported as the total of the undifferentiated d and l enantiomers. Ephedrine or pseudoephedrine can be detected with high levels of methamphetamine. Both can be used as precursors of illicitly manufactured methamphetamine.

MDA is a metabolite of MDMA and MDEA but can be also abused on its own.

NOTE: This diagram includes compounds that can be detected by urine Broad Spectrum Toxicology Screen (BST) offered by LifeLabs ON

DRUGS OF ABUSE METABOLIC PATHWAYS - REFERENCE DOCUMENT

Figure 4. Novel Psychoactive Substances (NPS) included in LifeLabs ON Broad Spectrum Tox Screen

Reported under BST Category of:	List of NPS compounds
OPIOIDS	• Mitragynine ('Kratom')
	Fentanyl Analogues/Derivatives: • Acetylfentanyl • Sufentanyl • Alfentanyl
AMPHETAMINES	**Subsituted Cathinones aka 'Bath Salts':** • Butylone • Ethylone • MDPV (Methylenedioxypyrovalerone) • Mephedrone • Methcathinone (also as manufacturing impurity of ephedrine and pseudoephedrine) • Methedrone • Methylone • Pentedrone • α-PVP (Desmethyl Pyrovalerone)
	Other 'Designer Drugs': • MBDB (N-methyl-1,3-benzodioxolylbutanamine) • PMA (*para*-Methoxyamphetamine) • TFMPP (3-Trifluoromethylphenylpiperazine)
CANNABINOIDS	**Synthetic Cannabinoids aka 'Spice':** • JWH-018 • JWH-019 • JWH-073 • UR-144 • XLR-11

Health Canada advises Canadians to exercise caution when taking gabapentin or pregabalin with opioids

Report a Concern (http://www.healthycanadians.gc.ca/report-signalez/index-eng.php)

Starting date:	September 17, 2019
Type of communication:	Information Update
Subcategory:	Drugs
Source of recall:	Health Canada
Issue:	Important Safety Information
Audience:	General Public, Healthcare Professionals
Identification number:	RA-71003

Last updated: 2019-09-17
September 17, 2019
For Immediate Release

OTTAWA – Health Canada is advising Canadians about the increased risk of opioid overdose and serious side effects when taking gabapentin (e.g., Neurontin) or pregabalin (e.g., Lyrica) with an opioid.

Gabapentin is authorized to treat epilepsy and pregabalin is authorized to treat nerve pain. Both drugs belong to a class of drugs called gabapentinoids, which have been marketed in Canada since 1994.

Opioids are drugs that are used primarily to treat pain. They include both prescription and non-prescription medications such as codeine, fentanyl, morphine, oxycodone, hydromorphone, tramadol, tapentadol, hydrocodone, methadone and buprenorphine. Opioids may also be prescribed for other conditions, such as moderate to severe diarrhea, moderate to severe cough, and opioid use disorder. Increasingly, opioids such as fentanyl can also be found in illegal drugs, including heroin and cocaine. Consuming as little as a few grains of salt worth of fentanyl alone can be deadly.

When used with opioids, gabapentinoids increase the risk of opioid overdose (https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/overdose.html). Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression (slowed breathing), increased sedation (sleepiness), dizziness, fainting, and death. If you suspect an overdose (https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/overdose.html), call for emergency help, administer naloxone if you have it, and stay with the person. Naloxone (https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/naloxone.html) is a fast-acting drug that can temporarily reverse the effects of an opioid overdose.

What you should do:

- Consult your healthcare practitioner if you currently use or have used gabapentinoids or opioids and are concerned about your health.
- Know the signs of an opioid overdose (https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/overdose.html).
- Stay informed and consult your healthcare practitioner on what other drugs and substances can increase the risk of overdose when mixed with opioids. Other substances, such as benzodiazepines and alcohol, can also increase the risk of opioid overdose.
- Report suspected adverse reaction to these or other health products to the Canada Vigilance Program of Health Canada at 1-866-234-2345, or by completing a Canada Vigilance Reporting Form (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php).
- Stay connected (https://www.canada.ca/en/services/health/stay-connected.html) with Health Canada to receive the latest advisories and product recalls.

Media Inquiries
Health Canada
(613) 957-2983
hc.media.sc@canada.ca (mailto:hc.media.sc@canada.ca)

Public Inquiries:
(613) 957-2991
1-866 225-0709

Date modified: 2019-09-17

Headache treatment handout
Written by Dr. Claire Sandoe, neurologist and headache specialist
Used with Dr. Sandoe's permission for teaching and clinical purposes
Handout provided by Dr. Mike Peterson, NeuPath Centre for Pain and Spine

Headache Treatment Plan Lifestyle:

1. Sleep: keep a consistent routine with the same bedtime and wake-up time including weekends, avoid napping. Consider trying the CBTi free app

2. Diet: don't skip meals, avoid artificial sweeteners, colors, and preservatives. Try to eat breakfast with 12-15 grams of protein within 30-60 minutes of awakening each day

3. Hydration: try to drink at least 1.5 litres of water each day

4. Caffeine: try to limit to 2 or fewer caffeinated drinks per day

5. Walk/move/exercise regularly

6. Stress management/mindfulness: even 5 minutes per day of mindfulness can be very
   beneficial for headaches

   - Apps: Headspace, Calm, Pacifica, StopBreatheThink, Mindshift, Smiling Mind, Sitting Still

   - Websites: www.dawnbuse.com ; www.smilingmind.com.au ; www.neuronovocentre.com ; w ww.mindful.ca ; choosemuse.com ; bigwhitewall.ca ; bouncebackOntario.ca ; MAST online program via St. Michael's Hospital

Headache Diary

Try keeping track of your headaches and any associated symptoms, triggers, and treatment effectiveness. The free app migraine buddy can be helpful, or use any paper calendar you like. Try looking back for 12 hours before the onset of your attacks to identify any triggers.

Internet Resources:

1. Canadian Headache Society: migrainecanada.org

2. American Headache Society: americanheadachesociety.org

3. American Migraine Foundation

Vitamins/Minerals

Several vitamins and minerals that occur naturally in the body have been studied and found to have benefit for migraine prevention. Not all vitamins are safe in pregnancy, and you should discuss these with your doctor if you are planning to become pregnant or if you become pregnant.

1. Magnesium citrate (may cause loose bowel movements). Start at 150mg nightly for 2 weeks, then increase to 300mg nightly, then up to a maximum of 450mg nightly. Patients with aura can try taking a dose of magnesium citrate 150mg at aura onset.

2. Vitamin B2 (riboflavin) (may cause bright yellow urine). Start at 100mg twice daily, then increase to 200mg twice daily

3. Vitamin D3 1000-2000 IU daily

4. Melatonin 3mg nightly 2-3 hours before bed [commentary by Dr. Peterson: melatonin can interact with many medications, including triptans, antidepressants for example, check with pharmacist and doctor before adding melatonin]

Acute Treatment

Most acute treatments, if taken too often, can lead to medication overuse headache (formerly called rebound headache), where your brain becomes dependent on the medication, starts to process pain differently, and the medications actually promote worsening of headache. You should try to limit your intake of medications such as ibuprofen, acetaminophen, and triptans to no more than 10 days per month total. Medications that include a narcotic such as codeine, for example acetaminophen with codeine or acetaminophen with oxycodone, can cause medication overuse headache when taken as little as 3 days per month.

Preventative Treatment

Most preventative treatments take 2-3 months to be effective. The goal of prevention is not to be headache-free, but to reduce the frequency and severity of your headaches.

Headache and pregnancy handout
Written by Dr. Claire Sandoe, neurologist and headache specialist
Used with Dr. Sandoe's permission for teaching and clinical purposes
Handout provided by Dr. Mike Peterson, NeuPath Centre for Pain and Spine

Headache and Pregnancy

Pregnancy and planning for pregnancy is an exciting time. Your healthcare team wants to help support you through this period, and to our best to help you to have a safe, healthy pregnancy. Some medications used when you are not pregnant can have a negative impact on you or a developing baby during pregnancy. This handout will help you understand some of the risks and benefits of headache treatments with respect to pregnancy and pregnancy planning.

Many women with migraine find that their headaches get better during pregnancy, often in the second and third trimesters. However, about 1/3 of women still have disabling headaches during their pregnancy, especially in the first several weeks. We will work with you to help find effective treatment strategies that are safe in pregnancy. We will try to balance the goals of a healthy pregnancy with a healthy mother – if you have severe headaches, it is harder for you to take care of yourself and your growing baby, and we want to help you enjoy this time.

If you notice a change in your headaches during pregnancy, speak to your healthcare team as soon as possible. The risk of more worrisome causes of headache such as preeclampsia or blood clots is increased during pregnancy. If you find that the way your headaches feel changes, they become more frequent, or you have new symptoms such as new neurological symptoms or auras, you should seek help right away.

Lifestyle

Fortunately, lifestyle modifications don’t need to be significantly changed during this time. Your sleep cycle may be interrupted by things such as increased need to urinate overnight. Maintaining your healthy habits will help keep headaches more manageable. During pregnancy it is ever more important to stay well hydrated and to eat more frequent smaller meals, especially with protein. Choose fresh foods over frozen over canned or processed/boxed foods. Try to eliminate caffeine, as then your body may be more responsive to safer medications such as acetaminophen combined with caffeine. If you experience nausea, avoid gingerale as the sodium benzoate it contains can trigger a migraine. Be sure to stay active and get into *Green Space* for walks and engage in mindfulness.

Vitamins

Not all vitamins are safe in pregnancy. Please talk to your healthcare team about vitamin dosing in pregnancy.

- Vitamin D: Vitamin D is typically safe in pregnancy, at doses from 1000 to 4000 IU daily.

- Vitamin B2 (riboflavin): We do not have good evidence about riboflavin use in pregnancy, but this is felt to be safe at lower doses of up to 100mg once daily.

- Magnesium: Recent studies have suggested that regular use of high-dose intravenous magnesium can lead to lower bone density in the developing fetus. We usually recommend that you either stop magnesium in pregnancy, or take much lower doses for this reason. It may be safe to take magnesium citrate 150mg once daily while you are pregnant; you should discuss this with your doctor. You can also consider taking magnesium citrate 150mg at headache onset.

- CoQ10: This is not well-studied in pregnancy and we do not recommend it due to concerns about increasing uterine contractions prematurely

- Melatonin: We do not have good evidence as to whether melatonin use is safe in pregnancy, and we therefore do not typically recommend melatonin during pregnancy.

- Folic acid: Folic acid has not specifically been studied in headache, but research shows that supplementation with 0.4 mg of folic acid prior to pregnancy can reduce the risk of some birth defects such as neural tube defects. The benefit is seen in women who begin to take folic acid several months before they become pregnant, so we typically recommend that any woman who could become pregnant take folic acid even before starting to plan pregnancy. Some women, such as those who have a family history of neural tube defects or are taking specific medications, should take a higher dose of folic acid. Speak to your doctor about the appropriate dose for you.

Non-medical therapies

- Cefaly: This TENS device stimulates the small nerves on your forehead and can be used to help prevent and treat migraine. It is felt to be safe in pregnancy since it has only a local effect on your nerves.
  Behavioral strategies: We continue to recommend meditation and mindfulness during pregnancy. Prenatal yoga may also be beneficial for both the body and the mind, if this is felt to be safe for you by your family doctor or obstetrician.
  Acupuncture: There is not good evidence to support acupuncture being effective in pregnancy. There are also some concerns about the possibility of miscarriage after acupuncture if the needle is placed inappropriately.

Acute Medications

- Triptans: There are only small studies of the triptans sumatriptan and rizatriptan in pregnancy. Different healthcare providers will recommend different things based on these studies. There was a trend towards an increased risk of early-pregnancy miscarriage and post-partum maternal bleeding with triptan use in some of the studies. However, this was not an entirely clear risk, and some headache specialists do recommend sumatriptan and/or rizatriptan in women with disabling headaches in pregnancy. This decision should only be made in discussion with your doctor. Our clinic finds that women who take a triptan and then have a (natural) miscarriage blame themselves for the pregnancy loss, whether this is related to the triptan or not, so we typically do not recommend triptans while you are pregnant except in special cases. When planning pregnancy, if your cycle is very regular, you can discuss with your health care provider how to use a triptan leading up to ovulation before you potentially conceive.

- Non-steroidal anti-inflammatories (NSAIDS): These include ibuprofen (Advil), naproxen (Aleve), aspirin, diclofenac (Cambia), nabumetone, and mefenamic acid (Ponstan), among others. We do not recommend NSAID use in pregnancy in general. These medications can increase the risk of early miscarriage before the end of the 1st trimester, and lead to risks of heart malformations in the 3rd trimester (premature closure of the ductus arteriosus) among others. Aspirin is sometimes recommended during pregnancy for women who have risk factors for specific conditions such as pre-eclampsia or blood clots, which you should discuss with your doctor. Otherwise, sometimes NSAIDs are felt to be safe in the 2nd trimester of pregnancy only. Again, it is best to speak to your doctor regarding these risks.

- Acetaminophen (Tylenol) is felt to be the safest option for women during pregnancy and can also be taken together with caffeine (Tylenol Ultra). Acetaminophen use should be limited to no more than 10 days per month to avoid medication overuse headache. There are some studies suggesting that using acetaminophen on a regular basis during pregnancy, or using acetaminophen in the 3rd trimester, leads to an increased risk of attention deficit hyperactivity disorder (ADHD).

- Codeine and other opioids such as Percocet are not recommended as they carry a high risk of medication overuse headache even when used as little as 3 days per month. There are also risks to the baby with high-frequency opioid use.

Anti-nausea medications

Metoclopramide: Metoclopramide is generally felt to be safe in pregnancy. You should not typically use this more than 3-6 days per month to avoid side effects such as unusual movements.

Preventative medications

Most commonly used migraine preventative medications are not safe in pregnancy. Of special note, Botox injections and the CGRP monoclonal antibody treatments (Aimovig and Emgality) should be stopped at least 6 months before you start trying to become pregnant since these medications are very long-lasting in the body and have not been proven safe in pregnancy.

If necessary, your doctor may discuss with you some less commonly used medications which are considered safe in pregnancy.

Other

Nerve blocks: A good option during pregnancy may be nerve blocks, using the local anesthetic lidocaine, to the occipital nerves at the back of your head. This can be used both as a treatment for a migraine lasting a few days, or on a more regular basis to help reduce your headache frequency and intensity.

You and your health care provider are partners in this Headache journey. Whenever possible, include your provider in your pregnancy planning to help achieve your best chance of headache control in pregnancy.

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Review Article

Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review

Rebecca Burch, MD

The peak prevalence of migraine occurs in women of reproductive age, and women experience a higher burden of migraine symptoms and disability compared to men. This increased burden of migraine in women is related to both developmental and temporally variable activational effects of female sex hormones. Changing levels of female sex hormones affect the expression of migraine during pregnancy, and, to a lesser degree, lactation, and are the mechanism underlying menstrual migraine. This review describes the evidence for sex differences in the expression of migraine across the reproductive epoch; reviews the epidemiology of migraine during pregnancy, lactation, and menses; and summarizes the available evidence for safety and efficacy of acute treatments during pregnancy and lactation and for menstrual migraine. Areas of controversy in treatment of migraine during pregnancy, including the use of magnesium, triptans vs butalbital combination medications, and onabotulinum toxin, are also explored.

Key words: migraine, treatment, epidemiology, pregnancy, lactation, menstrual migraine

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INTRODUCTION

Migraine is more common in women, with a sex prevalence ratio of around 3:1.[1] Although the diagnostic criteria for migraine are the same for men and for women, the clinical profile of migraine expression is more severe in women compared to men.[2-4] Women with migraine are more likely than men to experience longer headaches, migraine-accompanying symptoms, migraine-related disability, a higher burden of comorbidity, and worsening with age.[4,5]

Migraine incidence and prevalence increase around the time of puberty, an effect highly correlated with pubertal stage.[6-8] This correlation between pubertal stage and migraine incidence suggests that it is the influence of female sex hormones that leads to the increased burden of migraine in women.[9] The higher burden of migraine in women is believed to be related to both developmental and activational effects of female sex hormones. Developmental effects take place during a critical period and put a permanent stamp on the nervous system, while activational effects are the direct influences of circulating hormones that vary by hormone level.[9] Social factors, including life stress, intimate partner violence, and a history of adverse childhood experiences may also contribute to the higher burden of migraine in women.[10-13]

There is substantial evidence to suggest sex related and sex hormone-related differences in brain function

From the John R. Graham Headache Center, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (R. Burch).

Address all correspondence to R. Burch, John R. Graham Headache Center, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 1153 Centre St Suite 4H, Jamaica Plain, Boston, MA 02130, USA, email: rburch@partners.org

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that may affect pain perception and processing. MRI studies have found that the brains of females with migraine show more disordered function in the resting state network compared to the brains of males with migraine.[14] Connectivity between the default mode network and executive control network is modulated by phase of the menstrual cycle, and by OCP use.[15] In animal models, female mice have lower pain thresholds to thermal, chemical, and mechanical painful stimuli.[14,16] Estrogen lowers the threshold for cortical spreading depression (CSD), while testosterone raises it.[17,18] Females thus have a lower baseline resting threshold for CSD, and estrous phase may have an additional influence on susceptibility to pain via other mechanisms.[16,19,20]

While nearly half of women may experience migraine in their life, the expression of migraine in those women may vary over the course of a woman's life.[21] This may be related to natural fluctuation in symptoms but is also influenced by specific hormonal states. Menarche brings an increased incidence in girls, menstruation may be a trigger for individual attacks, stable high levels of estrogen during pregnancy may change the expression of migraine, expression of migraine often shifts in the postpartum period, and the menopausal transition often provokes an initial worsening of headache activity followed by sustained improvement.[9,22] This narrative review addresses the epidemiology and treatment of migraine during 3 of these hormonal epochs: menstrual migraine, migraine during pregnancy, and migraine during lactation.

MIGRAINE DURING PREGNANCY

Epidemiology of Migraine.—The prevalence of migraine is the highest in women of reproductive age.[23] An estimated 21-28% of women of reproductive age experience migraine each year.[23,24] Studies of the natural history of migraine during pregnancy show that up to 80% of these women will continue to have migraines at some time during their pregnancy.[25] Migraine tends to be most active during the first trimester and to improve as pregnancy progresses. Around 50% of women with migraine report improvement by the 12th week of pregnancy, and around 80% see improvement by the second trimester.[26] Evidence from prospective studies suggests that women with migraine with aura are a subgroup who may be less likely to improve.[27]

The phenotype of migraine may change during pregnancy.[28] Migraine with aura may present for the first time during pregnancy, an effect related to the decreased threshold for CSD due to rising estrogen levels.[29,30] A retrospective hospital-based study found that 70% of women who reported migraine with aura during pregnancy had no prior history of aura.[28]

While this review focuses on migraine during pregnancy, it is worth noting that pregnancy is a risk factor for many types of secondary headache.[31] One study of patients seeking acute evaluation for migraine during pregnancy found that 35% of the sample was ultimately diagnosed with a secondary headache.[28] Migraine is not protective against the development of secondary headache, and in fact migraine is a risk factor for the development of cerebral venous thrombosis (CVT), pregnancy-associated stroke, and preeclampsia.[32] Any new headache, change in headache type, or headache associated with hypertension, fever, or neurologic signs or symptoms should raise suspicion for secondary headache.[31] Noncontrast MRI can be performed with little risk during pregnancy, while CT is generally avoided when possible.[33] Gadolinium should be avoided during pregnancy due to embryocidal effects.[33]

Over one half of women with migraine will experience recurrence of headaches within the first month after delivery.[26] Most of these headaches are due to migraine, but increased risk for reversible cerebral vasoconstriction syndrome and preeclampsia/eclampsia persists for around 6 weeks into the postpartum period.[34] Postdural puncture headache is the most common cause of secondary headache in the puerperium, however.[35,36] In a retrospective hospital-based study of patients presenting for evaluation of headache in the postpartum period, secondary headache was diagnosed more often than primary headaches such as migraine.[36] It is therefore important to consider secondary causes of headache in the immediate postpartum period.

Several studies have examined the effect of migraine on risk of pregnancy outcomes. Migraine has consistently been associated with a 1.5-3-fold increased risk of preeclampsia and other hypertensive disorders.[37,38] Low birth weight and preterm birth are also more common, with odds ratios of 1.1-1.8 and 1.2-1.7, respectively.[37,38]

A Danish study using population-based registries to compare women with migraine to those without evaluated outcomes in infants within the first year of life.[37] This study found that intensive care unit stays, hospitalizations, respiratory distress syndrome, and febrile seizures were all slightly more common in infants born to women with migraine, with adjusted risk ratios of 1.2-1.3. Based on these findings, women with migraine should be monitored for the development of complications during pregnancy, particularly vascular conditions. There are no studies to support any specific intervention other than monitoring, however.

Approach to Treatment of Migraine During Pregnancy.—First-line interventions for management of migraine during pregnancy are optimization of lifestyle factors and introduction of nonpharmacologic techniques and therapies. Lifestyle factors that may reduce the burden of migraine during pregnancy include improvement of sleep duration and quality, maintaining regular meals and good hydration, and a good schedule of physical activity.[39] Nonpharmacologic treatments including relaxation training and biofeedback have shown efficacy for prevention of migraine and are most effective when practiced regularly.[40] Starting these techniques prior to conception ensures that the patient is able to use them early during pregnancy. Relaxation techniques are sometimes effective when used as an acute strategy early in a headache in addition to their role in migraine prevention. These behavioral techniques can be combined with pharmacologic treatments, and clinical trial data suggest that these approaches are more effective in combination.[41]

The effects of most medications on fetal development and pregnancy outcomes are poorly studied, and this is generally true of medications used for migraine as well.[42] The majority of available safety data come from observational studies due to ethical restrictions on the inclusion of pregnant women in clinical trials.[43] The paucity of data in this area has long been identified as a significant gap in medication safety literature. To address this, the European Innovative Medicines Initiative launched the ConcePTION project in June 2019.[44] This project is intended to "Build a pan-European ecosystem for generating, monitoring, and providing robust information on medication safety in pregnancy and breastfeeding."[44] Initiatives in the United States are also being considered. Until data from these projects are available, the best sources for information regarding pregnancy safety are databases such as ReproTox® (requires subscription, but often available through institutions).

Prior to 2014, the U.S. Food and Drug Administration used a letter ranking system, with A being best and X being worst, to summarize the safety of medications during pregnancy. This system was not replaced after retirement in 2014, and clinicians were instead advised to substitute their understanding of the available evidence.[45] Although the letter rating system is sometimes still used, it is increasingly out of date. In this review, a summary of the safety evidence has been used to categorize treatments as "preferred," "second line," "avoid when possible," or "always avoid."

