Risk Management

Putting It All Together

Pain is
"*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*"

- **International Association for the Study of Pain, 2020**

The management of pain, particularly that of chronic pain, is highly complex. Medical providers are challenged not only by careful consideration of the risks and benefits of individual medications and non-medication treatments, but also by comparative considerations of the wide range of alternatives primarily considered. For example, it is widely known that opioids have a substantial risk for death, primarily due to respiratory depression in overdose. In studies in which data is stated or from which it can be calculated, 0.02-0.08% of patients prescribed an opioid expire from an opioid-related overdose[1,2,3,4,5]. Opioids have well-documented additional risks with long term use including osteoporosis, depression, weight gain, pneumonia, and increased pain through opioid-induced hyperalgesia. However, it must be recognized that serious adverse events occur with other medications as well. Non-steroidal anti-inflammatory drugs (NSAIDs), which are often used as first-line agents, have been associated with a gastro-intestinal (GI) bleed death rate of 0.02%[6] - the same order of magnitude as opioid-related overdose death even when mortality associated with NSAID-related cardiovascular (CV) and renal consequences is not included.

For clinicians - not simply those in pain management – competence is needed in three domains:

1. Knowledge
2. Application of knowledge
3. Documentation

With respect to pain management, these general skill sets are required in two separate but interrelated management tracks: 1) Pain Management and 2) Risk Management.

Pain Management

Pain evaluation and its subsequent management is multifaceted and difficult. In brief, the following elements should be addressed with respect to the patient's history of pain complaints:

1. Pain descriptors: intensity, character (nociceptive, centralized, both), location, radiation, aggravating factors, ameliorating factors, red flags, neurologic correlates
2. Function descriptors: prior / current status (work, home, school, social), current status with / without current treatment
3. Pain onset: gradual / abrupt, injury (describe mechanism)
4. Diagnostic studies / results

5. Pain course: overall, diagnoses, efficacy and problems with medications / modalities / procedures / surgeries

Further evaluation, then, encompasses the following:

1. Pain-directed physical examination
2. Laboratory evaluation
3. Imaging
4. Neurodiagnostics
5. Diagnostic procedures

Outside of the acute / postop pain setting, chronic pain is traditionally defined as pain that persists most days over the previous three months. Defined in that manner 19% or 39.4 million Americans have chronic pain[7]. It is this pain - chronic *and* intractable - that is relatively resistant to therapies and is particularly challenging to patients and medical providers alike.

In general, preferential treatments are non-opioid options. To begin, there is value to determining the sensory (pain) phenotype as nociceptive, centralized (most commonly neuropathic), or a combination. This aids in treatment decision-making, since centralized pain (burning, lightning, electric, shock-like, dysesthetic) is more likely to respond to non-opioid analgesics[8]. Similarly, inflammatory pain may be better addressed with the use of anti-inflammatories, assuming patients are not at high risk for this class of medication[9,10]. Medications (*viz.,* substances to solve a problem) which provide analgesia can be categorized based upon their predominant neurophysiologic mechanism (*e.g.*, the primary receptor at which the agent is active) or on the reason for which they were originally used (*e.g.*, antidepressants found later to provide analgesia). The options below are listed primarily by receptor effects when known. Some are available in various delivery options with dermal applications advantageous at times as they may provide fewer adverse reactions though generally with weaker researched support. Options include:

1. Anti-inflammatories (often 1st line: corticosteroids [though not for low back pain[11]], NSAIDs - diclofenac > celecoxib)[11,12,13,14]
2. Acetaminophen[11,13,15] (limited utility[14,16,17,18,19,20], complex neuropharmacology[14,21])
3. Selective Serotonin Reuptake Inhibitors (SSRIs)[22,23,24,25] (minimal benefit[14]; not for headache[26])
4. Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)[13,22-25] (especially duloxetine[13414,27,28,29]; milnacipran for fibromyalgia only[14,30,31]; not for headache[14])
5. Tricyclic Antidepressants (TCAs)[21-24,28] (some utility, more side effects than that for other antidepressants)
6. Calcium channel modulators[14,28,32,33,34,35,36] (gabapentinoids: gabapentin, pregabalin)
7. Sodium channel agents (topical lidocaine[37,38,39,40], anticonvulsants - evidence mixed[11,41,42])
8. N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA) receptor antagonists (memantine for fibromyalgia[14], methadone[43], ketamine[44,45,46])
9. Skeletal muscle relaxants[11,47,48,49] (limited utility as adjunctive medications)
10. Benzodiazepines[50] (analgesic utility only for burning mouth and stiff person syndromes)
11. Stimulants[51] including caffeine[52] (rare analgesic utility as adjunctive medications)
12. Cannabinoids[53,54,55] (mixed results, adverse reactions of concern[56])
13. Other phyto-chemicals and dietary supplements for various pain conditions for short-term use: avacado-soybean unsoponifiables[57,58,59], collagen hydrolysate[59], passion fruit peel extract[59], *Curcuma longa* extract[59], *Boswellia serrata* extract[59], curcumin[59], pycnogenol[59], L-carnitine[59], undenatured type II collagen[59], methylsulfonylmethane[59], diacerein[59], glucosamine[59], chondroitin[59], capsaicin[60], alpha-lipoic acid[61,62,63], and theramine[64].

When possible and efficacious, non-medication approaches are often preferable as they may afford analgesic and functional benefit without as high a risk of adverse outcomes (not always) as medications:

Self-Directed after Training

1. Structured exercise
2. Mind-Body Therapies: Biofeedback, Movement meditation, Mindfulness, Relaxation
3. Music
4. Neurostimulators
5. Nutritional approaches
6. Thermal modalities / Balneotherapy (spa)
7. Sleep hygiene
8. Spray and stretch
9. Spiritual practices
10. Tobacco cessation
11. Weight reduction

Professionally Directed

1. Physical Approaches
    a. Acupuncture
    b. Assistive devices
    c. Blocks / Ablation
    d. Ergonomic modifications
    e. Light therapies
    f. Massage
    g. Osteo-manipulation