Although it can be challenging to synthesize safety data for medications during pregnancy, it is important to adequately treat migraine during pregnancy. Migraine attacks with associated vomiting can lead to dehydration and electrolyte imbalances, particularly if they occur in the setting of poor intake related to pregnancy-associated nausea.[46] Treatment may reduce migraine-related presenteeism and absenteeism, particularly important given the backdrop of pregnancy-related job discrimination that women may experience.[47,48] Ongoing pain has also been associated with physical and mental health conditions both during pregnancy and after delivery.[49,50] Treatment of migraine should therefore be considered a necessary part of prenatal care.

Acute Treatment of Migraine During Pregnancy.—Table 1 summarizes the safety of acute medications during pregnancy. Several acute treatments have good evidence for safe use during pregnancy, including acetaminophen, metoclopramide, and diphenhydramine (used as an adjunct nausea and sedating rescue medication).[43] Acetaminophen has been associated with increased risk of attention deficit disorder in offspring, an effect that more strongly correlates with longer use and use in the third trimester.[43] Confounding by indication likely contributes to this association. As is the case with all acute medications during pregnancy, acetaminophen should be used for the shortest period possible to minimize any possible risk. Peripheral nerve blocks with lidocaine or ropivacaine are considered

Table 1.—Safety of Commonly Used Abortive Medications for Migraine During Pregnancy

Medication	Available Pregnancy Safety Information
Preferred	
Acetaminophen	Good evidence for safety. No increased risk of teratogenic effects, spontaneous abortion, or stillbirth. Case reports of prenatal closure of the ductus arteriosus reported with use during the third trimester; increased risk of early childhood respiratory disorders reported with frequent maternal use. Prolonged use and use in the third trimester associated with increased risk of attention deficit disorder
Diphenhydramine	Good evidence for safety. No increased risk of major congenital malformations or other adverse outcomes; possible neonatal withdrawal with prolonged maternal use in third trimester
Lidocaine SQ	Limited data; existing studies show no increased risk of major congenital malformations; animal studies showed no teratogenic effects
Metoclopramide	Good evidence for safety. Many studies; no increased risk of adverse pregnancy-related outcomes. May cause extrapyramidal signs and methemoglobinemia in neonates with maternal exposure during delivery
NSAIDs (ibuprofen, naproxen, diclofenac)	*During second trimester only*. Use in first trimester linked to increased risk of spontaneous abortion. Use in third trimester may cause premature closure of the ductus arteriosus. Ibuprofen has the best data for safety
Second line	
Triptans	Better evidence for safety than butalbital. No increased risk of major congenital malformations; studies conflicting about possible increased risk of premature birth; evidence best for sumatriptan, naratriptan, and rizatriptan
Butalbital	Triptans now preferred based on safety data. Long history of use in pregnancy. One large study showed possible increase in risk of fetal heart defects when butalbital used in periconceptual period; another large study showed no increase in risk. Withdrawal seizures and barbiturate withdrawal symptoms have been reported in infants following maternal use in the third trimester
Ondansetron	Conflicting evidence. No increased risk of spontaneous abortion or stillbirth; studies conflicting about possible increased risk of congenital heart malformations; the balance of evidence suggests against but study quality is challenging
Prednisone (short acting)	Likely safe with rare use, short duration. Avoid delayed release formulations. Increased risk of cleft lip or cleft palate, low birth weight; risks more strongly associated with chronic rather than episodic use; monitor infants for hypoadrenalism with chronic maternal use
Prochlorperazine	No increased risk of fetal malformations in good quality studies. May cause infant jaundice, reflex changes, extrapyramidal symptoms, and potentially severe withdrawal effects after maternal use in the third trimester
Promethazine	No increased risk of fetal malformations in good quality studies. May cause platelet aggregation inhibition, irritability, or extrapyramidal effects in infants after maternal use within 2 weeks prior to delivery
Avoid when possible	
Aspirin	Avoid for migraine treatment indication. Increased risk of fetal/neonatal hemorrhage, perinatal mortality by intrauterine growth restriction and teratogenic effects with chronic medium to high doses. In third trimester, may cause premature closure of the ductus arteriosus
Indomethacin	Poor evidence compared to other NSAIDs. Use in first trimester linked to increased risk of spontaneous abortion. Use in third trimester may cause premature closure of the ductus arteriosus
Opiates (oxycodone, hydromorphone, hydrocodone, codeine)	Avoid due to the risk of medication overuse; rare use unlikely to worsen fetal outcomes. Either no information regarding risk of fetal malformations or no increase in risk of major congenital malformations; neonatal abstinence syndromes seen after prolonged use in later pregnancy
Always avoid	
Ergots (dihydroergotamine, ergotamine)	Do not use. Former FDA pregnancy category X. Increased risk of spontaneous abortion

Information in this table obtained from Micromedex, Natural Medicine, and Reprotox databases.

safe and may be helpful in both rescue and preventive applications.[51] There is less evidence for safety of bupivacaine. Noninvasive devices have a benign safety profile and many providers feel comfortable using them during pregnancy. These devices include the supraorbital nerve stimulator and transcranial magnetic stimulators. Safety of these devices has not been formally studied, however.

Many NSAIDs, including ibuprofen and naproxen, are considered safe for use during the second trimester only. Use during the first trimester may increase the risk of miscarriage.[52] Use in the third trimester can lead to premature closure of the fetal ductus arteriosus. Opiates are generally avoided due to risk of overuse and neonatal abstinence syndrome, but rare use in the second and early third trimester is unlikely to cause significant problems.[43] Dihydroergotamine and other ergot derivatives are contraindicated during pregnancy as they cause decreased blood flow to the uterus and thus increase the risk of spontaneous abortion.

The antiemetics promethazine and prochlorperazine have not been associated with fetal malformations in good quality studies. The one study that did show a relationship had significant methodological problems. These are considered second-line agents because evidence for metoclopramide is more robust. Data regarding the effect of ondansetron on fetal malformations is conflicting.[53] Some studies have shown an increased risk of fetal heart malformations and cleft palate, while others show no such increased risk. The balance of evidence at this point leans toward safety, but enough concerns remain that ondansetron is not preferred during pregnancy.

Several population-based and registry studies support the safety of triptans during pregnancy.[54] In a 2015 meta-analysis including 4208 infants exposed to triptans, the authors found no increase in spontaneous abortions, major congenital malformations, or premature birth among triptan users compared to women with migraine who did not use triptans. A cohort study published in 2018 included 432 pregnant triptan users and also showed no increase in adverse outcomes related to triptans.[55] While the butalbital/acetaminophen/caffeine combination medication has historically been favored as the second line treatment for women during pregnancy, safety has not been rigorously studied. One available study instead raises safety concerns. A case-control National Birth Defects Prevention Study included 73 cases of butalbital exposure and 15 controls.[56] This study found a 3-fold increase in risk of congenital heart defects in infants exposed to maternal butalbital. Given the positive safety data for triptans, the uncertain safety data for butalbital combination medications, and the greater efficacy of triptans compared to butalbital, triptans are increasingly recommended for second-line treatment of migraine during pregnancy.[57]

Preventive Treatment of Migraine During Pregnancy.—Table 2 summarizes the safety of preventive medications during pregnancy. The medication with the best evidence for safety during pregnancy is propranolol, which is a former FDA pregnancy category C but has a long history of safe use. Many medications are considered second line due to either a combination of lack of evidence in humans combined with animal studies showing no teratogenic effects, or to harms in humans only documented in case reports.[58] Of the second-line treatments, coenzyme Q10, cyclobenzaprine, and memantine are likely the safest choices. Although memantine has not historically been used for prevention of migraine during pregnancy, it does have evidence for efficacy in migraine prevention. Cyclobenzaprine may be used as either a preventive or a sedating acute treatment. Other second-line choices, including amitriptyline, venlafaxine, and verapamil, are typically initiated or continued only if there is a significant need for treatment that outweighs the potential risks. Topiramate, lisinopril, and candesartan have all been conclusively linked to fetal malformations. Given the number of safer options, these medications are almost never continued through pregnancy. Sodium valproate was listed as an FDA pregnancy category X, meaning it should never be used for migraine prevention during pregnancy due to its teratogenic effects. Because half of all pregnancies are unintended, valproate should also not be prescribed to any women who is at risk for pregnancy. There is no evidence to suggest that the teratogenic risk of any oral preventive medication extends beyond its typical half-life. There is therefore no need for a prolonged oral preventive washout period prior to attempting pregnancy.

The safety of onabotulinum toxin A during pregnancy is uncertain. Available data come from a

Table 2.—Safety of Commonly Used Preventive Medications for Migraine During Pregnancy

Medication	Available Pregnancy Safety Information
Preferred	
Propranolol	Observational studies show small increase in risk of intrauterine growth retardation, small placenta, and congenital abnormalities; neonatal bradycardia, respiratory depression, and hypoglycemia with late term use
Second line	
Amitriptyline	Case reports of limb deformities, developmental delay but no causal relationship established. Monitor for infant irritability, urinary retention or constipation with late term exposure
CoQ10	Likely safe. Limited data; a single RCT of CoQ10 200 mg daily in the second half of pregnancy did not show increased risk of adverse fetal outcomes
Cyclobenzaprine	Likely safe. Preferred second line. No data in humans; animal studies showed no teratogenic effects
Memantine	Likely safe. Preferred second line. No data in humans; animal studies showed no teratogenic effects
Nortriptyline	Less information available than for amitriptyline; risks believed to be the same
Venlafaxine	No increase in fetal congenital malformations; possible increased risk of spontaneous abortion; neonatal seizures, neonatal abstinence syndrome, or serotonergic toxicity possible with maternal use in third trimester
Verapamil	No increase in fetal congenital malformations; may cause fetal bradycardia, hypotension, heart block; case report of congenital cardiomyopathy after IV treatment x2
Third line	
Gabapentin	Limited data; no increase in fetal congenital malformations; possible increased risk of preterm birth
Magnesium	Oral safety unclear; avoid intravenous use for >5 days Prolonged IV magnesium sulfate treatment associated with fetal skeletal abnormalities; oral magnesium not associated with increased risk of congenital malformations, but skeletal defects not specifically assessed
Pregabalin	Limited data; possible increase in major congenital malformations
Vitamin B2	Safety unknown. Safe at physiologic doses; no evidence for use at supraphysiologic doses
Avoid when possible	
Candesartan	Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants.
CGRP monoclonal antibodies (Erenumab, Fremanezumab, galcanezumab)	No data in humans; animal studies showed no teratogenic effects; concern based on animal studies that lowering CGRP levels may increase risk of preeclampsia
Lisinopril	Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants
Onabotulinum Toxin A	Use not currently recommended; limited data; registry data do not show an increased risk of major congenital malformations
Topiramate	Increased risk of cleft lip or palate, small for gestational age; concern for metabolic acidosis
Always avoid	
Feverfew	May cause uterine contractions and spontaneous abortion
Valproic acid	Always avoid. Former FDA Pregnancy Category X. Use for migraine prophylaxis contraindicated. Increased risk of neural tube defects, craniofacial defects, cardiovascular malformations, autism, decreased IQ, and other teratogenic effects

Information in this table obtained from Micromedex, Natural Medicine, and Reprotox databases.

postmarketing registry including 137 prospective pregnancies with known outcomes and 95 retrospective pregnancies, and from 16 cases of botulism poisoning during pregnancy.[59,60] These case reports of botulism poisoning suggest that botulinum toxin, which is a large protein, does not cross the placenta, although maternal botulism caused preterm delivery in 6 cases.[60] The prospective registry data found that rates of fetal malformations and pregnancy loss were similar to those seen in the general population.[59] The rate of pregnancy loss was 15.1% in the prospective onabotulinum toxin A registry vs 17.0% for the U.S. general population. Fetal malformations were seen in 2.7% of cases, and major fetal malformations in 1.8%, in the prospective onabotulinum toxin A registry, compared to 3% and 2%, respectively, in the general population. Although the registry data do not show an increased risk, the sample size is too small to show an increase in risk of rare but serious events. For this reason, most providers strongly prefer to withhold onabotulinum toxin during pregnancy. Onabotulinum toxin is active for approximately 12 weeks after injection, and should therefore be stopped about 3 months prior to attempting pregnancy.

The safety of calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) during pregnancy has not been determined. Animal studies did not show any increased risk but data in humans are lacking.[61] A postmarketing registry for pregnancy safety of erenumab was recommended by the FDA at the time of drug approval.[62] Animal and human studies suggest that CGRP levels may affect the development of preeclampsia.[63,64] Women with migraine are at higher risk for preeclampsia, and the effect of inhibiting CGRP during pregnancy is not known.[65] For this reason, CGRP mAbs should not be continued during pregnancy. These treatments have a long half-life, and the current recommendation is to withhold CGRP mAbs starting 4-6 months prior to attempted conception.

Magnesium has historically been recommended as a first-line treatment for prevention of migraine during pregnancy.[39] The pregnancy safety of oral magnesium has been called into question since 2013, however, due to an unclear FDA safety reclassification in 2014.[53] Prior to 2013, all forms of magnesium were rated as a pregnancy safety category A or B. Due to increasing evidence that intravenous magnesium sulfate for longer than 5 days increased the risk of fetal bone malformations, the FDA reclassified IV magnesium sulfate from a category A to a category D in 2013.[66] No statement was made about the safety of oral magnesium. Interpretations of this lack of comment on oral magnesium have varied, with some providers believing that all magnesium should be considered a category D and others believing that it is still a category A or B. The question of whether oral magnesium increases the risk of fetal malformations has not been specifically addressed. The FDA declined to comment on this issue in personal communications with the author, citing retirement of the letter categories.[67]

Herbs and supraphysiologic doses of vitamins and supplements are very poorly studied for safety during pregnancy.[68] Coenzyme Q10 demonstrated a positive safety profile in 1 small clinical trial.[69] Feverfew and butterbur should both be specifically avoided during pregnancy due to increased risk of miscarriage. Providers should be particularly cautious about supplements that combine multiple neutraceuticals. Many contain herbs that should not be used during pregnancy, and the ingredients are often not described by the product name.[70]

MIGRAINE DURING LACTATION

Epidemiology and Treatment Approach.—Two prospective studies have evaluated whether there is an effect of breastfeeding on migraine recurrence after delivery. A study including 208 women showed no effect of breastfeeding, while a study of 49 women found that breastfeeding was protective.[26,71] While the safety of migraine medications during breastfeeding is poorly studied, the evidence that is available suggests that, on balance, there are more options for treatment during lactation than during pregnancy.[53,72] Since there is no evidence to suggest that breastfeeding worsens migraine, and because there are many safe treatment options available, migraine is almost never a reason to withhold breastfeeding. The exception may be a woman whose migraines are refractory to typical oral treatments and who is dependent on onabotulinum toxin or a CGRP monoclonal antibody. Since the safety of these treatments has not been established during

lactation, the need to use such a treatment after pregnancy is one of the few clinical scenarios in which breastfeeding may need to be stopped due to migraines.

The National Library of Medicine Drugs and Lactation (LactMed®) database is a comprehensive, easy to use, and freely available resource for safety of medications during pregnancy (and the effect of medications on milk supply). It can be found at https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm (accessed August 12, 2019). The book "Medications and Mother's Milk" by Thomas Hale is another frequently used reference for medication safety during lactation.[73]

Acute Treatment of Migraine During Lactation.—Many frequently used acute medications for migraine are considered safe during lactation (summarized in Table 3). Acetaminophen, ibuprofen, and diclofenac are considered safe; there is less evidence for naproxen and indomethacin. Aspirin should be avoided as a first-line treatment due to risk of hemolysis and bleeding conditions in the newborn, although a recent study found infant exposure to be very minimal with low-dose aspirin.[74,75] Triptans have not been well studied during lactation but are categorized as "usually compatible" with breastfeeding by the American Academy of Pediatrics "Transfer of drugs and other chemicals into human milk" evaluation.[76] Eletriptan is more highly protein bound than other triptans and is theoretically less likely to be transferred into breastmilk.[72] Other safe treatments for migraine during lactation include peripheral nerve blocks or trigger point injections with local anesthetics. Lidocaine, ropivacaine, and bupivacaine are not excreted into breastmilk at high levels and are not well absorbed by the infant.[77] Noninvasive devices including nerve stimulators and transcranial magnetic stimulators are also compatible with breastfeeding based on their benign safety profile.

Antiemetics have varying effects on milk supply. Metoclopramide may increase milk supply and is sometimes used as a galactagogue to stimulate milk production.[78] It should be avoided in women who do not wish to breastfeed for the first 8 weeks after delivery. Prochlorperazine may also support milk production by increasing prolactin levels, but is typically considered a third tier medication due to the lack of evidence for safety.[79] Promethazine and diphenhydramine may both lower milk production.[80] Diphenhydramine should be avoided throughout breastfeeding, while promethazine could be used after milk supply is well established; it is less preferred due to lack of safety information.

Dihydroergotamine and other ergots should never be used during breastfeeding both due to effects on milk supply and due to reports of weakness in the infant.[81] Opiates may cause sedation in infants and are therefore not a first choice for migraine treatment. Codeine and hydrocodone may cause a rare but very serious opiate reaction in infants due to hypermetabolism in mothers, and should therefore be avoided.[82]

Infant exposure to acute migraine medications can be minimized by either pumping and discarding the milk once after medication use, or by taking the medication just before an anticipated longer stretch between feedings. Most acute medications considered second line do not require such precautions in healthy infants over 6-8 weeks of age when used at normal doses. If there are lingering concerns, the infant's pediatrician may also be a helpful resource.

Preventive Treatment of Migraine During Lactation.—Preventive medications considered compatible with breastfeeding, summarized in Table 4, include verapamil, propranolol, magnesium, and sodium valproate.[83] Amitriptyline is considered a second-line treatment due to concerns about sedation in infants. This concern generally decreases as the infant grows older. Topiramate was associated with infant diarrhea in one case report and was otherwise well tolerated by breastfeeding infants.

The safety of CGRP mAbs during breastfeeding has not been studied, although they are unlikely to be transferred to infant circulation via an oral route.[84] At this point the recommendation is therefore to withhold CGRP mAbs during lactation. Likewise, the safety of onabotulium toxin during breastfeeding is unknown.[85] The only available evidence is a case report describing a lactating woman who contracted botulism and who had no measurable botulinum toxin in breastmilk.[86] Some headache providers choose to withhold onabotulinum toxin during lactation, while others feel comfortable administering onabotulinum toxin after a documented informed consent discussion regarding risks and benefits.

Table 3.—Safety of Acute Migraine Medications During Lactation

Medication	Hale's Lactation Risk Rating	Available Lactation Safety Information
Preferred		
Acetaminophen	L1 (compatible)	Preferred. Infant exposure in breastmilk much lower than typically used therapeutic doses used for infants
Lidocaine SQ	L2 (probably compatible)	Compatible with breastfeeding
NSAIDs	L1 (compatible): Ibuprofen; L2 (probably compatible): Diclofenac; L3 (no data – probably compatible): Naproxen, indomethacin	Adverse events not reported in breastfeeding infants. Avoid in mothers of infants with platelet dysfunction or thrombocytopenia. Best evidence for ibuprofen; poor data for indomethacin
Second line		
Diphenhydramine	L2 (probably compatible)	Other agents preferred; monitor for drowsiness or irritability; may reduce milk supply
Metoclopramide	L2 (probably compatible)	Infants may experience intestinal discomfort and gas; monitor infants for extrapyramidal symptoms and methemoglobinemia
Ondansetron	L2 (probably compatible)	No evidence
Prednisone	L2 (probably compatible)	Generally considered compatible with breastfeeding; infant exposure less than 0.1% of maternal dose; can pump and discard for 4 hours if concern remains
Triptans	L3 (no data – probably compatible)	No information available; eletriptan is likely to have lowest concentrations in breastmilk; avoid long acting triptans (naratriptan and frovatriptan); option to discard pumped milk 12 hours after dose if high concern
Avoid if possible		
Aspirin	L2 (probably compatible)	Other agents strongly preferred. Avoid chronic use; with occasional use, monitor infant for hemolysis, prolonged bleeding, metabolic acidosis
Butalbital	L3 (no data – probably compatible)	Concern for sedation in infant
Opiates (Morphine, Oxycodone, Hydromorphone)	L3 (no data – probably compatible): Oxycodone, hydromorphone;	Morphine preferred; Monitor infants for respiratory depression
Prochlorperazine	L3 (no data – probably compatible)	Effects unknown; other agents strongly preferred
Promethazine	L3 (no data – probably compatible)	Other agents preferred. May cause sedation or irritability in infants. May interfere with establishment of milk supply
Always avoid		
Ergots (dihydroergotamine, ergotamine)	L4 (potentially hazardous)	Avoid; may cause gastrointestinal distress and weakness in infant; may suppress milk production
Opiates (Hydrocodone, Codeine)	L3 (no data – probably compatible): hydrocodone; L4 (potentially hazardous): codeine	Codeine was associated with 1 fetal death; hydrocodone metabolized through same pathway as hydrocodone; monitor infants exposed to codeine for sedation, apnea, bradycardia, cyanosis

Information in this table obtained from Micromedex, Hale's Medications and Mother's Milk, and the Lactmed database, and from "The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics," 2103, Hari Cheryl Sachs, MD, FAAP*, and COMMITTEE ON DRUGS.

MENSTRUAL MIGRAINE

Definition and Epidemiology.—On a population level, migraines are more likely to occur in women during the menstrual cycle.[87] This effect is driven by a group of women who have migraines strongly time linked to the menstrual cycle (menstrual migraine). The International Classification of Headache Disorders differentiates between 2 types of migraines related to the menstrual cycle.[2] The classification criteria for pure menstrual migraine and menstrually related migraine are found

Table 4.—Safety of Commonly Used Preventive Medications for Migraine During Lactation

Medication	Hale's Lactation Safety Rating	Available Lactation Safety Information
Preferred		
Propranolol	L2 (probably compatible)	Compatible with breastfeeding. Monitor infant for bradycardia, hypoglycemia
Magnesium	L1 (compatible)	Safe; levels in breastmilk not affected by dietary intake
Verapamil	L2 (probably compatible)	Compatible with breastfeeding. Exposure less than 1% of maternal dose
Second line		
Amitriptyline	L2 (probably compatible)	May be compatible. Report of infant sedation at maternal doses as low as 10 mg/day. Second line for migraine prevention; monitor infant for sedation, poor feeding
Cyclobenzaprine	L3 (no data – probably compatible)	Low levels in breastmilk; monitor for sedation though this has not been reported
Gabapentin	L2 (probably compatible)	Possibly compatible; monitor infant for sedation, poor feeding
Topiramate	L3 (no data – probably compatible)	Infant watery diarrhea in 1 case report; all other case reports described good tolerability.
Valproic acid	L4 (potentially hazardous)	Generally compatible with breastfeeding. Monitor infant for jaundice, hepatoxicity, hematologic abnormalities
Vitamin B2	L1 (compatible) at physiologic doses	No evidence for supraphysiologic doses
Avoid if possible		
Nortriptyline	L2 (probably compatible)	Infant serum concentrations exceeding 10% of maternal plasma concentrations
Pregabalin	L3 (no data – probably compatible)	May cause poor feeding
Venlafaxine	L2 (probably compatible)	Infant serum concentrations exceeding 10% of maternal plasma concentrations; Use during lactation generally restricted to migraine with psychiatric comorbidity
Avoid due to lack of evidence		
Candesartan	L3 (no data – probably compatible)	
CGRP monoclonal antibodies (erenumab, fremenezumab, galcanezumab)	N/A	Per the LactMed database: "Because [CGRP mAbs are] large protein molecules … the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract."
CoQ10	L3 (no data – probably compatible)	
Feverfew	N/A	
Lisinopril	L3 (no data – probably compatible)	
Memantine	L3 (no data – probably compatible)	
Onabotulinum Toxin A	L3 (no data – probably compatible)	No evidence; current recommendation is to avoid use though practices differ

Information in this table obtained from Micromedex, Hale's Medications and Mother's Milk, and the Lactmed database.

in Box 1. Both types of migraine appear in the appendix of the ICHD. Menstrual migraine is diagnosed when migraine attacks occur from 2 days prior to 3 days after onset of menses. If the attacks do not occur at other times of the month, it is classified as pure menstrual migraine. It is classified as menstrually related migraine if attacks also occur at other times of the month. The second edition of the ICHD only recognized migraine without aura as having a menstrual relationship, but the third edition allows either migraine with or without aura.[88] Pure menstrual migraine is estimated to occur in about 8% of all women with migraine, or 1-2% of the female population, with 13% of women with migraine or 5-7% of the female population having menstrually

Box 1 Classification Criteria for Pure Menstrual Migraine and Menstrually Related Migraine

Pure Menstrual Migraine
- Attacks fulfill criteria for migraine with or without aura
- Occur only on days −2 to +3 of menstruation in at least 2 out of 3 menstrual cycles and at no other times of the cycle.

Menstrually Related Migraine
- Attacks fulfill criteria for migraine with or without aura
- Occur on days −2 to +3 of menstruation in at least 2 out of 3 menstrual cycles, and additionally at other times of the cycle.

Adapted from the International Classification of Headache Disorders, 3rd edition

related migraine, though estimates vary widely based on methodology.[89-91]

Why menses are a strong trigger for headaches in some women is not completely understood. Diary studies show that in addition to migraine, headaches with a tension-type phenotype are more common during menses.[92] The postovulatory estrogen decrease is also associated with increased migraine activity.[87] Fluctuations in female sex hormones are therefore the clear underlying cause for the menstrual peak in headache activity, but whether migraine attacks are triggered directly by declining estrogen; by downstream effects on endogenous opioid tone, prostaglandin levels, altered responsiveness of cerebral vasculature to serotonin, and/or sensitivity of dopamine and serotonin receptors; or a combination of these and other mechanisms is unclear.[14,93-95] A diary study including 262 women who were using combined hormonal contraceptives (CHCs) with less than 35-mcg ethinyl estradiol (EE) found that headaches during the hormone free ("placebo") week were very common, with 70% of women reporting headaches.[96]

Many women report that their menstrual migraines are more severe and refractory to treatment compared to migraines that occur at other times of the month.[97-99] The question of whether menstrual migraines are characteristically different has been examined in both diary and epidemiologic studies. These have shown that menstrual migraines are more disabling, longer, and associated with more nausea than migraines that occur outside of the menstrual window.[97,100] Several randomized controlled trials (RCTs) have examined treatment response to triptans in women with menstrual migraine.[101] The results from RCTs including at least 3 different triptans did not support decreased efficacy for triptans in menstrual migraine.[102-104] Diary and questionnaire studies, however, show that women report lower rates of pain freedom, sustained pain freedom, and pain relief when taking triptans to treat menstrual migraine compared to nonmenstrual migraine.[99,100,105]

Nonhormonal Treatment of Menstrual Migraine.— Many menstrual migraines respond well to triptans and do not persist. It is therefore reasonable for the initial treatment approach to menstrual migraine to be similar to that of nonmenstrual migraine. Most of the triptans have been studied as treatments for menstrual migraine and have shown efficacy vs placebo.[101] Frequency of triptan use can be liberalized beyond the typically recommended 2-3 days/week during the menstrual week. Many women are able to successfully treat their migraines using maximum daily triptan dosing for several days in a row.

If treatment with triptans and/or NSAIDs and antiemetics is ineffective, short-term prevention (also called mini-prophylaxis) is often the next step.[106] Scheduled dosing of triptans, particularly the long-acting triptans naratriptan and frovatriptan, have good evidence for efficacy in preventing menstrual migraine.[106,107] Zolmitriptan, a shorter acting triptan, has also shown efficacy in clinical trials. Frovatriptan has an advantage over the other triptans in that the allowable maximum daily dose is 3 times the single dose strength. This allows treatment of breakthrough migraines with an additional triptan dose, which is not possible with either naratriptan or zolmitriptan dosed BID. Scheduled dosing of the

NSAIDs naproxen and mefenamic acid has also been studied, with moderate evidence for benefit.[108-110] As triptans and NSAIDs can be taken together, NSAIDs can be used to treat migraines that break through triptan prophylaxis and vice versa. Anecdotally, one caution is that some women develop withdrawal headaches at the end of an extended period of scheduled acute medications. The mini-prophylaxis approach is usually not helpful for women in whom this effect occurs.

Preventive treatment regimens for menstrual migraine, both hormonal and nonhormonal, are listed in Table 5.

Hormonal Treatment of Menstrual Migraine.—The finding that declining estrogen levels are correlated with migraine activity has led to two hormonal treatment strategies for prevention of menstrual migraine. Both are aimed at limiting the decline of estrogen in the menstrual week. Two clinical trials have evaluated whether supplementing low-dose estrogen during the menstrual week is effective.[111,112] Both trials of a 1.5-mg estradiol gel used the menstrual week were positive. There are several CHC formulations that include supplementary estrogen during the "placebo" week. These have not formally been studied for prevention of menstrual migraine but may be tried. An increasingly common strategy is suppression of hormonal cycling via the use of continuous or extended duration monophasic CHCs. The effect of continuous monophasic CHCs for 168 days was evaluated in 2 studies.[113,114] Both studies showed a reduction in headache burden. This approach is more commonly used in clinical practice than replacement estrogen, likely because there are other potential health benefits related to menstrual suppression, and because many women find it convenient.[115]

Women and the providers who care for them often have questions about what effect a specific exogenous hormone formulation will have, if any, on migraine expression.[116] Unfortunately, the effect of different combinations of exogenous estrogen and progestogen on migraine is poorly studied; the quality of evidence is universally low.[117] Given that caveat, progestogen only formulations may be associated with a lower burden of headache in women with migraine.[117,118] Cyclic use of high-dose estrogen, 50-mcg EE, was found to exacerbate menstrual migraine.[119] Modern CHCs typically use much lower doses of EE and it is not clear whether the menstrual effect is also decreased. Studies evaluating tolerability of individual

Table 5.—Treatment Strategies for Menstrual Migraine

Medication	Dosing Regimen	Level of Evidence
Hormones		
Ethinyl estradiol 1.5 mg gel	Start 2 days prior to expected onset of menstrual migraine, total of 7 days	2 positive trials
Combined hormonal contraceptives with continued low dose estrogen during "placebo" duration	28-day cycle	Not formally studied for migraine prevention
Extended duration/continuous combined hormonal contraceptives	Continuous, possibly with q 90-day hormone-free interval	Not formally studied for migraine prevention
Triptans		
Frovatriptan 2.5 mg	BID or daily starting 2 days prior to expected onset of menstrual migraine, total of 5-6 days	Level A in 2012 AHS guidelines
Naratriptan 1-2.5 mg	BID starting 2-3 days prior to menses, total of 5-6 days	Level B in 2012 AHS guidelines
Zolmitriptan 2.5 mg	BID-TID starting 2 days prior to menses, total of 7 days	Level B in 2012 AHS guidelines
NSAIDs		
Mefanamic acid 500 mg	TID, started at the onset of menstrual migraine and continued for duration of menses	1 positive trial
Naproxen 550 mg	Daily-BID for 5 days	1 positive trial, 1 negative

preparations of CHCs do not typically collect information about headache in a systematic and detailed manner. Further complicating this question, initial worsening of migraines after initiation of a CHC may improve after several months.[120] Clinical practice suggests that an individual patient's response to a specific CHC is unpredictable and idiosyncratic. At this time, there is no evidence to support withholding CHCs in a woman with migraine unless she has migraine with aura.[117]

SUMMARY

The expression of migraine in women varies over the course of a lifetime. The developmental effects of female sex hormones lead to a female predisposition to migraine that persists throughout the reproductive period. Within this epoch, fluctuations in hormones related to menses and to reproductive events change the expression of migraine. Life events also have a significant effect on the expression of migraine. Although pregnancy, lactation, and menstrual migraine are often considered "special situations" in migraine treatment, most women with migraine experience at least one of these situations over the course of their life. More research is needed to better guide women regarding treatment safety during pregnancy and lactation. Regardless, women should be reassured that numerous pharmacologic and nonpharmacologic treatments are available.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Rebecca Burch

(b) Acquisition of Data

Rebecca Burch

(c) Analysis and Interpretation of Data

Rebecca Burch

Category 2

(a) Drafting the Manuscript

Rebecca Burch

(b) Revising It for Intellectual Content

Rebecca Burch

Category 3

(a) Final Approval of the Completed Manuscript

Rebecca Burch

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PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF HEADACHE WITH PAIN (D BUSE, SECTION EDITOR)

Exercise and Migraine Prevention: a Review of the Literature

Mark Barber[1] · Anna Pace[2]

Abstract

Purpose of Review This review intends to characterize the recent literature pertaining to the role of aerobic exercise in the prevention of migraine. Areas of consensus within that literature may be used to guide clinical practice, allowing for the promulgation of evidence-based practice recommendations.

Recent Findings The past decade has seen the publication of numerous high-quality studies that explore aspects of exercise's effects on migraine prevention, including its success as a stand-alone prevention strategy, as well as its non-inferiority to some pharmacologic preventive measures.

Summary Exercise often tops providers' lists of recommended lifestyle modifications that help reduce migraine burden. Biologically, exercise suppresses inflammatory modulators, including numerous cytokines, and stress hormones, like growth hormone and cortisol. Exercise has also been shown to affect microvascular health, which may be implicated in cortical spreading depression. Psychologically, there is evidence that exercise improves migraine self-efficacy and internalizes the locus of control, leading to reduced migraine burden.

Randomized control trials have demonstrated that a sufficiently rigorous aerobic exercise regimen alone is sufficient to yield a statistically significant reduction in migraine frequency, intensity, and duration. Higher-intensity training appears to confer more benefit. Studies have also demonstrated non-inferiority of exercise compared with certain pharmacologic prophylactic interventions, like topiramate. However, the addition of exercise to a traditional preventive regimen may provide added benefit. Special populations, like those with comorbid neck pain or tension headache, may benefit from exercise; and patients who cannot tolerate high-impact exercise may even benefit from low-impact exercise like yoga. Therefore, exercise is a reasonable evidence-based recommendation for migraine prevention.

Keywords Migraine · Aerobic exercise · Low-impact exercise · Yoga · Exercise-induced migraine

Introduction

Aerobic exercise is often promoted to patients as an effective management strategy, either alone or in combination with medication, for the prevention of both episodic and chronic migraine [1]. This review seeks to characterize the recent literature surrounding this topic in an effort to present consensus practice recommendations, if possible, and to suggest avenues for continued investigation.

Despite near-universal agreement that regular aerobic exercise should be included among the management strategies offered to patients with migraine, this consensus belies a paucity of agreement on specifics [2••]. Open questions include which individuals might benefit most from exercise, whether there is a dose-response relationship, and whether there is an ideal type or duration of exercise. Additional questions include whether exercise is appropriate as a stand-alone preventive strategy, whether there is a synergistic benefit when it is combined with pharmacotherapy, and what biological and/or psychological mechanisms underlie the observed benefits. Answers

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✉ Anna Pace
anna.pace@mssm.edu

[1] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

[2] Center for Headache and Pain Medicine, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

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are confounded by inconsistent study designs and outcome measures in the available literature.

These questions nonetheless remain urgently relevant. Migraine is extraordinarily prevalent and burdensome, with some estimating that approximately 13% of the US population has been affected by migraine [3]. Its attendant economic impact and effect on quality of life are significant. Although patients with migraine have been found to exercise less than the general population, investigators have found that they are more likely to engage in complementary and alternative medicine practices, like yoga [3]. Adding to these seemingly contradictory observations is the fact that many patients are medication-adverse and may prefer to initially try nonpharmacologic interventions for migraine prevention. There is a pressing need for clarity surrounding the role that exercise may play in migraine prevention.

Mechanisms

Numerous investigators have sought to characterize the mechanisms that underlie the perceived benefit exercise has on migraine. These mechanisms can be divided into two categories: biological and psychological. Further research is needed in both of these domains, but a 2016 review by Irby and colleagues offers a helpful explication of proposed mechanisms by which exercise may prevent migraine. They suggest that a better understanding of these mechanisms will offer guidance in the creation of more effective exercise regimens for migraine prevention [2••].

Biological Mechanisms

Biological pathways explaining how exercise improves health exist in both the exercise literature and migraine literature, and represent a mechanistic nexus that may tie the two domains together. A neuroinflammatory model is described in Irby's 2016 review, suggesting that since elevation of certain inflammatory markers (CRP), cytokines (CGRP, substance P), and adipocytokines (TNF-a, IL-6) has been observed in the setting of migraine, perhaps the well-demonstrated suppressive effect of regular aerobic exercise on these same inflammatory mediators may explain improvement in migraine frequency, duration, and intensity over time [2••].

A neurovascular pathway has also been proposed to explain how exercise may positively affect migraine [4]. Investigators note that migraine has been associated with an adverse vascular risk profile, including "endothelial dysfunction, impaired cerebral and peripheral vascular function, as well as an increased risk for hypercoagulability and inflammation" [4]. The researchers developed multiple exercise regimens and sought to elucidate whether exercise intensity affected number of migraine days per month. A secondary outcome was those regimens' effects on retinal vessel diameters, which have been validated as microvascular biomarkers of cardiovascular health. The investigators focus on microvascular outcomes because changes in small cerebral vessels have been postulated to trigger cortical spreading depression, one of the proposed mechanisms of migraine pathogenesis. With results showing that higher-intensity exercise regimens led to significant retinal arteriolar dilatation as well as reduction in migraine days, the authors concluded that there is a link between improved cerebral blood flow and reduction in migraine frequency [4].

In a 2011 study, investigators crafted a 10-week aerobic exercise regimen for migraine patients in an effort to prove the preventive effects of exercise on migraine [5]. They base their hypothesis on research that has shown that long-term aerobic exercise raises people's pain threshold through mediation of stress hormones like growth hormone, and to a lesser extent, ACTH, cortisol, and prolactin [6]. The authors sought the input of sports scientists to design a regimen that would increase physical fitness. The authors use PWC 150 (physical cardiopulmonary working capacity) as a measure, which describes the mechanical cardiac output of a person at a fixed heart rate of 150 beats per minute, measuring it before and after a 10-week training phase and correlating the regimen's implementation with improved migraine outcomes including frequency, duration, and intensity. It is suggested, then, that improved physical fitness from exercise can improve migraine on a biological level.

Psychological Mechanisms

Biological and psychological effects of exercise on migraine are not mutually exclusive. The two categories are a useful artificial distinction that may, in reality, be more of a continuum. Biological pathways have been harnessed to explain the psychological and behavioral benefits of aerobic exercise on migraine.

Noting the comorbid psychiatric factors that often exacerbate disability in migraine patients (like anxiety), a 2017 study examined whether the investigators' prior findings regarding the elevation of the proinflammatory cytokine IL-12p70 in women with migraines could be tempered by engagement in a regular moderate aerobic exercise regimen [7]. Not only did they find that exercise helped to prevent migraine and reduce anxiety symptoms, but they also found that these favorable outcomes were accompanied by a corresponding, and statistically significant, reduction in plasma IL-12p70 levels. They postulate, then, that this inflammatory cytokine may be correlated with anxiety and elevated migraine frequency, so by modifying this, exercise may exert both a biological and psychological benefit.

Even while studies have demonstrated how exercise may reduce the production of neuromodulators like

proinflammatory cytokines, others have demonstrated how exercise may promote production of beneficial neuromodulators like endorphins. Köseoglu and colleagues launched their investigation into the relationship between exercise, endorphins, and migraine incidence by citing an earlier study that correlated cerebrospinal fluid beta endorphin levels with disease severity, where higher beta endorphin levels are negatively correlated with disease severity [8]. Although they could not definitively correlate changes in endorphin levels with changes in headache parameters, they did find that patients with lower basal endorphin levels before the exercise intervention seemed to benefit more from exercise compared with other participants. This is interesting because it addresses one of the fundamental questions posed by research, namely determining which migraine patients would be expected to benefit most from an exercise regimen.

Additional work has been done investigating the intersection of exercise and its effect on subjective psychological markers like self-efficacy, locus of control, outcome expectations, and perceptions of psychological stress and mood in patients with depression. Irby and colleagues note that there is well-established literature demonstrating improved migraine control in patients who have better headache self-efficacy and internal headache locus of control [2••]. A 2010 study demonstrated that the addition of a behavioral migraine management program to standard preventive medication dramatically increased participants' perception about their ability to manage their migraines [9]. Although the authors did not evaluate an exercise regimen, they promoted the benefit of their behavioral program as it relates to headache self-efficacy. They note that broadly speaking, interventions to increase a patient's sense that his or her own behavior can influence migraine control can in fact lead to improved control. Irby and colleagues subsequently use this study to suggest that exercise, which they note had previously been proven to improve self-efficacy among patients with depression, could similarly be harnessed to improve self-efficacy among patients with migraine, and potentially reduce migraine burden [2••].

Exercise Alone for Migraine Prevention

In clinical practice, exercise is often recommended as one among numerous interventions for migraine prevention, in combination with other lifestyle modifications as well as prophylactic pharmacotherapy. However, many of the studies over the past decade that investigate the relationship between aerobic exercise and migraine examine exercise as the sole strategy for prevention of migraine. This research design helpfully minimizes other variables that may confound the relationship between exercise and migraine prevention, though it limits the generalizability of the results.

Investigators surveyed the existing literature in 2008 to see whether ubiquitous recommendations regarding exercise in migraine prevention were based on sufficient and accurate data [1]. The investigators found nine studies and five case reports that pointed to exercise as an effective intervention for prevention of migraine. Numerous factors limited the ability to extract generalizable conclusions, including the fact that some studies did not use ICHD criteria for migraine diagnosis, there was wide variation in the migraine measures tracked, and many studies were underpowered. The review was ultimately unable to recommend physical activity alone as a prevention strategy for migraine, suggesting "multidisciplinary therapies in long-time pain disorders and migraine are considered to be superior to a single treatment option." This review was important because it offered suggestions for how to more systematically design and assess future research, but exercise alone could not be recommended as an evidence-based preventive approach at that time.

Fast-forward to 2019 when another group of investigators undertook a similar project to survey the interval literature since Busch's essential 2008 review [10••]. In the studies examined by Lemmens and colleagues, many of the limitations that characterized earlier studies had been corrected: headache measures were more standardized, studies were better powered, and conclusions were more clinically applicable. This was a systematic review meta-analysis specifically designed "to investigate the result of aerobic exercise on the number of migraine days, duration and pain intensity in patients with migraine" [10••]. The analysis included six important studies, by Bond, Darabaneanu, Hanssen, Kroll, Santiago, and Varkey, many of which are discussed here and elsewhere.

Despite variability in the exercise regimens investigated by each study (jogging, cross-training, cycling, and some in combination), authors universally measured exercise intensity with physiologic tools like the Borg scale of perceived exertion, maximum oxygen uptake (VO_2 max), and others. There was also consistency among migraine measures tracked, including "the number of migraine days, attack duration, pain intensity and the use of analgesic medication." Thanks to greater consistency in study design, unlike Busch a decade earlier, these investigators were ultimately able to conclude that there was moderate quality evidence that aerobic exercise decreases number of migraine days. Specifically, three out of six included studies reported a statistically significant decrease in number of migraine days per month, ranging from a decrease of 22 to 78%. The pooled data suggested a mean decrease of 0.6 ± 0.3 migraine days per month in the overall intervention groups. The authors found moderate-to-low-quality evidence that exercise can improve pain intensity, noting a decrease of 20 to 54%. They also found low-quality evidence that exercise can shorten attack duration, noting a decrease by 20 to 27% on average, with one included study citing a decrease of 20 migraine hours per month post-

treatment. These lower-quality conclusions were limited by the heterogeneity of data regarding those metrics from the individual included studies [10••].

One of the studies included in the Lemmens meta-analysis studied exercise when used as a prevention/treatment strategy for more than just migraine alone [11]. Patient populations with comorbid tension-type headache and neck pain, they postulated, could benefit from an exercise regimen as treatment for their pain syndromes. The investigators recruited participants with a minimum of two migraine days per month plus at least 1 day of tension-type headache and 1 day of neck pain per month. Seventy patients were recruited and were randomized into exercise and control groups. They completed three 45-min sessions per week for 3 months; one session each week was supervised by a physiotherapist and the other two could be completed at home or a gym. Regimens consisted of a combination of cross-training, biking, and brisk walking, whose intensity was confirmed by Borg scale. (The Borg scale is a validated numerical scale of perceived exertion that accounts for differences in baseline fitness levels among users.) The investigators found a statistically significant decrease in migraine days from 9.2 to 7.2 per month after intervention [11]. This study is noteworthy because the significant population of patients with migraine who experience comorbid neck pain and/or tension headache may experience similar benefits as those with migraine, both for their migraine and for their other pain syndromes.

Exercise Compared with Traditional Preventive Therapy

Other investigators have sought to compare the effectiveness of aerobic exercise with traditional pharmacologic strategies for migraine prevention. In 2011, investigators compared exercise with topiramate for prevention of migraine [12•]. Patients were randomized into exercise, topiramate, and relaxation technique groups. The exercise regimen consisted of a 40-min cycling session three times weekly, and intensity was measured using VO_2 max. In the topiramate group, the medication dose was increased weekly by 25 mg as tolerated to a maximum dose of 200 mg per day. The primary efficacy outcome was reduction in migraine attacks per month. Investigators found a mean reduction in migraine attacks by 0.93 per month in the exercise group, a reduction by 0.97 per month in the topiramate group, and a reduction by 0.83 per month in the relaxation technique group [12•]. These results were not statistically significant compared with baseline, nor was there a statistically significant difference among the three groups. Investigators acknowledged that their results may have been limited by the need for a larger sample size (91 patients were randomized) to appreciate subtle differences among groups, even though the study was adequately powered. Nonetheless, the finding that there was no difference between pharmacotherapy and exercise for prevention of migraine attacks is worthy of mention here and may suggest that exercise is as efficacious as topiramate and relaxation for migraine prevention.

Santiago and colleagues wondered whether aerobic exercise in combination with a standard preventive medication could yield improved migraine control in patients with chronic migraine [13]. They randomized participants into two groups: amitriptyline alone (25 mg daily) and amitriptyline plus exercise. The exercise regimen consisted of 40 min of fast walking three times weekly for 12 weeks, with intensity measured by the Borg scale, along with measures of heart rate during the first and last walks, as well as one meeting with a physiotherapist [13]. Since this study examined patients with chronic and not episodic migraine, many had been overusing abortive medications, so there was a medication washout leading up to the study. During the study itself, patients were only allowed to use naproxen no more than twice weekly as an abortive. Investigators ultimately found statistically significant improvement on nearly all measures among the amitriptyline plus exercise group, including headache frequency, duration, and intensity. Improvement in secondary outcome measures was also observed, including body mass index and mood inventories [13]. This study is noteworthy because many of the other studies mentioned in this review examined episodic and not chronic migraine; it lends credence to the notion that exercise is a worthy adjuvant to a standard pharmacologic prevention strategy for patients with chronic migraine.

Types of Exercise

One of the unanswered questions about using exercise as prevention for migraine, and one of the more vexing questions for providers attempting to counsel patients about the benefits of exercise, is what type of exercise is most protective. Few investigators have sought to compare the effectiveness of different types of exercise among subjects in the same study. More commonly, investigators craft an aerobic exercise regimen, and use that specific regimen as a representative of all physical exercise. It seems reasonable to suspect, however, that there may be variation in the benefits conferred by different exercise regimens. A future investigation may consider pooling studies by exercise type or intensity and comparing improvement in migraine incidence based on those measures.

A 2018 study was one that sought to compare exercises of different intensities and their effect on migraine prevention [4]. The investigators sought the input of their sports medicine colleagues in crafting two distinct exercise regimens into which they could randomize participants. They compare the effect on migraine frequency using high-intensity training

(HIT) versus moderate continuous training (MCT) in people with episodic migraine. Enhancing the quality of this study is that patients were actually blinded as to which exercise group they had been randomized (though controls were not blinded). Participants were excluded if they were already on pharmacologic prevention or already participated in regular exercise. The investigators concluded that there was more pronounced migraine day reduction in the HIT group compared with the MCT group, where the HIT group showed a decrease in migraine days from 3.8 to 1.4, and the MCT group showed a decrease in migraine days from 4.5 to 3.2. The investigators employed a magnitude-based interference analysis that suggested there was an 89% likely beneficial reduction in migraine days for HIT compared with MCT [4]. This study suggests that higher-intensity aerobic exercise may be more beneficial for migraine prevention.

No other studies surveyed for this review compared multiple exercise regimens with each other, though there was wide variation in the types of regimens deployed. Darabaneanu used a jogging regimen (three times weekly, 50 min per session including a warmup and cooldown period) that increased in intensity over the course of the study as participants' exercise tolerance increased, and found improvement in number of migraine days per month [5]. Kroll used a cross-training regimen that included biking, cross-training, and brisk walking, and was tailored to the participants' exercise tolerance. At least one out of three sessions weekly had to be biking and at least one also had to be cross-training, but the investigators left the exact makeup up to the discretion of the participant. They also found a statistically significant reduction in migraine days per month [11]. Santiago used a fast-walking regimen that provided improvement in migraine days per month when combined with amitriptyline compared with amitriptyline alone [13]. Varkey used an indoor cycling regimen that did not demonstrate significant improvement in migraine days per month when compared with topiramate or relaxation [12•]. Köseoglu used a treadmill regimen tailored to the exercise tolerance of participants and found a significant decrease in migraine days per month [8]. On the whole, then, the data available do not point to one specific type of exercise that is more effective in migraine prevention than another. Most regimens consisted of three sessions per week, meeting some minimum intensity threshold. Further studies warrant a more rigorous exploration of this topic.

Exercise as Migraine Trigger

Some patients do anecdotally report that exercise may induce migraine attacks, and there have been some studies suggesting certain exercise may be considered a trigger for migraine-type attacks. One study by Koppen and colleagues found that in a population of 103 patients, the lifetime prevalence of migraine attacks triggered by exercise was 38% [14]. Of those patients with exercise-induced migraine, 56% found the migraine to begin during the exercise; of those with migraines that began after exercise, the average length of time prior to onset was reported to be 160 min after cessation of exercise [14]. The study also found that neck pain was often an initial symptom described by these patients during their normal attacks as well as their exercise-induced migraines. The type of offending exercise was not well described in this study, but researchers did report that almost half of those patients with exercise-induced migraine stopped playing the sport or participating in the exercise regimen [14].

There are some proposed mechanisms to why exercise may induce migraine attacks. The production of lactate during exercise may play a role, as one study has shown that a higher frequency of migraine correlates with increased brain lactate levels [15]. A second theory invokes calcitonin gene-related peptide (CGRP); CGRP levels rise during exercise and reportedly may cause muscle soreness experienced by people who exercise; however, CGRP has not been directly measured in patients who experience migraine during exercise, so its role is still not entirely clear [15]. A third theory proposes that the rise in systolic blood pressure and cardiac output can trigger a migraine as it has been suggested that patients with migraine have "impaired control of cerebral vasculoreactivity" [14]. Despite these theories, the data available are not sufficient to describe the mechanism further in detail, and so the pathophysiology of exercise-induced migraine is still not fully understood.

Low-Impact Exercise and Migraine

One might deduce, then, that for these patients with exercise-induced migraine attacks, low-impact or nonaerobic exercise may still afford some benefit. Yoga, for example, is a low-impact exercise that has some data for prevention of primary headache syndromes, along with other conditions that are often comorbid with migraine, including fibromyalgia, anxiety, and depression. A meta-analysis conducted in 2012 looked to evaluate the effect of yoga on pain-associated disability in pain conditions. Sixteen studies were included, and researchers concluded that overall yoga was found to have positive effects on pain and pain-related disability, most notably for patients with headache, back pain, muscle soreness, and irritable bowel syndrome [16]. Focusing on one study included in the aforementioned meta-analysis, a randomized controlled trial of seventy-two patients with migraine without aura assigned patients to either a self-care group or a yoga group for 12 weeks. The yoga group sessions involved traditional yoga poses along with yoga breathing 5 days a week for an hour each session. Researchers found that the patients in the yoga group had a reduction in headache frequency, pain

intensity, and symptomatic medication use and lower anxiety and depression scores [17]. The proposed mechanism for how yoga can improve pain for patients involves improvement in flexibility, strength, and coordination, as well as its psychological effects of reducing stress and anxiety and improving mood [16]. Interestingly, researchers postulated that if patients are able to be physically active despite the chronic pain they experience, they may feel improved self-awareness and self-competence which improves their quality of life [16]. Therefore, it may be prudent to consider recommending a yoga practice for those patients either with particularly debilitating chronic migraine or with exercise-induced migraine attacks.

Conclusions

In the past decade since the Busch review [1], there have been rich new contributions to the existing migraine prevention literature by investigators who have employed more rigorous randomized control study designs, chosen more consistent study populations based on ICHD criteria, and tracked similar markers of migraine burden, like migraine frequency, intensity, and duration and the use of analgesia. Despite agreement about high-level findings regarding exercise and migraine prevention in the studies included in this review, a wide variety of research questions on numerous aspects of this topic remain incompletely answered.

Returning to the list of questions posed by Irby and included in the "Introduction" section of this review, some answers now nonetheless start to emerge to help guide clinical practice [2••]. Regarding which individuals might benefit from exercise, studies have shown that exercise can be beneficial whether alone [5, 8, 11] or in combination with medication [12•, 13]. It may be especially beneficial for those with low basal plasma endorphins [8], or even as part of an umbrella treatment strategy for those with comorbid neck pain and/or tension headache [11]. Overall, studies seem to suggest exercise may be useful in the treatment of episodic migraine, with some suggesting it can be helpful in patients with chronic migraine when incorporated as an adjunct to traditional pharmacotherapy. Regarding whether there is a dose-response relationship, there is evidence that high-intensity training may be more effective than moderate continuous training [4]. There seems to be less evidence about the best type or duration of exercise, but there is evidence that despite assumptions about aerobic exercise being preferred, even low-impact exercise like yoga may have preventive effects [17]. This is an especially useful consideration for patients who may be subject to exercise-induced migraine. Additional research is needed to further clarify the underlying mechanisms by which exercise helps prevent migraine, as well as to explore which exercise regimens are most effective.

Taken together, what does all this mean for clinical practice? Most reassuringly, it means that when providers advise their patients that exercise will aid in the prevention of their migraines, the advice is not merely an informed suspicion, but rather an evidence-based recommendation. A conversation about exercise can help patients exert some volitional control over a condition that may often seem prone to the whimsy of a mysterious personal biology or the many pills they have been prescribed as an attempted remedy. The recommendation to engage in aerobic exercise comes with a favorable side effect profile, as well as the promise that the therapeutic alliance has not yet been exhausted of tools to continue the fight against migraine.

Compliance with Ethical Standards

Conflict of Interest Mark Barber and Anna Pace declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Talking points with patients: Visit 2

Introducing non-opioid/non-pharmacological treatments

Bringing up the topic	**Introduction:** "I want to work with you to provide the best possible pain management plan.[1] This means reviewing how you are doing on your treatments." **For patients with incomplete pain relief or side effects on opioids:** "From what you have been telling me, these medications aren't as effective as you would like. Let's think about trying something different."[1]
Explaining the benefits of non-pharmacological treatments	• "Opioids aren't the best treatment for pain in the long term. They probably won't take away your pain completely. And for most people, their effects wear off over time. I'd like to try some new approaches to see if we can do better." [1] • "Patients who expect drugs to control their pain are usually disappointed. With or without chronic pain, my patients who are doing better use multiple approaches. Let's talk about what might help you be able to do more things that you enjoy." [1] • "We are learning that active options that patients have more control over can be more effective over the long-run than prescriptions for pain medications that carry greater risks." [1] • "A person with chronic pain is like a car with four flat tires. Medication only puts air in one of the tires. You need to fill the other three tires. Self-management programs, support groups, cognitive behavioral therapy, acupuncture, massage, sleep, physical activity, yoga, and nutritional support are a few ways to fill the tires. Of those options, did one stand out to you?" [2]
Offering non-opioid/non-pharmacological resources	"There are a lot of things that make pain worse, like not sleeping well, or doing too little or too much exercise. When the pain is really bad, people do things that make it worse, like shallow breathing, tensing muscles, and thinking that the pain will never get better. These resources have helped other patients of mine with chronic pain. They give a lot of different ideas for ways to manage chronic pain:" [1] • "Better choices, better health": an online self-management program: https://www.selfmanagementontario.ca/ • "Understanding pain in 5 minutes, and what to do about it": https://www.youtube.com/watch?v=C_3phB93rvI
Understanding what patients mean by "I tried it, but it didn't work"	"To make sure we consider all options in managing your pain, let's discuss other treatments you have tried in the past and how they worked for you. Tell me what happened when you tried this treatment." Probe for details as needed: • "How long did you try the treatment?" • "What dose you were taking? (for medications)" • "How often were you using it? (for all treatments)" • "What was your pain on a scale of 0 to 10 before trying this treatment, and how did this change with treatment? How about your function?" • "How well did it work compared with other treatments you tried?" • "Did you have any side effects, and if so, did they interfere with your daily activities?" • "Why was the treatment stopped?"[3]

Starting opioids: Explaining a "trial" and eliciting expectations

Explaining an "opioid trial"	"Opioids may or may not help you, and they have some risks. This is why we usually do what is called a 'trial'. We will start the medication slowly and gradually increase the dose to see if we can find a dose that improves your pain and function without causing side effects that you can't live with."[4]
Eliciting expectations about benefit	Gather information about patient expectations: • "How are you hoping that this medication will help you?" • "How much improvement are you expecting in your function and pain?" • "How important is this benefit to you?" [4] Help patient to focus on function and quality of life rather than just on pain: • "What activities are you hoping will be easier to do after you start this medication?" • "What would you be doing if you had less pain?" [10]
Eliciting expectations about risk	"What have you heard about the risks of these medications?" "Is there anything that worries you about starting opioid treatment? What difficulties do you think you might have?" [4]
Explaining potential benefits of opioids	**Reduced pain**: "Opioid medications may or may not help with your pain. With treatment, we may be able to reduce your pain by about 30% or a couple of points on the pain scale, for example, from a 7 to a 5 (out of 10)." [4] **Improved function:** "With treatment, we hope to improve your ability to do the activities that are important to you. However, the effect of the medication on function may be small. Function can improve even when pain is still present. It's important not to overuse the medication, or function may actually get worse." [4,5]
Explaining limitations of opioids	• "If you don't respond to opioids within about 3 months, we are going to taper you off of these medications." [6] • "For most people, the benefits wear off as the body gets used to the medications. Then they're stuck on a medicine that isn't really doing much for them." [1] • "There is no good evidence that that opioids improve pain or function with long-term use. [4] Risks of harms, however, persist."
Explaining potential harms of opioids	**Common side effects:** "The most common side effects are nausea and constipation. These can usually be managed by using anti-nausea drugs and anti-constipation drugs while on an opioid. Anti-nausea drugs are generally used short-term until the nausea side effect wears off. Anti-constipation drugs are generally used long-term while you are on the opioid." [4] **Long-term side effects:** "Long-term use of opioids can lead to serious problems such as accidental overdoses, sleep disorders, memory loss, weak bones, sleep problems, car accidents, and increased sensitivity to pain. It can also decrease your sex drive and fertility." [4]

	Overdose risk: "We used to think the dose didn't matter if we went up slowly, but now we know higher doses lead to higher risks of serious injuries and accidental death. And higher doses don't seem to reduce pain over the long run." [1] **Addiction risk:** "We used to think people suffering from pain did not become addicted to prescription pain medicines. We now know that you can become addicted to pain killers used for chronic pain, even if you haven't had problems with drugs or alcohol in the past." [1] **Overdose:** "Avoid mixing opioids with alcohol or sleeping pills because this increase the risk of overdose. Signs of overdose include slurred or drawling speech, becoming upset or crying easily, poor balance, or "nodding off" during conversation or activity." [4] **Driving/operating machinery:** "Don't drive while your dose is being gradually increased or if the medication is making you feel sleepy or confused." [4] **Withdrawal:** "If you stop taking your medication abruptly, you will experience withdrawal symptoms. This may feel like the flu: nausea, diarrhea, and chills. Withdrawal can be uncomfortable, but it is not dangerous. It does not mean that you are addicted, just that you stopped the drug too quickly. If you stop your medication for 3 days or more, check with me before restarting it, because restarting opioids at your usual dose can have a significant risk of overdose and even death. The same thing can happen if you try to return to a higher dose that you used previously." [4] **Safe storage:** "Your body will get used to the dose that we set for you, but this same dose can be very dangerous for others. Store your medication safely at home; consider storing it in a lockbox, especially if there are children in the home. Do not store it in the medicine cabinet, as others will know to look for it there. Do not share your medication with others." [4] **Naloxone:** "We recommend that you keep naloxone on hand in case of an accidental overdose. Naloxone is a medication that can reverse the effects of an opioid. You can get naloxone at your local pharmacy without a prescription. The pharmacist will show you and your family how to safely use and store it." [4,7]
Introducing the treatment agreement	"To help us tell whether the opioid trial is working for you, we will use a treatment agreement together. A treatment agreement helps outline safeguards as well as our goals and expectations for the trial, and how the trial will work." [4]

Setting SMART goals when starting opioids

Framing the conversation to focus on SMART goals	• "Let's work together to come up with some goals for your pain management plan. This will help us be on the same page about what to expect from your treatments and whether they are working." [11]
	• "We'll make better progress if we use something called "SMART goals". You may have heard of SMART goals. They are goals that are **S**pecific, **M**easurable, **A**ction-oriented, **R**ealistic, and **T**imed. This allows us both to see clearly whether we are on track to meeting a goal."
	• Examples:
	  ○ "I'd like to be able to take my kids to the playground for a half-hour every week by the end of this month."
	  ○ "I would like to walk from my couch to my front door at least once a day by the end of this month."
	  ○ "I would like to be able to return to work 3 days a week within the next 2 months." [8,9,10]

Setting SMART goals for pain and function	• Focusing on function: "When choosing your goals, it can help to focus on function rather than pain. Think about what you'd like to be doing if pain were less of an issue." [10] • Finding a support person: "Sometimes it can help have someone check in with you and hold you accountable for achieving your goal. This person doesn't need to be a healthcare provider; it could be someone supportive in your life. Can you think of someone who might be able to do that?" [11] • Testing if a goal is SMART: ○ "What would we be able to specifically see you do once you've met your goal?" [11]
Identifying clinically meaningful changes and setting expectations.	• "It's important to focus on your ability to function and your overall well-being rather than just a number on the pain scale. That's because there's a limit to how much medications and other treatments can reduce pain scores. [10] Usually we can expect a 30% decrease at most, or a couple of points on a 10-point pain scale. [5] When people get caught up in the numbers, it can lead to a vicious circle where they search for a solution to a problem that cannot be fully controlled. What you can control is how you learn to cope." [10]
Providing positive reinforcement for effort	• "You've worked really hard towards your goal." • "You've made a real commitment to reaching your goal." • "You didn't give up, even when things get tough." • "You've really come a long way since we started." [12]

Saying "No" when an opioid is not indicated

General tips	• Maintain professionalism: Don't back down, don't become defensive, and don't argue. • Take a deep breath. Keep your voice and body language calm. • Keep the focus on the patient's safety and optimal pain management. [13]

Getting to "No": Use the "Elicit-Provide-Elicit" technique	**If you have already set a boundary to not prescribe an opioid for this patient at this time, state this up front:**
	"Your safety is highly important, and I would not feel comfortable prescribing an opioid for you at this time. I would like to begin exploring the other options, as well as your expectations and goals."
	
	Elicit how patient feels they would benefit from an opioid:
	• Explore the patient's underlying concerns and expectations.[14] Ask probing questions (use "what" and "how" rather than "why", as this tends to put the patient on the defensive).
	  ○ "You mentioned you would like to try an opioid. How are you hoping it will help you?"
	  ○ "You're interested in trying an opioid. What benefits do you hope to get from the opioid?" [15]
	• Paraphrase the patient's responses to ensure you have understood.
	• Use "disarming statements":
	  ○ "I see your point."
	  ○ "I can understand that."
	  ○ "Your concern is understandable."
	  ○ "I hear you." [15]
	Provide information on why you are not recommending an opioid right now:
	• "Opioids may seem like they are very strong and effective drugs for pain; however, they are not effective for all types of pain. When opioids are effective, your pain may be reduced by about 2 or 3 points on a scale from 0 to 10 and you may notice a small improvement in your ability to function. They also come with risks, and sometimes this means that opioids are not a safe and effective approach for pain relief. I would not feel comfortable prescribing an opioid for you at this time. I would like to begin exploring the other options, which could work better for you."[16]
	Elicit the patient's thoughts:
	• "How do you feel about trying some non-opioid options? What do you think makes sense for you right now?" [16]

How to respond to "But I've tried everything else!" or "But nothing else works!"	**Explore what "tried it" means. Was there an adequate trial (adequate dose, duration, and support)?** • See scripts for "Understanding what patients mean by "I tried it, but it didn't work'", above. • Ask whether the treatment was used as part of multidisciplinary pain management strategy including non-pharmacological therapy and support. If not, the chances of an optimal response are lower. [17]

	• Keep in mind that while pain intensity may respond within 2-4 weeks on optimal doses of medication, improvements in function can take longer.[3] **Explore whether the patient's expectations were reasonable (i.e., were they expecting the treatment to get them to "zero pain"?).** • "How much improvement were you expecting from the treatment in your function and pain?"[10]

Transitions from acute to chronic pain management

Key counselling points for opioids in acute pain[18]	SET EXPECTATIONS "Some pain is normal. You should be able to walk and do light activity, but may be sore for a few days. This will gradually get better." SET NORMS "Usually opioids are only needed for up to 3 days, and rarely more than 7 days." NON-OPIOIDS "Take acetaminophen and ibuprofen around the clock for the next 24-72 hours, and use the stronger pain pills only as needed for breakthrough pain." *Note: Avoid NSAIDs in patients with active peptic ulcer disease and associated risk factors (smoking, drinking), NSAID-related bleeding risk, renal disease, and specific operations at surgeon discretion (e.g. those that result in high risk of post-surgical bleeding).* APPROPRIATE USE "These pills are for pain from your surgery, and should not be shared or used to treat pain from other conditions." [Or substitute "injury" or "dental procedure" for "surgery" as required] ADVERSE AFFECTS "We are careful about opioids because they have been shown to be addictive, cause you harm, and even cause an accidental overdose." SAFE DISPOSAL "Disposing of these pills prevents others, including children, from accidentally overdosing. You can bring the pills to your pharmacy, or mix pills with kitty litter in a bag and throw them in the trash."[18]
How to explain why opioids should not be used long-term for acute pain	"In most cases, opioids should not be used for more than 3 to 7 days. Three days is usually enough to treat the pain, and more than 7 days is rarely needed. If opioids are used for longer periods of time, your body will become dependent on them, and it can be hard to stop taking them. [19] It's a good idea to avoid using opioids over the long

	term, because the longer you take opioids, the higher your risk of serious problems such as accidental overdoses, sleep disorders, memory loss, falls, sleep problems, car accidents, increased sensitivity to pain, and decreased sex drive."[20]
Transitioning patient expectations from acute to chronic pain management	"If you have just had surgery or an injury, pain is a natural and expected part of the process. Sometimes, this short-term pain can cause changes in the body that make the pain last much longer than expected, beyond the point where it serves a useful purpose in the body. This is called chronic pain.[21] Treating chronic pain is different from treating short-term pain. With chronic pain we will focus more on your ability to function than on the level of pain. While opioids may sometimes be used for short-term pain, they are not the best way to treat long-term pain. Instead, we will use a combination of options to give you the best possible pain management, including medications and non-medication options such as yoga, mindfulness, and pacing your activities.[4] If our treatment plan is working, you can expect small gradual improvements in your ability to function and your pain to go down by about 2 or 3 points on a 10-point scale.[5]"
How to explain loss of opioid benefit over time with chronic use	"For most people, the benefits of opioids wear off over time as the body gets used to the medications. Then they end up stuck on a drug that isn't doing much for them."[1]
How to explain why you are deprescribing opioids when original reason for opioid use is resolved	"Opioids are an option for treating pain, but when the reason for the pain is gone, opioids are no longer the best option. There is no proof that they work well over time. And the longer you use opioids, the higher your risk of side effects such as fatigue, depression, falls, car accidents, low sex drive, or sleep problems.[19] Other treatments may work better than opioids and have fewer risks. That's why in your case, it may be time to consider slowly reducing the dose of opioids."[21]

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Talking points with patients

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Assessing readiness for a taper

a. Introduce the topic: "As your healthcare provider, it's my job to help you manage your pain, but also to be mindful of how pain medications can harm you, sometimes in ways that are hard to recognize."[1]
b. Assess readiness to taper: "For all my patients, I check in from time to time to make sure the benefits of opioid pain medications still outweigh the risks. In your case, it may be time to consider reducing the dose. **On a scale of 0 to 10, how ready are you to consider that?"**
c. Tailor the discussion/intervention to the level of readiness to change[2,3]

Precontemplation[2]		
Score*	Technique	Talking points
0-3	Elicit patient's perceived negative consequences	"What has been the downside for you of taking opioids for pain? Have you noticed any problems with your focus, energy levels, memory, or sex life?"
	Express concern for the patient's health	"I'm concerned about the risk of harm from the opioid dose you are on."
	Offer information	"Would you like more information about the risks and how opioids could be affecting your health, even if you use them carefully?"
	Support and follow-up (offer help without pressure)	"I understand that you aren't ready to talk about opioid tapering today and that's OK. I would like to ask about it again at your next appointment. Is that OK?"

* Score = Patient's answer to the question "On a scale of 0 to 10, how ready are you to consider that?"

Contemplation[2]		
Score*	Technique	Talking points
4-7	Elicit patient's motivation to change	• Express empathy: "It sounds like you might want to explore the idea of tapering, but have some concerns." • Explore ambivalence by asking about pros and cons: ○ "What do you like about the idea of tapering?" ○ "How do you think things will improve once we have reduced your opioid dose?" ○ "In your mind, what are the possible downsides of tapering?" ○ Ask why they chose that score out of 10: "Why a 5 and not a 2?" "Why a 5 and not a 9?" • Develop discrepancy: ○ "On one hand, you're concerned about being on a high opioid dose, but on the other hand you're worried about what could happen to your pain control if you try to reduce the dose." ○ "You mentioned that being more alert is important to you. Opioids can affect your central nervous system –

		they may be causing fatigue or lessening your ability to do daily activities. It is common to see one's alertness and function level go down when the opioid dose goes up." ○ "Sounds like your pain has not improved even with the high dose you have been trying. It may be time to consider a lower dose." [7]
	Negotiate a plan	• Respect autonomy by offering choices: "Would you prefer to reduce the morning or evening dose?" • Roll with resistance: ○ "Sounds like you feel this could be difficult." ○ "You're not happy about the idea of reducing your dose."
	Offer support and follow-up	Support self-efficacy: "You've shown a lot of strength and determination in learning other ways to manage your pain. These strengths can help you with opioid tapering."

* Score = Patient's answer to the question "On a scale of 0 to 10, how ready are you to consider that?"

Preparation and Action[2]		
Score*	Technique	Talking points
8-10	Help patient develop an action plan	• Introduce the topic by reminding the patient of their own motivation to taper: "You don't like the way opioids affect your focus at work and you'd like to reduce your dose. Let's discuss our plan to do this." • Discuss expectations • Develop a tapering plan
	Identify resources/support	• Explain that you will be providing support to the patient during the taper (be clear about what form the support will take and how much support is reasonable) • Identify other support people: "Who's been supportive of you before? How could this person help as we start the opioid taper?"
	Instill hope	"You've shown a lot of strength in learning to manage your pain. This strength can help you do the opioid taper. And once we're done you may even find, as many people do, that you have less pain and better function than before."

* Score = Patient's answer to the question "On a scale of 0 to 10, how ready are you to consider that?"

Talking points with patients

Discussing an opioid rotation, taper or discontinuation[4]

Switch	"Sometimes a medication is appropriate when it is started but becomes less appropriate as time goes on and things change. I usually review my patients' pain medications regularly to make sure they are still on the best treatment for them. At this point, it seems that you might benefit from switching to a different opioid. How would you feel about that?"
Taper/ Discontinuation	"Sometimes a medication is appropriate when it is started but becomes less appropriate as time goes on and things change. I usually review my patients' pain medications regularly to make sure they are still on the best treatment for them. At this point, it seems that your opioid medication is no longer giving you enough benefits to warrant the risks of using it. How would you feel about trying to slowly decrease the dose?"

Talking points with patients

Teach-back approach

Plan your approach	Before the patient's visit, consider when and how you will use teach-back. In general, it's a good idea to use teach-back whenever you explain an important concept. [5]
Chunk and check	Chunk information into small segments and have your patient teach it back (rather than waiting until the end of the visit). [5]
Ask the patient to explain things in their own words (using simple, non-judgmental language)	• "We talked about opioid rotation today. I want to make sure I explained the benefits and risks of opioid rotation clearly. Can you tell me how you would explain tapering to a friend or family member?" • "I want to make sure I was clear about the possible withdrawal symptoms you may experience during an opioid taper. Could you tell me about the possible withdrawal symptoms you may have and what you can do if they happen?" • "I want to check how well I explained our plan for managing your pain during the opioid taper. Please tell me, in your own words, about the options we discussed for managing your pain."[6]
If teach-back shows the patient does not understand, explain again a different way	• "I must not have done a good job explaining. Let me try again." • Explain the information a second time using a different approach (e.g., make a simple drawing, show a model, or demonstrate the behaviour) • Use teach-back again to test for comprehension. [6]

Talking points with patients

Eliciting patient expectations

Frame the conversation around external benefits/harms[7]	• "I want to make sure your pain management is as safe as possible." • "I want to help you get back to your regular activities." [8]
Provide information about why a taper might be needed	• "Chronic pain is a complex disease and opioids alone cannot adequately address all of your pain-related needs." [9] • "Taking high doses of opioids may not provide good pain relief over a long period of time. The amount of pain relief from opioids can become less at higher doses because of tolerance. Sometimes, opioids can actually cause your pain to get worse. This is called *opioid induced hyperalgesia*." • "Most of the evidence for benefits with opioids in chronic non-cancer pain has been with relatively low doses, and higher doses often tend to cause more harm than good."[9] • "The many side effects of opioids, such as fatigue, depression, falls, car accidents, low sex drive, or impaired breathing during sleeping, increase with higher doses. Sometimes people using opioids do not connect certain side effects to the medication. That is why many people who try a gradual taper to lower doses, report less pain, and better mood, function and overall quality of life. Sometimes, it is only after such a taper that patients appreciate how opioids were not helping as much as they thought."[10] ○ Tip: The fact that opioids can cause low testosterone and tapering could increase testosterone levels can be motivating for men who may otherwise be resistant to tapering.[11] ○ Tip: Patients are more motivated by concrete, specific risks (e.g., "Your memory may not be as good, and your focus may not be as good") than abstract risks (e.g., "studies show that risks are greater than benefits at higher doses").[11] ○ Tip: Patients perceive a low risk of overdose and prioritize the immediate risk of increased pain with opioid tapering.[12]
Ensure patients have clear expectations of tapering	• "Dose reduction or discontinuation of opioids could lead to withdrawal symptoms and during this time your pain may get worse for a brief period, but your pain will improve as your withdrawal symptoms improve." • "This pain may be the same pain you are being treated for, as well as total body joint and muscle aches. The pain associated with withdrawal generally passes in most people within 1-2 weeks, and is lessened by tapering doses very slowly. Many people report that the pain that the opioid was originally being taken for does not worsen when opioids are reduced. We will develop a plan for managing pain you may experience during tapering. This plan may include other medications, non-drug pain treatments, as well as support from our healthcare team."

	"Opioid withdrawal symptoms can be very unpleasant but are generally not life threatening. However, they sometimes cause people to seek opioids from non-medical sources, which can be very dangerous. Withdrawal symptoms are similar to a flu-like illness and can begin 6-36 hours after your last dose of opioid. Some people will feel generally tired and unwell for several weeks and may feel "down" or not quite themselves for several months, particularly if they have been taking very high doses of opioids."[11] • "We will lower the dose gradually and adjust the rate of the taper to how you are doing." • "We are not necessarily going to stop the opioids altogether, but lower them to a safer dose that improves mood and function while still keeping the pain manageable."[8]

Talking points with patients

Navigating difficult conversations

Situation	What you can do to help

Patient feels intimidated by the situation and surroundings	• Set the stage for collaboration:
	  ○ Sit beside the patient
	  ○ Use open non-threatening body language and a calm voice
	  ○ Ask questions with a neutral tone
	  ○ Pay attention to the patient's non-verbal cues of discomfort
	• Use active listening skills and reflect the patient's words back to show you are listening:
	  ○ "It sounds like there's a lot of stress in your life right now."
	  ○ "You're saying the pain is making you feel desperate and edgy."
	  ○ "I know you're going through a tough time right now, and I'm really sorry to hear about that."[13]

Patient feels like they are being attacked	• Emphasize your concern for the patient's safety. [13]
	• Acknowledge the patient's pain experience and express empathy,[10] but do not let it change your decision to taper opioids.[14]
	• Explain that your main goal is to support them and help them safely and effectively manage their pain.
	• Reframe the issue as a biomedical problem rather than a moral failing, and offer help without blame.
	• Actively involve them in decision-making, and treat them as valued partners and members of the care team.
	• Use "Elicit-provide-elicit" technique:
	  ○ Elicit: "Would it be okay if I told you about…"
	  ○ Provide information: "It may seem hard to believe, but if we pull back on the opioids you may actually feel better that you do now."
	  ○ Elicit feedback: "What are your thoughts about that?" [13]

Patient feels abandoned during the taper	• Provide an alternate plan to show that you still support your patient. Encourage non-pharmacological therapies; offer non-opioid medications. Potentially, advise the patient that the pain may resolve on its own without opioids. Referring to a colleague for a second opinion may be helpful. Refer to an addictions medicine specialist if necessary. • Provide reassurance that the opioid will be tapered slowly to minimize withdrawal symptoms. Aim to be polite but firm! [13]
Patient becomes aggressive or angry	General tips: • Stay in the medical expert role. • Express concern for the patient's safety. • Speak to what is behind the patient's comment, not the comment itself. • Validate hard feelings and provide reassurance[15] • If you feel pressured or threatened, it's OK to excuse yourself from the room and/or confer with a colleague. [16, 14] • Avoid responding to emotion with emotion, and avoid prescribing emotionally. Try to keep your feelings and the medical facts separated. [14] • Where possible, separate the conversation about prescribing from the actual act of prescribing.

	Responses to specific concerns:
	• "Are you accusing me of being an addict?"
	  ○ "I've never accused people of diabetes but I've diagnosed them with it, and that is what I'm trying to do now, diagnose."
	• "Do you want me to have to get these medications from the street?"
	  ○ "I want you to have safe and effective pain control and it is my medical opinion that your current medicine won't give you that, and that it will be safer for you to slowly reduce your dose."
	• "Do you want me to lie awake all night in pain?"
	  ○ "I know you're suffering and I'm sure we can work together to reduce pain so you don't have to suffer. I know it seems hard to believe, but many people find their pain improves after tapering opioids."[15]

Patient threatens/implies inability to cope without opioids	• Boundaries are established in part to prevent manipulation. The threat may be real, manipulative, or both.
	• Drug seekers are often highly skilled at getting what they are desperate for; however, expression of this desperation reveals the need to change approach to treatment of pain which now has an added psychiatric and safety component.
	  ○ "So our discussion of tapering your opioid is resulting in self-harm thoughts? This raises an even greater concern regarding your safety with these medications. Can we explore this a bit more; What have you been thinking? Should we consider getting you a psychiatric consult?"
	  ○ "For your safety, I think we need to re-review our pain management plan together and potentially incorporate a psychiatric consult."
	• Behind the effort to manipulate could be an intense fear of losing the medication that seems to be the only thing that works; the conversation therefore needs to be refocused on safety rather than taking something away from the patient.
	  ○ "I can understand your concern. I am not going to pull the rug out from under you. We will continue to explore ways to best cope with your pain which do not put you at further risk of harm."

Talking points with patients

Reassessing for tapering

Situation	Approach/language to use
Patient does not want to try an initial taper	• Consider using a motivational interviewing approach: "Sounds like you aren't ready to talk about opioid tapering today. I would like to ask about it again at your next appointment, since I am concerned that this dose may be doing you more harm than good. Would that be OK? Please call if you have any questions." • Explore why the patient wants to continue in the face of "no benefit." • Consider extending the trial period (e.g. for 3 more months) with clear criteria for how a decision will be made at that time. Use this opportunity to motivate further application of non-pharmacological interventions. • If there is clearly no benefit seen/documented & only potential harms, advise that all factors point to deprescribing as the safest option. "It is OK to say no." • Alternately, consider referral for a 2nd opinion before making a final decision. [13]
Initial taper is not successful (due to deterioration of pain/function or persistent withdrawal symptoms)	• Hold off on further taper and at that time, discuss when you will reassess/restart the taper: "Even though the taper didn't work out this time, I'll still glad we tried it. It could be that the time isn't right yet, but things change. Over time, opioids can increase your sensitivity to pain and start to work less well for you. The next time you visit, I'd like to revisit the possibility of trying another taper. Would that be OK?" • Give consistent messaging at each visit that being on opioids is not going to last forever, so that when the time comes to try another taper, the patient is not surprised.[10]

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CEP Centre for Effective Practice

SMART Goals for Pain Management

Why set goals?

- You and your doctor will be "on the same page" about what you hope to gain from the treatment.
- You'll have a better idea of what's realistic and when to expect changes to happen.
- You'll make faster progress in improving your quality of life.[1,2]
- You and your doctor will be able to see if your treatment is working and when it might be time to switch to another treatment.

What are SMART goals?[3]

			Examples of SMART goals:	EXAMPLES of Unrealistic or Poorly Defined Goals:
S	**Specific**	Clear, short and to the point, so you'll know what you're aiming for.	"I want to reduce my pain from 8/10 to 7/10 so I can vaccum my living room within 4 weeks after starting treatment."	"I want to completely get rid of my pain." (unrealistic)
M	**Measurable**	Able to be easily measured, so you'll know when you get there.	"I want to do some gardening for 15 minutes a day within 4 weeks after starting treatment."	"I want to have less pain." (poorly defined)
A	**Action oriented**	Based on actions you can take that are within your direct control.	"I want to be able to walk my dog around the block each day within 4 weeks after starting treatment."	"I want to function better." (poorly defined)
R	**Realistic**	Small steps that are within your reach. Choose something you're 90% confident you can do.		
T	**Time-based**	Tied to a deadline.		

How do I know what's realistic?

Things you can measure if a treatment works	What's realistic?	What may not be realistic?
Pain (often measured to know on a scale of 0 to 10)	Up to a 30% reduction in pain (for example, if your pain is 7/10, it could go down to a 5/10).[4]	**Zero pain** (for example, if your pain is 7/10, it's unlikely to go down to 0/10).
Function (ability to do daily activities)	Small, gradual improvements in function and your ability to cope. Focus on what you can do now that you couldn't do a few months ago (rather than comparing to what you could do before the pain started).	Being able to do everything you did before the pain started. Expecting all pain to be gone before you can work on your goals for improving your ability to do daily activities.
Side effects	Side effects that don't interfere too much with your life.	Zero side effects.

Pain myths and facts:[1]

Myth	Fact
All my pain must be gone before I can start doing physical activity or working on my SMART goals.	Pain may never be gone, but you can still learn to be physically active safely, and to make slow and steady progress towards your SMART goals.
Pain causes long-term harm to my body.	While pain can be the body's way to tell us something is wrong, it's different with chronic pain. Pain should not stop you from working on your SMART goals.
The main focus of my treatment is to relieve pain.	Focus more on your ability to function than on your pain. Aim for small, gradual improvements in your ability to function.
My treatment should get my pain to zero.	Treatment is not likely to get you to zero pain. That's why it's so important to learn coping strategies.
I can expect to make the same amount of progress each day.	You'll have good days and bad days, but it's the overall progress over time that matters.

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Example categories for SMART goals:

- Exercise, physical activity
- Relaxation, meditation, quieting responses
- Social support, social activity
- Meaningful activities (work, volunteer, responsibilities to family/community)
- Pleasurable activities (hobbies, interest, diversions, distractions, social)
- Attitude, mood, thinking

SMART goal (short-term):

	Progress	Barrier(s)	Solution(s)
Date:			
Date:			
Date:			
Date:			
Date:			

SMART goal (long-term):

	Progress	Barrier(s)	Solution(s)
Date:			
Date:			
Date:			
Date:			
Date:			

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Rx FILES

Getting back on the road of life

It can be helpful to think of chronic pain as a car with four flat tires.[1]

We may be looking for a single treatment, like medication, to manage pain, but this would be like putting air in only one tire.

You need to fill the other three tires to get where you want to go. There are lots of different ways to fill up the tires. Most of these involve taking an active role in your treatment. Keep your goals in mind so you know what you are working towards.

Psychological therapy[2]

- ☐ Cognitive-behaviour therapy (CBT)
- ☐ Mindfulness based interventions
- ☐ Acceptance and commitment therapy
- ☐ Respondent behavioural therapies (e.g. biofeedback, progressive relaxation)

Instructions:

Preventative treatments and self-management[2, 6]

- ☐ Self-management programs
- ☐ Pacing household chores and activities
- ☐ Ergonomic set-up at home and work
- ☐ Healthy sleep patterns
- ☐ Healthy eating

Instructions:

Physical interventions

Physical therapy (passive)[2]

- ☐ Manual therapy (e.g. physiotherapy, massage, joint manipulation)
- ☐ Transcutaneous electrical nerve stimulation (TENS)
- ☐ Low level laser therapy
- ☐ Heat/cold

Instructions (e.g. frequency and duration):

Physical activity (active)[2]

Movement is good medicine for chronic pain. Every little bit helps – you can start with as little as 5 minutes every other day![3, 4] Mid-morning or early afternoon may be the best times for activity.[5]

- ☐ Aerobic exercise (e.g. walking)
- ☐ Strengthening exercise (e.g. lifting weights)
- ☐ Core stabilizing exercises (e.g. pilates)
- ☐ Tai Chi
- ☐ Yoga
- ☐ Therapeutic aquatic exercise

Instructions (e.g. frequency and duration):

Medication[2, 6]

- Ask your doctor which medications match your type of pain.
- Ask which side effects to expect and how to manage them.
- Find out how to take the medication properly and for how long you will need to take it.
- Ask how much you can expect the medication to help with your pain and function.
- Follow any instructions on safe use, storage and disposal.
- Do not share medications with others. What is safe for you may be dangerous for someone else.

☐ Over the counter medication(s): _____

Instructions:

SMART goals (specific, measurable, action-orientated, realistic, timed):

This patient material is intended to support a conversation between provider and patient.
It has been developed in partnership by the Centre for Effective Practice and RxFiles.

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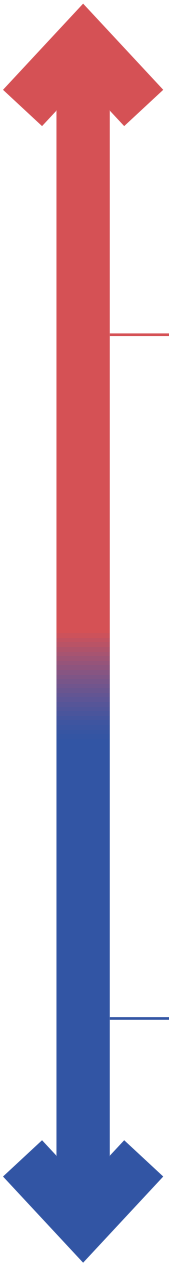
Factors that increase or decrease the experience of pain[1]



Factors that INCREASE the experience of pain[1,2]

Factor	Influence on pain experience
Stress (e.g. family, social, work)	! ♿
Fear and worry	🚶
Anxiety	♿
Depression or depressed mood (does not fulfill the diagnostic criteria for depression)	♿
Catastrophizing (exaggerated negative reaction where the worst possible outcome is imagined)	!
Negative thoughts and beliefs	! ♿
Avoidance behaviour	♿

Factor	Influence on pain experience
Unlimited activity (overactivity)	!
Pain expectations not being fulfilled (e.g. if a patient expects to recover from neck pain in 4 weeks and this does not occur)	!
Beliefs that set the stage for activity restrictions (e.g. "hurt is harm", "pain is a signal to stop what you are doing", "rest is the best medicine")	🚶 ♿
Poor eating habits	!
Smoking	!
Inadequate sleep	!

Factors that DECREASE the experience of pain[1,2]

Factor	Influence on pain experience
Positive emotions	!
Coping strategies (e.g. relaxation, visualization), pain management skills and education	!
Stress reduction	!
Adequate sleep	!

Factor	Influence on pain experience
Good eating habits	!
Appropriate levels of activity (moderate activity)	!
Social support	!
Distraction	!

Legend

! Increase in pain intensity	! Increase in psychological distress	! Decrease in pain intensity	! Decrease in psychological distress
♿ Increase in pain disability	🚶 Increase in avoidance behaviour	! Decrease in psychological distress	🚶 Decrease in avoidance behaviour

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Ontario College of Family Physicians

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(en français)

Osteoarthritis pain getting you down? Duloxetine

Clinical Question: Do Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), specifically Duloxetine, improve pain in patients with osteoarthritis?

Bottom Line: Duloxetine can meaningfully reduce osteoarthritis pain scores (by at least 30%) for ~60% of patients compared to ~40% on placebo. An average pain of ~6 (scale 0-10) will be reduced by ~2.5 points, compared to 1.7 on placebo. Duloxetine adverse effects lead to withdrawal in 12% of patients versus 6% on placebo.

Evidence:

- Six systematic reviews with 2-7 randomized controlled trials (RCTs) and 487-2102 patients.[1-6] Duloxetine 60-120mg daily versus placebo, results statistically significant unless indicated.
  - Proportion of patients attaining a meaningful pain reduction (generally =30% reduction in pain score):
    - Systematic review (6 RCTs, 2060 patients)[1] of hip or knee osteoarthritis, over 10-18 weeks: 64% taking duloxetine versus 43% taking placebo, number needed to treat (NNT)=5.
    - Other systematic reviews found similar:[3,5-6] NNT=6-9.
    - One RCT (231 patients) randomized patients to 60mg or 120mg and found no difference.[7]
  - Improvement in baseline pain scores (0-10 point scale, lower scores indicate less pain):
    - Systematic review (5 RCTs, 2059 patients),[5] patients started with an average score of 5.8: duloxetine improved pain 0.8 more than placebo, achieving a mean pain score of 3.3 versus 4.1 for placebo which is likely clinically meaningful.
    - Another systematic review found similar.[3]
  - Adverse events:
    - Overall adverse events:[4] 55% versus 37% (placebo), number needed to harm (NNH)=6.
      - Most common adverse events:[4] gastrointestinal 36% versus 8% (placebo), (NNH=4).
        - Specifically[6] nausea (NNH 16), fatigue (NNH 17), constipation (NNH 19), erectile dysfunction (NNH 20), abdominal pain (NNH 34).
    - Withdrawal due to adverse events:[4] 12% versus 6% (placebo), NNH=17.
    - Other systematic reviews found similar.[1-6]
  - Limitations: all industry-funded studies.

Context:

- No RCTs looked at venlafaxine to treat osteoarthritis pain.
- Duloxetine is "conditionally recommended" by the Osteoarthritis Research Society International guidelines and by the American College of Rheumatology, however, tolerability needs to be considered.[8-9]
- A PEER Simplified Decision Aid on osteoarthritis can assist with patient informed decision making and is available online.[10]

Authors:

Betsy Thomas BSc Pharm, Joey Ton PharmD, Mike Allan MD CCFP

Disclosures:

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La douleur de l'arthrose vous déprime? Duloxétine

Question clinique : Les inhibiteurs de la recapture de la sérotonine et de la noradrénaline (IRSN), en particulier la duloxétine, soulagent-ils la douleur chez les patients souffrant d'arthrose?

Conclusion : La duloxétine peut réduire de manière significative les scores de douleur de l'arthrose (d'au moins 30 %) chez environ 60 % des patients, contre environ 40 % pour le placebo. Une douleur moyenne d'environ 6 (échelle de 0 à 10) sera réduite d'environ 2,5 points, contre 1,7 point pour le placebo. Les effets indésirables de la duloxétine entraînent le retrait de 12 % des patients, contre 6 % pour le placebo.

Données probantes

- Six revues systématiques portant sur deux à sept essais cliniques randomisés (ECR) regroupant de 487 à 2102 patients[1-6]. De 60 à 120 mg de duloxétine par jour par rapport au placebo; résultats statistiquement significatifs, sauf indication contraire.
  - Proportion de patients atteignant une réduction significative de la douleur (généralement une réduction de 30 % ou plus du score de la douleur) :
    - Revue systématique (six ECR, 2060 patients[1] souffrant de l'arthrose de la hanche ou du genou), sur 10 à 18 semaines : 64 % prenaient de la duloxétine et 43 % prenaient un placebo, nombre de sujets à traiter (NST)=5;
    - Résultats similaires pour d'autres revues systématiques[3,5-6] : NST=de 6 à 9.
    - Dans un ECR (231 patients), les patients ont été randomisés pour recevoir 60 mg ou 120 mg; aucune différence n'a été constatée[7].
  - Amélioration des scores de base de la douleur (échelle de 0 à 10 points, les scores plus faibles indiquant une moindre douleur) :
    - Revue systématique (cinq ECR, 2059 patients)[5], les patients ayant au départ un score moyen de 5,8 : la duloxétine a réduit la douleur de 0,8 de plus que le placebo, permettant d'atteindre un score moyen de 3,3 contre 4,1 pour le placebo, ce qui est probablement significatif sur le plan clinique.
    - Une autre revue systématique a révélé des résultats similaires[3].
  - Événements indésirables :
    - Événements indésirables globaux[4] : 55 % contre 37 % (placebo), nombre nécessaire pour obtenir un effet nocif (NNN)=6.
    - Événements indésirables les plus fréquents[4] : gastro-intestinaux - 36 % contre 8 % (placebo) (NNN=4).
      - Plus précisément[6] : nausée (NNN=16), fatigue (NNN=17), constipation (NNN=19), dysfonctionnement érectile (NNN=20), douleur abdominale (NNN=34).
    - Retrait en raison d'événements indésirables[4] : 12 % contre 6 % (placebo), NNN=17.
    - D'autres revues systématiques ont trouvé des résultats similaires[1-6].
  - Limites : toutes les études ont été financées par l'industrie.

Contexte

- Aucun ECR ne s'est penché sur la venlafaxine pour traiter la douleur liée à l'arthrose.
- Les lignes directrices de l'Osteoarthritis Research Society International et de l'American College of Rheumatology recommandent la duloxétine sous certaines conditions, mais la tolérance doit être prise en compte[8-9].
- L'aide décisionnelle simplifiée de PEER sur l'arthrose peut aider les patients à prendre des décisions en connaissance de cause et est disponible en ligne[10].

Auteurs

Betsy Thomas, B. Sc. (pharm.), Joey Ton, Pharm. D., et Mike Allan, M.D., CCMF

Divulgation

Les auteurs n'ont aucun conflit d'intérêts à divulguer.

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Editor's key points

- Serotonin syndrome, more aptly named *serotonin toxicity,* is a potentially fatal drug-induced condition caused by too much serotonin in synapses in the brain. Patients present with a combination of neuromuscular, autonomic, and mental status symptoms.
- Most cases involve 2 drugs that increase serotonin in different ways or an overdose of 1 serotonin drug. Monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors are the most common culprits. The use of 2 high-dose serotonin drugs at the same time should be avoided.
- Prevention of serotonin toxicity is key. Education of prescribers and patients is important to avoid and detect serotonin toxicity.

Demystifying serotonin syndrome (or *serotonin toxicity*)

Ai-Leng Foong PharmD Kelly A. Grindrod PharmD MSc
Tejal Patel PharmD Jamie Kellar PharmD

Abstract

Objective To review the symptoms of serotonin toxicity (commonly referred to as *serotonin syndrome*) and the causative drugs and their mechanisms of action, and to equip primary care providers with practical strategies to prevent and identify serotonin toxicity.

Quality of evidence PubMed and Google Scholar were searched for relevant articles on serotonin toxicity, the causes, and the differential diagnosis using search terms related to serotonin toxicity (*serotonin syndrome, serotonin toxicity, serotonin overdose*), causes (individual names of drug classes, individual drug names), and diagnosis (*differential diagnosis, neuroleptic malignant syndrome, anticholinergic toxicity, discontinuation syndrome, malignant hyperthermia, serotonin symptoms*). Experts in psychiatric medicine, psychiatric pharmacy, clinical pharmacology, and medical toxicology were consulted. Evidence is level II and III.

Main message Serotonin toxicity is a drug-induced condition caused by too much serotonin in synapses in the brain. Cases requiring hospitalization are rare, and mild cases caused by serotonin-mediated side effects are unlikely to be fatal. Patients present with a combination of neuromuscular, autonomic, and mental status symptoms. Serotonin-elevating drugs include monoamine oxidase inhibitors, serotonin reuptake inhibitors, and serotonin releasers. Most cases involve 2 drugs that increase serotonin in different ways; the most concerning combination is a monoamine oxidase inhibitor with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.

Conclusion Family physicians play a key role in identifying and preventing serotonin syndrome by teaching patients to recognize symptoms and monitoring patients throughout therapy.

Serotonin toxicity (commonly referred to as *serotonin syndrome*) is a potentially life-threatening drug-induced condition caused by too much serotonin in the synapses of the brain.[1-3] Patients present with a combination of neuromuscular, autonomic, and mental status symptoms. Most cases involve 2 drugs that increase serotonin in different ways or an overdose of 1 serotonin-elevating drug.[1-3] While the most common culprits are monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs), the list of potential contributors is long and includes often-overlooked substances such as herbals and illicit drugs.[1-3]

Cases of serotonin syndrome resulting in hospitalization or death are rare. Most cases do not require medication intervention, but can be managed by stopping the drug or decreasing the dose. Mild toxicity appears to be rare but is likely under-reported, unrecognized, or confused with other syndromes.[2] The lack of agreed-upon diagnostic criteria, inconsistencies in clinical symptoms, and clinicians who are not trained to identify it mean that case reports are published even when patients do not experience serotonin toxicity, which complicates the literature.[1,2,4] With the ever increasing use of antidepressants

for mood and other conditions such as anxiety, pain, sleep, and menopausal hot flashes, clarity is needed to help health care professionals prevent, identify, and manage serotonin toxicity.[5,6]

The objective of this update is to review the symptoms of serotonin toxicity and the causative drugs and their mechanisms of action, and to equip primary care providers with practical strategies to prevent and identify serotonin toxicity.

Quality of evidence

We searched PubMed and Google Scholar for relevant articles on serotonin toxicity, the causes, and the differential diagnoses. A selection of search terms related to serotonin toxicity (*serotonin syndrome, serotonin toxicity, serotonin overdose*), causes (individual names of drug classes, individual drug names), and diagnosis (*differential diagnosis, neuroleptic malignant syndrome, anticholinergic toxicity, discontinuation syndrome, malignant hyperthermia, serotonin symptoms*) was used. We consulted with experts in psychiatric medicine, psychiatric pharmacy, clinical pharmacology, and medical toxicology. Recommendations were based on the criteria outlined by *Canadian Family Physician,* where level I evidence includes at least 1 properly conducted randomized controlled trial, systematic review, or meta-analysis; level II includes other comparison trials and non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than 1 study; and level III includes expert opinion or consensus statements. Recommendations are based on level II and III evidence.

Main message

We developed the infographic in **Figure 1** based on the best available evidence (**Table 1**).[1-4,7-12] The infographic and an English-only patient handout are available at **CFPlus**.*

Assess the patient. The best available information on the symptoms of serotonin toxicity is from a retrospective analysis of prospective data collected by the Hunter Area Toxicology Service in Australia (level II evidence).[1] Patients present with a triad of neuromuscular, autonomic, and mental status changes that start within hours to 1 day of increasing a dose or adding a serotonergic drug (**Table 2**).[1,2,12,13] If untreated, serotonin toxicity escalates quickly and can be fatal.[2] Because toxicity presents on a spectrum rather than as a defined set of signs and symptoms (ie, a syndrome), *serotonin toxicity* is more accurate than *serotonin syndrome*.[1]

Mild symptoms, which include nervousness, insomnia, nausea, diarrhea, tremor, and dilated pupils, can progress to moderate symptoms such as hyperreflexia (increased reflexes), sweating, agitation, restlessness, clonus (rhythmic muscle spasms), and ocular clonus (side-to-side eye movements). Patients with severe symptoms should be referred to the hospital immediately; severe symptoms include temperature greater than 38.5°C (101.3°F), confusion, delirium, sustained clonus or rigidity, and rhabdomyolysis.

Cases of serotonin toxicity that require hospitalization are straightforward to diagnose, as severe symptoms (such as bilateral, symmetric clonus in the legs more than in the arms) are not common in other conditions. The combination of nonspecific autonomic manifestations, a range of possible signs and symptoms, and a lack of definitive laboratory tests makes milder cases less straightforward to diagnose, although such cases are unlikely to be fatal.

Assess the drug. Because serotonin toxicity is a drug-induced condition, an accurate drug history is necessary for diagnosis, especially when a patient has recently used an MAOI or another serotonin-elevating drug. Serotonin toxicity most often happens when 2 or more serotonin-elevating drugs are used together, especially if they increase serotonin in different ways.[1,2,12,13] An MAOI with an SSRI, an SNRI, or another MAOI is the riskiest combination, but other combinations can also result in toxicity. Some experts report that therapeutic doses of a single drug can cause toxicity, but the risk is low, as it is a dose-related drug toxicity.[1,2,14]

Serotonin is formed from dietary tryptophan and stored in the presynaptic terminal.[15] It is released into the synapse where it acts on the presynaptic and postsynaptic terminals, and is taken back up into the presynaptic terminal to be degraded by monoamine oxidase (**Figure 2**).[15] Drugs that increase synaptic concentrations of serotonin include MAOIs, serotonin reuptake inhibitors, and serotonin releasers.[4]

Monoamine oxidase inhibitors: Monoamine oxidase inhibitors slow the breakdown of serotonin by blocking monoamine oxidase.[15] This class of drugs is most concerning, specifically MAOIs that bind irreversibly and non-selectively to both types of monoamine oxidase (MAO-A and MAO-B); MAO-A inhibitors are more likely to cause toxicity because MAO-A plays a larger role in the breakdown of serotonin.[1,15] Combination of 2 MAOIs or an MAOI and another serotonergic drug carries the greatest risk of serotonin toxicity. Although not common anymore, the most recognizable MAOIs are those used to treat depression, such as phenelzine, isocarboxazid, tranylcypromine, and moclobemide. Other agents less frequently recognized as MAOIs include the antibiotics isoniazid (irreversible, non-selective) and linezolid (reversible, non-selective).[3,16]

*The **infographic** (**Figure 1**) and an English-only **patient handout** are available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Figure 1

Target Serotonin Syndrome

def. Toxicity caused by excessive serotonin levels that results from a drug overdose or interaction

Assess the patient

Symptoms start within hours to 1 day of increasing a dose or adding a drug

Mild	Moderate	Severe
Nervousness	Hyperreflexia	Fever >38.5°C/101.3°F
Insomnia	Sweating	Confusion/delirium
Nausea/diarrhea	Agitation/restlessness	Sustained clonus/rigidity
Tremor	Inducible clonus	Rhabdomyolysis
Big pupils	Side-to-side eye movements	Death

Assess all drugs

Most cases involve 2 drugs that increase serotonin in different ways – full list on back

Prescription drugs

OTC and natural drugs

Illicit drugs

Rule out

Serotonin syndrome can look like other things; diagnosis requires an accurate drug history

Similar-looking conditions:
- Antidepressant Discontinuation
- Anticholinergic Toxicity
- Malignant Hyperthermia
- Neuroleptic Malignant Syndrome
- Meningitis/Encephalitis
- Drug Overdose
- Alcohol/Benzo Withdrawal

Remind all patients: Non-toxic increases in serotonin can cause anxiety, restlessness and irritability for 1-2 weeks

If you suspect serotonin syndrome

Don't wait, take action – it progresses rapidly

Stop the drug(s)

Refer patient to hospital

once symptoms are gone

Try other drugs or restart low doses slowly

Prevent serotonin syndrome

Stay alert – most cases can be prevented

- ✓ Use lowest effective dose
- ✓ Ask about illicit drug use
- ✓ Check drug monographs for tapering and wash-out periods
- ✓ Follow up 1-2 days after upping a dose or starting a new drug
- ✓ Reassess the need for a serotonin drug yearly
- ✓ Teach patients to recognize serotonin syndrome

AVOID: Group A with Group A or Group A with Group B

CAUTION: TWO or more Group B drugs especially when ONE is used at a high dose

MONITOR: If a patient uses a Group B drug and a second Group B drug is added, start low, increase the dose cautiously, and watch for symptoms for 24-48h after every change

Group A

Non-selective and irreversible MAOi A and B
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine

Non-selective and reversible MAOi A and B
Linezolid

Selective and irreversible MAOi B
Selegiline (non-selective at higher doses)
Rasagiline

Selective and reversible MAOi A
Moclobemide
Methylene blue (non-selective at higher doses)

Group B

Antidepressants
Selective Serotonin Reuptake Inhibitors (SSRI): Paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine

Serotonin Norepinephrine Inhibitors (SNRI): Venlafaxine, desvenlafaxine, duloxetine

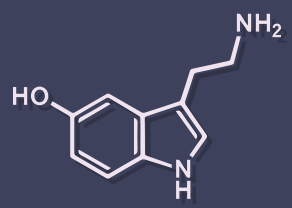
Tricyclic Antidepressants: Clomipramine, imipramine

Opioids and other pain medications
Tramadol, meperidine, methadone, fentanyl (unlikely with morphine, codeine, oxycodone, buprenorphine)

Cough, cold and allergy
Dextromethorphan ("DM"), chlorpheniramine

Natural health products
St. John's wort, L-tryptophan, diet pills

Illicit drugs
Ecstasy (MDMA), amphetamine, cocaine



Commonly listed but unlikely to cause serotonin syndrome
Triptans (e.g., sumatriptan)

Antidepressants: amitriptyline, mirtazapine, trazodone

Antiemetics: 5HT3 receptor antagonists (e.g., ondansetron), metoclopramide

Buspirone, lithium

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Content by Kelly Grindrod, PharmD; Tejal Patel, PharmD; Jamie Kellar, PharmD; Ai-Leng Foong, BSc. Design by Adrian Poon, BA

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

Table 1. Evidence supporting the key considerations for practice

CLINICAL CONSIDERATIONS	EVIDENCE RATING	REFERENCES
The best available evidence for the clinical presentation of toxicity is from the Hunter Area Toxicology Service in Australia	Level II*	1
Serotonin toxicity most often happens when 2 serotonin-elevating drugs are used together. The use of an MAOI with an SSRI, an SNRI, or another MAOI is the most concerning drug combination	Level III†	1,3
Some drugs thought to cause serotonin toxicity do not (eg, triptans, ondansetron)	Level III†	1,4,7-11
Prevention of serotonin toxicity through good prescribing practices and monitoring is important	Level III†	2,12

MAOI—monoamine oxidase inhibitor, SNRI—serotonin-norepinephrine reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor.
*Level II: Comparison trials other than randomized controlled trials, systematic reviews, or meta analyses; non-randomized, cohort, case-control, or epidemiologic studies; and preferably more than 1 study.
†Level III: Expert opinion or consensus statements.

Table 2. Signs and symptoms of serotonin toxicity

CATEGORY	SIGNS AND SYMPTOMS
Neuromuscular	• Tremor • Hyperreflexia (increased reflexes)* • Clonus (rhythmic muscle spasms that can be spontaneous, inducible, or ocular)*
Autonomic	• Mydriasis (dilated pupils) • Diaphoresis (sweating) • Tachycardia (increased heart rate) • Tachypnea (increased breathing rate)
Mental status	• Agitation • Excitement • Restlessness • Confusion • Delirium

Data from Dunkley et al,[1] Boyer and Shannon,[2] Ables and Nagubilli,[12] and Isbister et al.[13]
*Hyperreflexia and clonus are often worse in the legs than in the arms.

Serotonin reuptake inhibitors: Serotonin reuptake inhibitors prevent the transport of serotonin from the synapse back into the presynaptic terminal to be degraded, keeping it at the site of action.[15] Drugs that prevent the reuptake of serotonin include SNRIs, SSRIs, tramadol, certain tricyclic antidepressants (TCAs), certain opioids, dextromethorphan, the antihistamines chlorpheniramine and brompheniramine, and herbals such as St John's wort.[7,13]

After MAOIs, SNRIs and SSRIs are the most concerning serotonergic drugs, as their main mechanism is to increase serotonin.[1,2] The SNRI venlafaxine causes toxicity more often than SSRIs do, possibly because it has another serotonergic mechanism other than a reuptake inhibitor.[3]

Certain synthetic opioids such as tramadol, methadone, meperidine, fentanyl, and dextromethorphan are weak serotonin reuptake inhibitors and can cause toxicity, but opioids with a structure similar to morphine are not reuptake inhibitors, meaning that morphine, codeine, oxycodone, and buprenorphine do not cause toxicity.[7] Because of the risk of dextromethorphan and the antihistamines chlorpheniramine and brompheniramine, remind patients who take serotonin drugs to talk to a physician or pharmacist before taking a cough and cold medication.

Tricyclic antidepressants are also serotonin reuptake inhibitors, with clomipramine and imipramine being the most potent and likely the only TCAs to be involved in serotonin toxicity; other TCAs such as amitriptyline are weaker inhibitors and are thus unlikely to cause toxicity.[3,7]

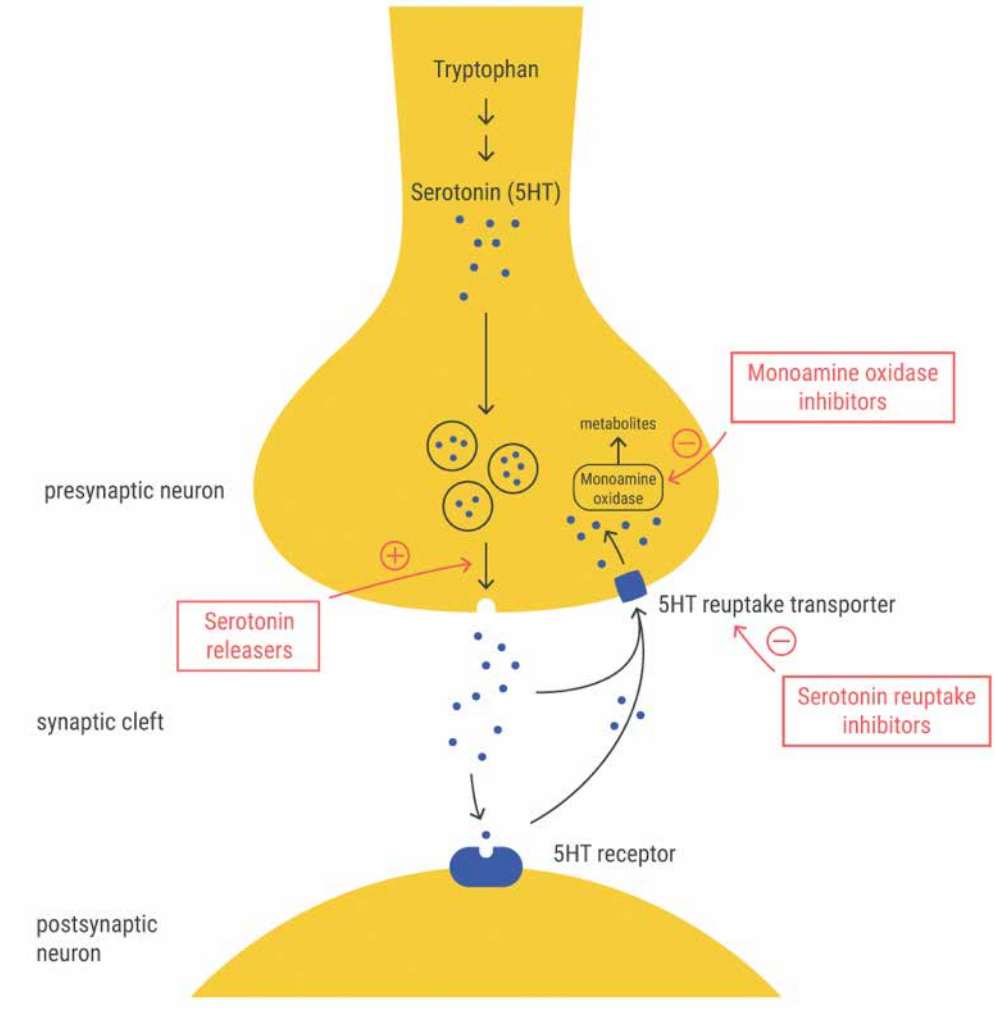
Serotonin releasers: Serotonin releasers cause more serotonin to be released from the presynaptic terminal into the synapse. Serotonin releasers include amphetamine, but not methylphenidate, and the illicit drug ecstasy (3,4-methylenedioxymethamphetamine).[3,7,12]

L-Tryptophan: A drug that does not fit into any of these 3 categories is L-tryptophan, which can be used for various mood disorders.[3] L-Tryptophan can increase serotonin levels because serotonin is made from tryptophan; however, the risk is low.

Controversies. Experts disagree on the list of implicated drugs. The lists of serotonin drugs published by the US Food and Drug Administration (FDA) and Health Canada include drugs that are unlikely to cause toxicity based on their mechanisms of action—either they work on different receptors than the ones involved in serotonin toxicity or they block rather than activate the receptors.[8,9] Examples include triptans (used for migraines), antiemetics such as ondansetron, olanzapine, mirtazapine, cyclobenzaprine, bupropion, trazodone, buspirone, lithium, and amitriptyline.[1,4,7-11] That these are unlikely to cause serotonin toxicity is supported by the lack of case reports implicating these drugs, through case series, by reviewing the evidence for case reports, and by understanding the pharmacology of these drugs.

In 2016, an FDA warning[8] stated that opioids interact with migraine medications (triptans), a warning partly based on poor-quality case reports that did not use validated criteria (eg, the Hunter Serotonin Toxicity Criteria) to diagnose serotonin toxcity.[4] Similarly, the FDA, Health Canada, and the World Health Organization issued warnings about 5-HT_3 antagonists (eg, antiemetics such as ondansetron and granisetron) despite a lack of high-quality evidence of this drug class causing toxicity.[8-10,17,18]

Figure 2. Serotonin physiology: *Serotonin is formed in the presynaptic terminal from tryptophan. Once packaged into vesicles, it is released into the synaptic cleft where it can bind to serotonin receptors on the postsynaptic neuron to exert its action. Serotonin is transported through a transporter to the presynaptic terminal where it is broken down by monoamine oxidase.[15] The 3 classes of drugs that increase serotonin in synapses are highlighted in red.*



5HT—5-hydroxytryptamine.

Based on these controversial data, there is a risk that inaccurate information has been incorporated into drug interaction–checking software used in pharmacies and physicians' offices. In Canada, RxVigilance and First Databank maintain updated databases that are used in electronic decision support tools for health care providers, such as the drug information needed for an interaction checker.[19,20] Although these companies recognize that the FDA and Health Canada have published information based on weak evidence, their interaction checkers still flag combinations of drugs that are unlikely to cause serotonin toxicity. As a result, prescribers might avoid prescribing a medication that might otherwise prove to be useful for a patient.

What to rule out. Other conditions look similar to serotonin toxicity.

Antidepressant discontinuation: Symptoms start within days of stopping or tapering a drug and are usually self-limited, lasting 1 week.[21] Symptoms include flu-like symptoms, nausea, imbalance, sensory disturbances, hyperarousal, and changes in mood, sleep, and appetite.[21]

Anticholinergic toxicity: Anticholinergic toxicity results from an overdose of anticholinergic medications. Symptoms include dry mouth, dry and flushed skin, urinary retention, decreased bowel sounds, dilated pupils, blurry vision, fever, agitation, delirium, and hallucinations.[22] A distinguishing feature is that muscle tone and reflexes are normal in anticholinergic toxicity.[22]

Malignant hyperthermia: Malignant hyperthermia is triggered by specific volatile anesthetics during or shortly after surgery. Telltale signs include hyperthermia (>39°C), tachycardia, tachypnea, acidosis, muscle rigidity, and rhabdomyolysis.[23] Family history is a factor.

Neuroleptic malignant syndrome: Unlike serotonin toxicity, neuroleptic malignant syndrome is not dose-related but is an idiosyncratic reaction to neuroleptic drugs. Onset is slower, taking place over days, and it is differentiated from serotonin toxicity by the presence of bradykinesia and lead-pipe or cogwheel rigidity.[23]

Other conditions: Other similar-looking conditions include meningitis or encephalitis, drug overdose, and alcohol or benzodiazepine withdrawal.[12,13] Notably, it is normal for nontoxic increases in serotonin to cause anxiety, restlessness, and irritability for 1 to 2 weeks after starting a drug or increasing a dose.[24]

If you suspect serotonin toxicity. If you suspect serotonin toxicity, stop the serotonin drugs. Refer patients with severe symptoms or patients who have ingested an MAOI and a serotonin reuptake inhibitor to the hospital, as their condition can worsen quickly.[13] Teach patients to recognize serotonin toxicity and tell them to call their primary practitioner if they suspect toxicity. Once signs and symptoms have resolved, try other drugs or restart low doses slowly, and rule out other contributing drugs such as over-the-counter medications or illicit drugs. For most patients who experience serotonin-mediated side effects, these changes to their medications will manage symptoms and prevent toxicity, and a hospital referral will not be required.

Preventing serotonin toxicity. Serotonin toxicity remains a confusing area for practitioners and can be a scary, potentially fatal experience for patients. As most cases are avoidable, learning to identify and prevent it is key.

Before prescribing a serotonin drug and at check-ups: Ask patients about over-the-counter drug, herbal, and illicit drug use. Remind patients to check with their prescribers or pharmacists before starting a new drug.

When prescribing: Make sure you use the lowest effective dose and avoid the use of 2 high-dose serotonin drugs at the same time.

If stopping or switching drugs: Check drug monographs for tapering and wash-out periods, and stress careful adherence to the crossover schedule.

After prescribing: Follow up with patients a few days after increasing the dose or starting a new drug, and check yearly if the patient still needs to be taking the drug.

Conclusion

Serotonin toxicity is an important topic for primary care providers. Education of both practitioners and patients is the only way to prevent serotonin toxicity.

Dr Foong completed her Doctor of Pharmacy degree at the University of Waterloo School of Pharmacy in Ontario. **Dr Grindrod** is Assistant Professor in the University of Waterloo School of Pharmacy and a clinical pharmacist at the Kitchener Downtown Community Health Centre. **Dr Patel** is Assistant Clinical Professor in the University of Waterloo School of Pharmacy, part-time Assistant Clinical Professor in the Michael G. DeGroote School of Medicine at McMaster University, a clinical pharmacist with the Memory Clinic at the Centre for Family Medicine Family Health Team in Kitchener, a research scientist at the Schlegel–University of Waterloo Research Institute for Aging, and an affiliate researcher with the Waterloo Institute for Complexity and Innovation. **Dr Kellar** is Assistant Professor and Acting Director of the Doctor of Pharmacy program at the Leslie Dan Faculty of Pharmacy at the University of Toronto in Ontario, an advanced practice hospital pharmacist at the Centre for Addiction and Mental Health in Toronto, a doctoral candidate in the School of Health Professions Education at Maastricht University in the Netherlands, and a research fellow at the Wilson Centre in Toronto.

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Contributors

Dr Grindrod conceived of the project. All authors were involved in drafting the infographic and the manuscript and approving the final draft.

Competing interests

None declared

Correspondence

Dr Kelly A. Grindrod; e-mail **kgrindrod@uwaterloo.ca**

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Radiology

ORIGINAL RESEARCH • SPECIAL REPORT

Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought?

Andrew J. Kompel, MD • Frank W. Roemer, MD • Akira M. Murakami, MD • Luis E. Diaz, MD • Michel D. Crema, MD • Ali Guermazi, MD, PhD

From the Department of Radiology, Boston University School of Medicine, 820 Harrison Ave, FGH Building, 3rd Floor, Boston, MA 02118 (A.J.K., F.W.R., A.M.M., L.E.D., M.D.C., A.G.); Department of Radiology, Friedrich-Alexander University Erlangen-Nürnberg (FAU) and University Hospital Erlangen, Erlangen, Germany (F.W.R.); Department of Radiology, Veterans Affairs Hospital, Boston, Mass (L.E.D., A.G.); and Institute of Sports Imaging, French National Institute of Sports (INSEP), Paris, France (M.D.C.). Received February 13, 2019; revision requested April 12; revision received August 8; accepted August 21. **Address correspondence to** A.G. (e-mail: *guermazi@bu.edu*).

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See also the editorial by Kijowski in this issue.

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Osteoarthritis (OA) of the hip and knee is among the most common joint disorders. Intra-articular corticosteroid (IACS) injections are frequently performed to treat OA and other joint-related pain syndromes; however, there is conflicting evidence on their potential benefit. There is a lack of prospective and large retrospective studies evaluating potential joint findings, including increased risk for accelerated OA progression or adverse joint events, after treatment with IACS injection. Four main adverse joint findings have been structurally observed in patients after IACS injections: accelerated OA progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction, including bone loss. Physicians, including radiologists, should be familiar with imaging findings and patient characteristics that may help them identify potential joints at risk for such events. The purpose of this report is to review the existing literature, describe observed adverse joint events after IACS injections, and provide an outlook on how this may affect clinical practice. Additional research endeavors are urgently needed to better understand and identify risk factors prior to intervention and to detect adverse joint events after injection as early as possible to prevent or minimize complications.

Osteoarthritis (OA) is among the most common joint diseases affecting the hip and knee, and the incidence is expected to increase with extended life expectancy and increasing obesity (1). Pain related to OA can be debilitating and can limit an individual's activity and quality of life (2,3). Nonsurgical approaches, including pain control, are the recommended first-line treatments prior to considering joint replacement in patients with late-stage disease (4). However, many patients with OA are not suitable candidates for joint replacement because of their older age, comorbidities, or both.

Injection of intra-articular corticosteroids (IACSs), usually combined with local anesthetics, is commonly performed to treat pain related to hip and knee OA (5,6). The American College of Rheumatology conditionally recommends IACS injection to treat OA (7), while the Osteoarthritis Research Society International recommends that IACS injection should be considered, particularly in patients with moderate to severe pain whose response to oral analgesic or anti-inflammatory agents is not satisfactory, as well as in those with symptomatic knee OA with effusions or other physical signs of local inflammation (4). Unlike the American College of Rheumatology and Osteoarthritis Research Society International, the American Academy of Orthopedic Surgeons does not currently have recommendations for or against the use of IACS injection of the knee and advises that practitioners should be alert for emerging evidence that clarifies or helps determine the balance between benefits and potential harm. Patient preference should have a substantial influence on the type of treatment selected (8).

In 2015, Jüni et al performed a systematic meta-analysis on behalf of the Cochrane Musculoskeletal Group to determine the pain and quality of life associated with and the function and safety of IACS when compared with sham injection or no treatment in patients with knee OA (9). That meta-analysis comprised 27 trials that included 1767 participants. The overall quality of evidence was graded as low for all outcomes because treatment effect estimates were inconsistent, there was substantial variation across trials, and most trials had a high or unclear risk of bias. The authors concluded that IACS injections might have resulted in a moderate improvement in pain and a small improvement in physical function; however, the quality of the evidence was low, and the overall results were inconclusive. They also showed that IACS injections appeared to cause as many side effects as the placebo (13% vs 15%), but they emphasized that there was a lack of precise and reliable information about side effects and that only a small number of trials reported adverse joint events. The listed side effects after injection include arthralgia, joint swelling, back pain, and joint stiffness. Maricar et al (10) evaluated structural changes in the knee at MRI and radiography and the response to IACS injections. The authors demonstrated that more severe meniscal damage, greater joint space narrowing, and higher Kellgren-Lawrence grade were associated with a decreased likelihood of a long-term response (6 months). Additionally, baseline synovitis did not correlate with a treatment response.

Another review performed by Law et al focused on current concepts on the use of IACS injections for knee

Abbreviations

IACS = intra-articular corticosteroid, OA = osteoarthritis, RPOA = rapid progressive OA, SIF = subchondral insufficiency fracture

Summary

An increased clinical awareness of adverse joint events after intra-articular corticosteroid injections has led to potential imaging findings and patient characteristics that may assist in identifying which joints could be at risk, although high-quality evidence regarding this topic is lacking.

Essentials

- Adverse joint events after intra-articular corticosteroid (IACS) injection, including accelerated osteoarthritis progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss, are becoming more recognized by physicians, including radiologists, who may consider adding these risks to the patient consent.
- Certain imaging findings and patient characteristics could potentially assist radiologists and other physicians in identifying which joints are at risk for complications after IACS injections combined with local anesthetics.
- The radiology community should actively engage in high-quality research to further understand these adverse joint findings and how they possibly relate to IACS injections to prevent or minimize complications.

OA, including potential contraindications. The authors concluded that contraindications to IACS injections are all relative based on the best available evidence (11). Contraindications include active superficial skin or soft-tissue infection, suspected joint infection, unstable coagulopathy, anticoagulant therapy, uncontrolled diabetes mellitus, and broken skin at the injection site (11). Of note, anticoagulation treatment is not a general contraindication for IACS injection. Neither contraindications regarding pre-existing articular structural changes nor damage to the joint after IACS injections are mentioned in this review.

Despite the relative safety of IACS injections regarding systemic side effects, in a meta-analysis focusing on the effects of corticosteroids on human chondrocytes in vitro and animal articular cartilage in vivo, Wernecke et al reported that corticosteroids can have an adverse effect on cartilage, especially at higher doses (18–24 mg per cumulative dose) (12). The action by which corticosteroids are chondrotoxic is complex, but it seems to affect cartilage proteins (especially aggrecan, type II collagen, and proteoglycan) by mediating protein production and breakdown (13,14). McAlindon and colleagues compared IACS injections with placebo injections and found that IACS injections resulted in greater cartilage volume loss than did placebo injections (−0.21 mm vs −0.10 mm) but no significant difference in knee pain at 2 years (15). Zeng et al recently confirmed and extended these findings in a large subsample from the Osteoarthritis Initiative cohort, with 65 knees (21.7 per 100 person-years) showing worsening of radiographic OA in the IACS injection group compared with 90 knees (7.1 per 100 person-years) in the control group (16).

Local anesthetics, especially those with higher concentrations and longer exposures, have been associated with chondrolysis. Studies including animal evaluation (17), in vitro analysis (18), and local anesthetic infusion after glenohumeral arthroscopy (19) have demonstrated chondrotoxicity to varying degrees. While demonstrating time, concentration, and drug-dependent chondrotoxicity of local anesthetics on human chondrocytes, Breu et al also showed cellular death rates were higher in osteoarthritic cartilage than in intact cartilage (18).

Another recent retrospective observational study by Simeone et al focused on IACS injection in the hip and subsequent joint events in 70 patients. They reported that 44% of patients who received IACS injections showed radiographic progression of OA and 17% developed articular surface collapse (20). In addition, they found that patients who received IACS injections had significantly more adverse joint events than did a control group of patients without hip injections or a control group of patients who underwent shoulder injections. However, to our knowledge, there have been no large (>200 subjects) retrospective reviews or randomized controlled studies with long-term (≥1 year) follow-up.

Protocol for IACS Injections and Joint Findings

Our institution is a city hospital that provides care for underserved individuals. Many patients have multiple comorbidities that are frequently not well controlled and may be contraindications for surgery; thus, referrals for IACS injections to treat painful hip or knee OA are common. All IACS injections in the hip and knee joints are performed with US guidance by two musculoskeletal radiologists with 7 (A.J.K.) and 10 (A.M.M.) years of experience, and approximately 500 IACS injections are performed annually for the hip and knee joints combined. In 2018, we performed 459 IACS hip and knee injections (Table). Because many patients referred for IACS injection have primarily been seen by an orthopedic clinician, a recent radiograph of the target joint is usually available. A minority of patients also have undergone preprocedural MRI, which is a relatively common procedure at our institution. The IACS injections in hip and knee joints at our institution are composed of 40 mg of triamcinolone, 2 mL of 1% lidocaine, and 2 mL of 0.25% bupivacaine.

Although the patients are not routinely called back for follow-up imaging at defined time points, some patients do return to the clinic after IACS injection, mainly because of insufficient pain relief or symptomatic worsening after an initial period of improvement, and they undergo additional imaging. Of the 459 patients who received an injection in 2018, 218 did not undergo radiographic or MRI follow-up or had total joint replacement without additional presurgical imaging. In addition to what has been reported by Simeone and colleagues (20) and others in the orthopedic and rheumatology literature (15,16), we have observed four main adverse joint findings in patients after IACS injections (Table): *(a)* accelerated OA progression (6%), *(b)* subchondral insufficiency fracture (0.9%), *(c)* complications of osteonecrosis (0.7%), and *(d)* rapid joint destruction, including bone loss (0.7%). Altogether, based on the available results of postprocedural imaging, we recorded 36 adverse joint events in 36 patients (19 women) out of a total of 459 IACS injections (8%). These patients were 37–79 years old

Adverse Joint Events after IACS Injections in Knee and Hip Joints

Adverse Event	Hip	Knee	Both Joints
No. of injections	307	152	459
RPOA 1	21 (7)	5 (3)	26 (6)
RPOA 2	2 (0.7)	1 (0.7)	3 (0.7)
ON	3 (1)	0	3 (0.7)
SIF	4 (1)	0	4 (0.9)
Total adverse joint events	30 (10)	6 (4)	36 (8)

Note.—Data are number of events, and data in parentheses are percentages. IACS = intra-articular corticosteroid; ON = osteonecrosis; RPOA 1 = rapid progressive osteoarthritis type 1; RPOA 2 = rapid progressive osteoarthritis type 2; SIF = subchondral insufficiency fracture.

(mean age, 57 years) and received one to three IACS injections (mean, 1.4 injections) with 2–15 months between the time of injection and imaging documentation of the joint event (mean time, 7 months). Most of the patients (72%) had preprocedural Kellgren-Lawrence (KL) moderate OA (KL grade 3) of the knee or hip (KL grade 0, $n = 1$; KL grade 2, $n = 8$; KL grade 3, $n = 26$; KL grade 4, $n = 1$).

In the following sections, we will detail these entities further, give an illustrative overview of case examples from our institution, provide an outlook on what this may mean for our clinical practice, and propose a potential radiologic research agenda on the topic.

Adverse Findings Observed after IACS Injection

Accelerated OA Progression

Rapid progressive OA (RPOA) or accelerated OA has been described by several authors (21–23). RPOA type 1 is synonymous with rapid loss of joint space on radiographs that is beyond the expected rate and was introduced in the context of clinical trials assessing the efficacy of nerve growth factor inhibitors, which are potent analgesics commonly administered as subcutaneous injections (24). Early trials of these nerve growth factor inhibitors have suggested that a minority of patients experience accelerated OA and require joint replacement earlier than expected (25). There is no clear definition of what exactly comprises RPOA type 1, but some authors have suggested that a joint space loss of more than 2 mm within a 12-month period represents accelerated joint space narrowing (24). The finding of joint space loss on radiographs commonly is a reflection of cartilage loss or meniscal tear and extrusion at MRI. However, when assessing interval joint space narrowing at radiography, minor variations in patient positioning have been shown to result in changes in joint space measurements without actual structural changes, and this needs to be considered when evaluating for interval changes (26). Associated findings of RPOA type 1, as detected with radiography, may include joint effusion, synovitis, adjacent soft-tissue changes, and subchondral bone changes, including extensive bone marrow edema and cystlike changes on the corresponding MRI (27) (Fig 1).

Subchondral Insufficiency Fracture

Subchondral insufficiency fracture (SIF) of the knee and hip is becoming a more recognized abnormality in the orthopedic and radiology communities (28–30). Although SIF was once believed to occur predominantly in older patients and those with osteopenia, more recent studies have shown that younger adults who are active or who may have increased bone mineral density can also have SIF (28–30). Patients typically present with acute pain, which gradually worsens for weeks without an identifiable trauma (31). The SIF is typically found in a weight-bearing area, and there may be associated cartilage loss and meniscal tearing (32,33). If SIF is diagnosed early and does not show signs of articular collapse, it can heal with no change to the overlying articular surface (33,34). However, if SIF is not diagnosed at an early stage, it can progress to articular surface collapse, necessitating joint replacement (35). The radiographic appearance of SIF can be normal, unless there is collapse of the articular surface in advanced stages. Radiographic findings can range from subtle flattening of the articular surface to marked loss of sphericity with a fragmented articular surface (36). Frequently, SIF on radiographs is associated with accelerated joint space loss (37). What was commonly understood to be spontaneous osteonecrosis of the knee is now recognized as SIF without the potential to heal, leading to eventual collapse of the articular surface (38,39).

At MRI, subchondral hypointensity with varying thickness and extent is an early finding of SIF (28). There is a marked surrounding bone marrow edema pattern that is more intense than would be expected for typical OA (34). In the hip, SIF is usually associated with cartilage loss in the anterior or anteromedial weight-bearing region (40) (Fig 2). In the knee, SIF is often associated with meniscal tears with extrusion in the same compartment, particularly posterior root radial tears, with or without cartilage loss (32,41) (Fig 3). The most common anatomic location for SIF in the knee is the medial femoral condyle, and periarticular soft-tissue edema involving the posterior and medial soft tissues, including the medial collateral ligament, is consistently observed (42). Prognosis seems to be determined by extent and thickness of the subchondral hypointensity (34). Advanced SIF showing fluid dissecting below the subchondral plate is irreversible and will progress to articular surface collapse and secondary OA (40,43).

Complications of Osteonecrosis

Osteonecrosis is a frequently encountered disease, most often occurring in the femoral head and condyles (44). Osteonecrosis without collapse of the articular surface is often radiographically occult, and MRI is needed for diagnosis (45). Patients can present with an insidious onset of pain and can be asymptomatic until the development of insufficiency fractures or articular surface collapse (46). Pain symptoms and treatment plans are related to the possibility or presence of subchondral bone plate collapse. At MRI, the size of the area of osteonecrosis and the associated bone marrow edema pattern are predictors of collapse (47). Collapse results in the development of secondary OA and persistent pain, and

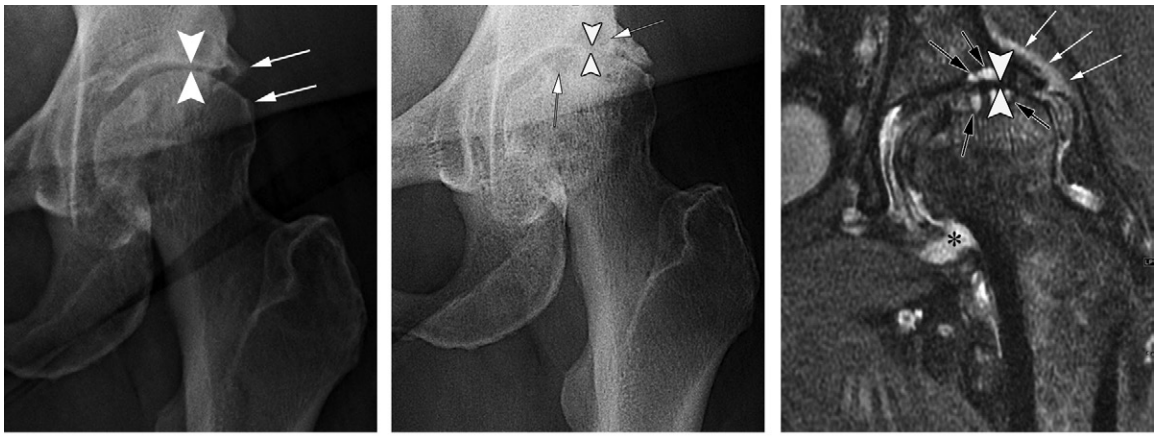

Figure 1: Rapid progressive osteoarthritis joint space loss (type 1) in a 61-year-old woman who presented with hip pain. **(a)** Anteroposterior left hip radiograph shows joint space narrowing (arrowheads) and femoral and acetabular osteophytic changes (arrows) consistent with Kellgren-Lawrence grade III hip osteoarthritis. She was referred for US-guided steroid injection. **(b)** Four months after intraarticular corticosteroid injection, she presented with worsening left hip pain. Anteroposterior hip radiograph shows severe interval joint space narrowing (arrowheads) and enlarging subchondral cysts (arrows). **(c)** Coronal intermediate-weighted fat-suppressed MRI obtained at the same time as **b** shows complete loss of the acetabular and femoral cartilage (arrowheads), with subchondral cystic changes (black arrows). In addition, there is joint effusion and synovitis (*) and periarticular soft-tissue edema (white arrows). This patient underwent total joint replacement 3 months later.

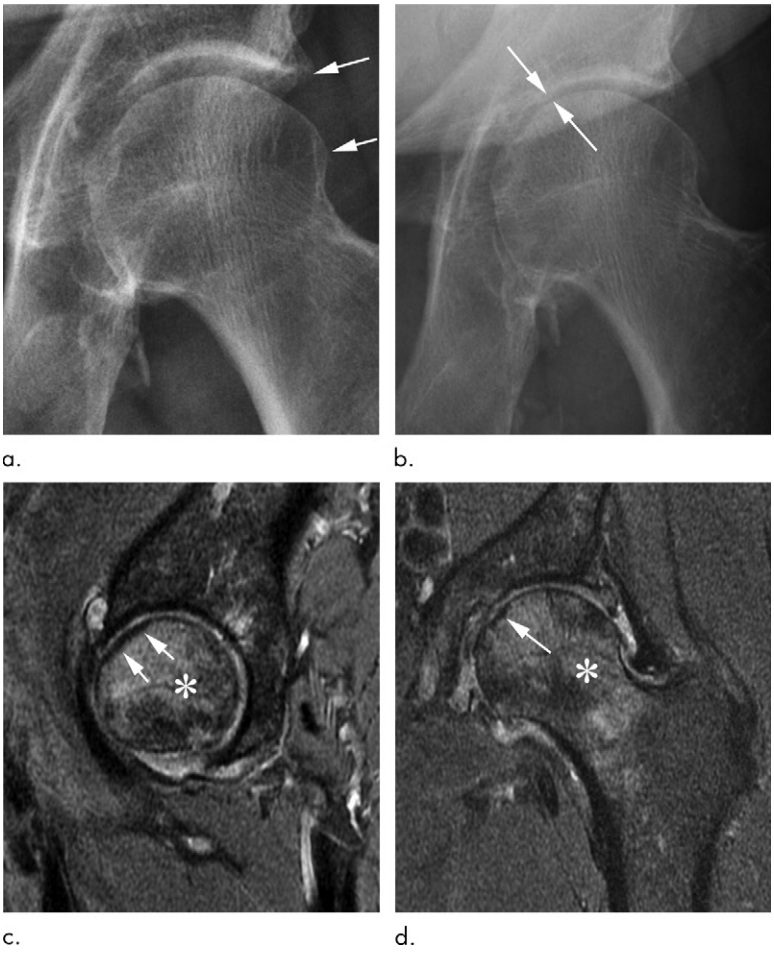

Figure 2: Rapid progressive osteoarthritis joint space loss (type 1) and subchondral insufficiency fracture in a 53-year-old man who presented with hip pain. **(a)** Anteroposterior left hip radiograph shows mild osteophytic changes (arrows) and no joint space loss. This patient was referred for intra-articular corticosteroid injection. **(b)** Seven weeks after injection, he returned with worsening hip pain. Repeat anteroposterior left hip radiograph shows accelerated loss of joint space (arrows). **(c)** Sagittal intermediate-weighted fat-suppressed MRI obtained at the same time as **b** shows a linear subchondral hypointensity representing subchondral insufficiency fracture of the anterior superior femoral head with subtle flattening of the overlying articular surface (arrows). Extensive bone marrow edema extends to the femoral neck (*). **(d)** Corresponding coronal intermediate-weighted fat-suppressed MRI enables us to confirm the presence of a subchondral insufficiency fracture (arrow) and depicts the true extent of bone marrow edema (*).

treatment options at this stage are limited to joint replacement. Patients with painful noncollapsed osteonecrosis of the femoral heads are often referred for IACS treatment (Fig 4). To our knowledge, there are no standardized treatment guidelines for these patients, and there is no recognized contraindication or benefit to these patients receiving an IACS (48).

Rapid Joint Destruction Including Bone Loss

RPOA type 2 is another term established in the context of clinical trials of nerve growth factor inhibitors and is defined as rapid articular destruction with accelerated bone loss not typically seen in patients with OA (49). Several case reports have described the potential cause of RPOA type 2, although there is a lack of larger studies given the relatively low prevalence of this disease (50). Initial reports attributed this entity to accelerated osteonecrosis, while others have suggested this is advanced joint destruction related to undiagnosed SIF (51,52). Although we have seen RPOA type 2 in patients receiving IACS injections (Fig 5), it has also been found to randomly occur in patients without prior intervention or underlying disease (53).

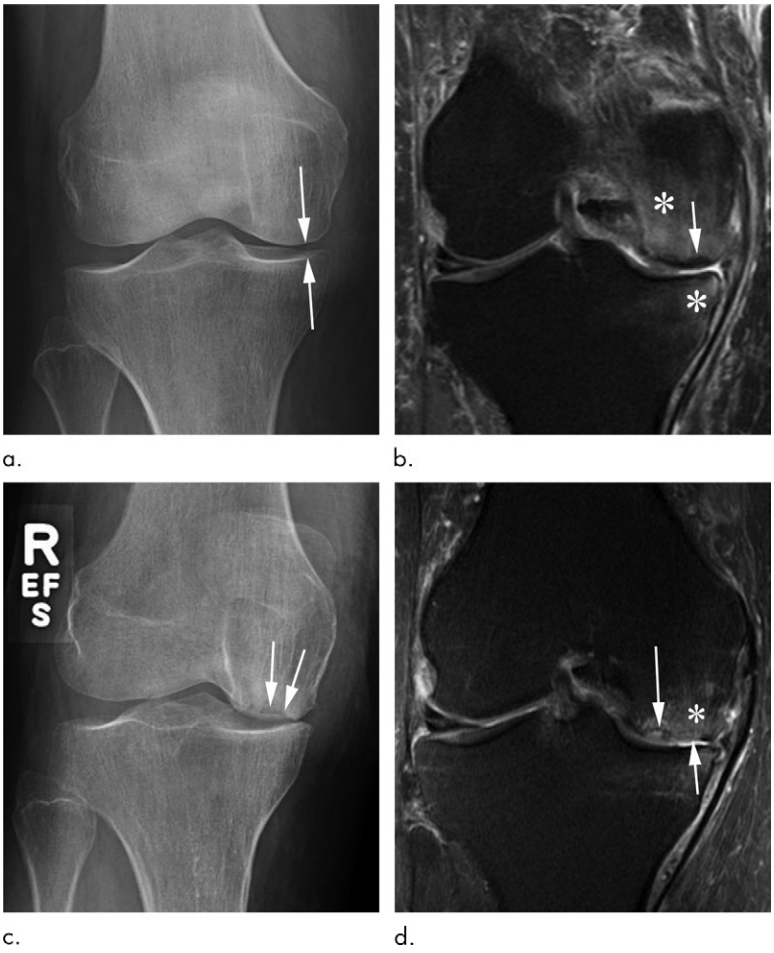

Figure 3: Subchondral insufficiency fracture in a 69-year-old woman who presented with acutely worsening knee pain without known trauma. **(a)** Anteroposterior radiograph of the right knee shows possible medial compartment joint space narrowing (arrows) without osteophytes. There are no signs of osteonecrosis or subchondral insufficiency fracture. **(b)** Coronal intermediate-weighted fat-suppressed MRI obtained at the same time as **a** shows a subchondral insufficiency fracture of the medial femoral condyle, without collapse of the articular surface (arrow). In addition, there is marked femoral and tibial bone marrow edema (*). This patient was not treated with conservative measures (ie, switch to non–weight-bearing activity) and received an intra-articular corticosteroid injection. **(c)** Eleven months later, she returned with continued right knee pain. Repeat anteroposterior radiograph of the right knee shows collapse of the medial femoral condyle articular surface (arrows). **(d)** Coronal intermediate-weighted MRI acquired at the same time as **c** demonstrates deformity of the articular surface (short arrow) of the medial femoral condyle in the area of a previously noted subchondral insufficiency fracture (long arrow). In addition, there is marked bone marrow edema (*).

Figures 1–5 are typical examples of these disease entities recently identified in our clinical practice. All patients had undergone IACS injection. We acknowledge that we do not have insight into whether these observed events were already ongoing at the time of injection or if these findings are an actual result or complication of the IACS injection itself.

Outlook

IACS injections are frequently performed for pain relief in patients with knee or hip OA. Recent reports and case series have suggested that certain preexisting conditions (older age, white race) may increase the risk for a negative joint outcome after IACS injection (54,55). Currently, to our knowledge, there is no recommendation for imaging before an IACS injection to detect such entities prior to the intervention. Subchondral insufficiency fracture and osteonecrosis can sometimes be diagnosed by using radiography, although the findings can be subtle or radiographically occult. However, given the relative ease of performance and the low cost of radiography, there should be a low threshold to obtain radiographs before performing an IACS injection, as the intervention may affect the disease course (ie, it may result in accelerated progression).

Identification of a subchondral insufficiency fracture before IACS injection is clinically important, as glucocorticoids may inhibit the healing process of such a fracture (56). The primary treatment of a subchondral insufficiency fracture is conservative, including protected weight-bearing or non–weight-bearing activities, and some authors have proposed the supportive use of bisphosphonates or prostacyclin analogs (57,58). There is little evidence regarding these supportive approaches, however, given the small number of treated patients and the potential underdiagnosis of subchondral insufficiency fracture due to lack of radiologic awareness. Performance of IACS injection in the presence of a subchondral insufficiency fracture could result in decreased joint pain, potentially leading to increased weight bearing and possible acceleration of subchondral insufficiency fracture to joint collapse. Additionally, if IACS injection is performed with US guidance, findings suggestive of an inflammatory process on preinjection US images, including a larger-than-expected joint effusion, extensive intraarticular debris, or synovial thickening and medial soft-tissue thickening with vascularity on Doppler US images, could indicate an on-going active joint process, including a radiographically occult subchondral insufficiency fracture, and may lead physicians to not perform the injection at that time but rather perform MRI prior to IACS injection.

In patients with no OA or only mild OA on a radiograph who are referred for IACS injection to treat joint pain, the indication for IACS injection should be closely scrutinized. Case series and retrospective reviews have shown that some patients who develop rapid progressive joint space loss or destructive OA tend to have no OA or only mild OA at initial presentation (50). Clinicians should consider obtaining a repeat radiograph before each subsequent IACS injection to evaluate for progressive narrowing of the joint space and any interval changes in the articular surface that can indicate subchondral insufficiency fracture or type 1 or 2 RPOA.

To our knowledge, overviews regarding the treatment of osteonecrosis do not discuss IACS injection to treat pain (59). Orthopedists do not have a contraindication for performing IACS injections in patients with osteonecrosis. Patients with already collapsed osteonecrosis could be candidates for IACS injection,

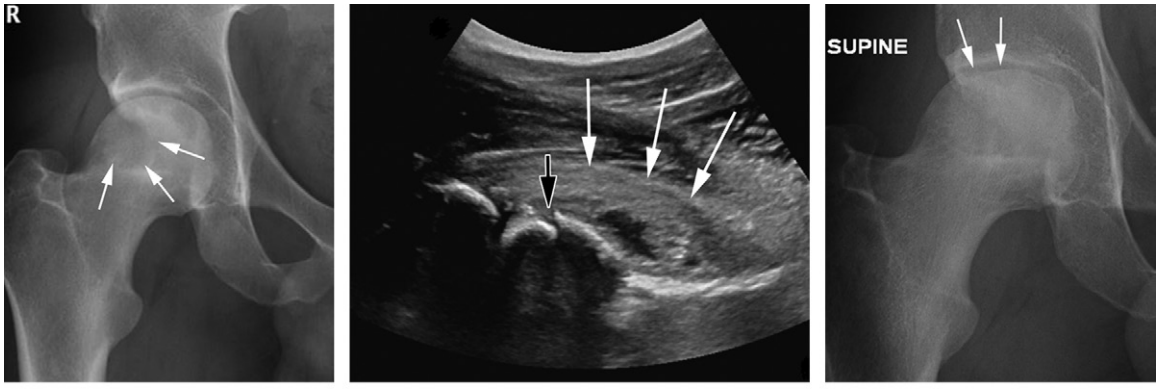

Figure 4: Osteonecrosis in a 29-year-old man who presented with right hip pain. **(a)** Anteroposterior radiograph of the pelvis shows osteonecrosis in the right femoral head, with preserved femoral head contours (arrows). He subsequently went to the sports medicine clinic and received a right hip joint corticosteroid injection for pain. **(b)** Three months later, he was referred to our institution for repeat intra-articular corticosteroid injection. The patient presented with a severe limp when walking and described the pain as worse than his original pain. Preprocedural sagittal US image shows a defect in the anterior right femoral head cortex (black arrow) and moderate joint effusion with a severely thickened anterior joint capsule (white arrows). The intra-articular corticosteroid injection was cancelled given the US findings, and the referring orthopedic physician was informed of the findings. **(c)** Repeat anteroposterior right hip radiograph obtained 1 week after US when the patient was seen in the orthopedic clinic for a follow-up visit enabled confirmation that the superior femoral head articular surface had collapsed (arrows), and the patient underwent right hip joint replacement.

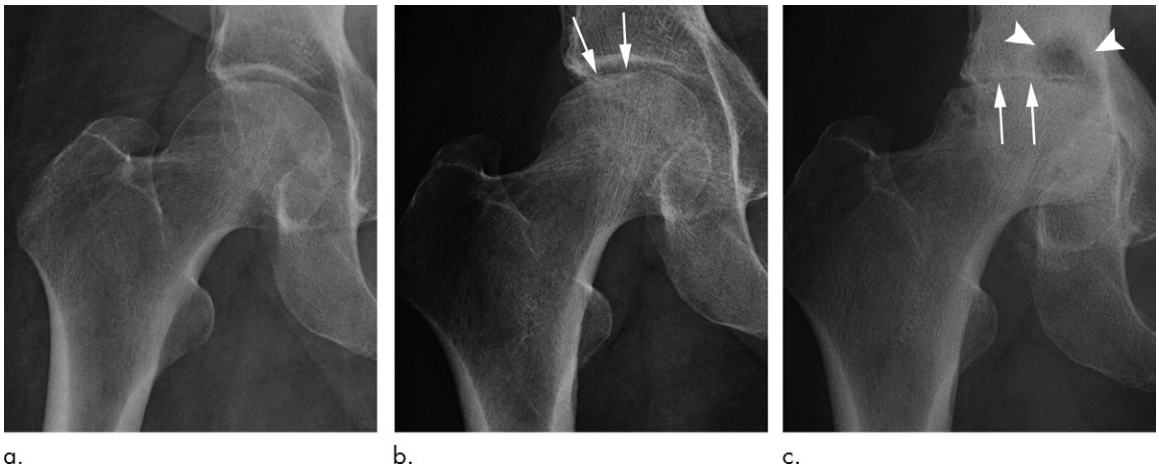

Figure 5: Rapid progressive osteoarthritis (RPOA) type 2 in an 81-year-old woman with right hip pain who was referred for right hip intra-articular corticosteroid injection. **(a)** Anteroposterior right hip radiograph shows no definite osteoarthritis. **(b)** Within 3 months after receiving the injection, this patient presented with worsening right hip pain. Repeat anteroposterior right hip radiograph shows subchondral insufficiency fracture, with collapse of the superior femoral head articular surface (arrows). **(c)** Pain increased markedly over the following month, and this repeat anteroposterior right hip radiograph shows bone loss and destruction of the femoral head with severe joint space loss, consistent with RPOA type 2 (arrows). In addition, there are extensive cystic changes at the acetabulum (arrowheads).

given that joint replacement would be their only other treatment option to relieve pain. Controversy arises when patients with a diagnosis of femoral head osteonecrosis are referred for IACS injection and have preserved femoral head contours. When a patient with femoral head osteonecrosis without collapse is referred to our clinic for IACS injection, the potential of accelerating the osteonecrosis leading to joint collapse, the potential for worsened pain, and the need for joint replacement to relieve the pain are now routinely included in the patient's informed consent at our institution.

In conclusion, intra-articular corticosteroid (IACS) injections are frequently performed with the hope of relieving joint pain. However, large retrospective analyses and prospective studies evaluating accelerated osteoarthritis (OA) or joint destruction after IACS injections are lacking. We believe that certain patient characteristics, including but not limited to acute change in pain not explained by using radiography and no or only mild OA at radiography, should lead to careful reconsideration of a planned IACS injection. In these circumstances, MRI may be helpful to further evaluate the actual cause of pain prior to a planned injection. Given that IACS injections are increasingly performed to treat pain in patients with hip or knee OA, we suggest that the radiologic community should actively engage in high-quality research on this topic to better understand potential at-risk conditions prior to intervention and to better understand potential adverse joint events after these procedures to avoid possible complications.

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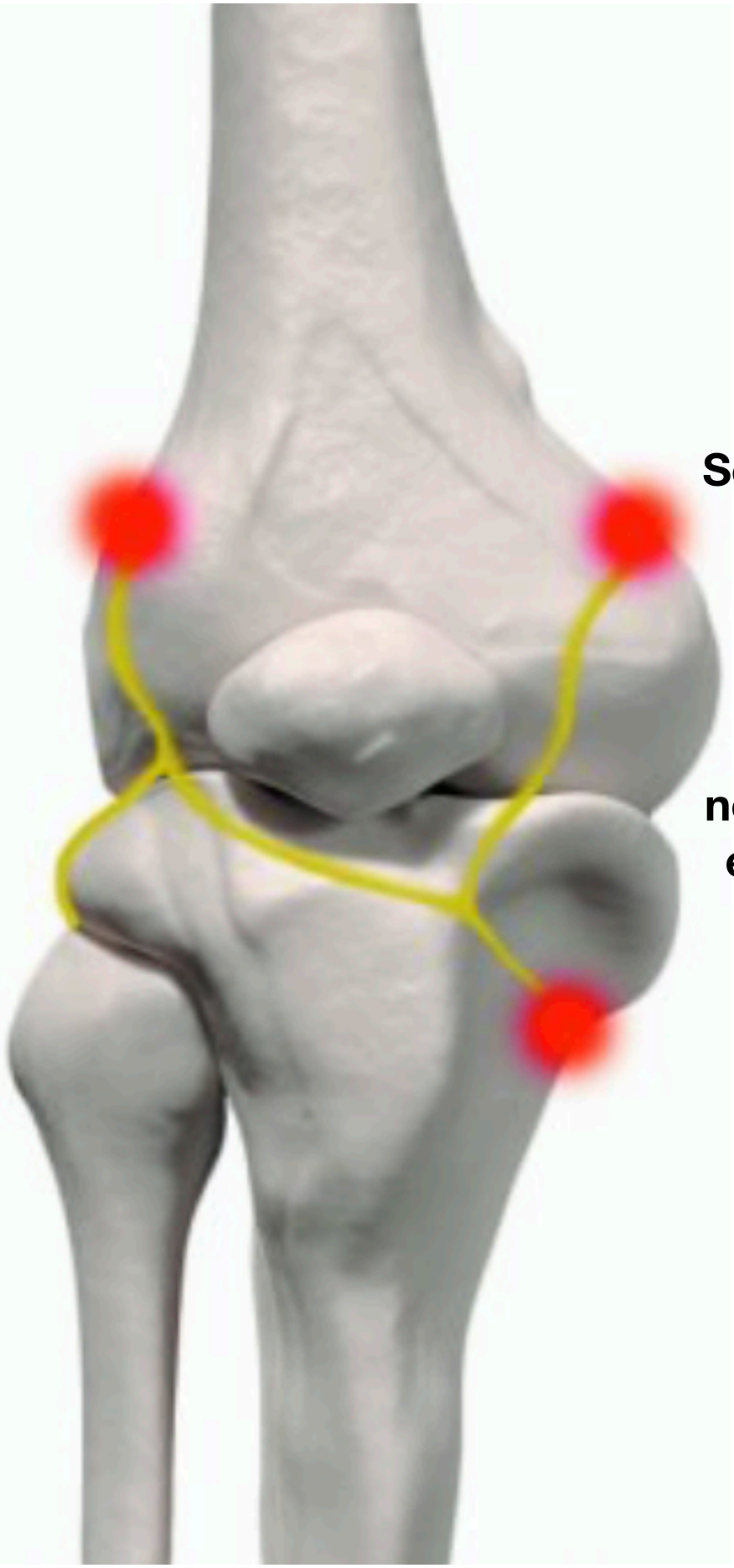

Genicular Nerve Block

OA/RA Knee Pain

No steroid used

Sensory block only, should not cause motor weakness

Can be done even if TKA

Can refer for RFA of these nerves and that is increasingly encouraged by the physiatry literature, however closest option seems to be GTA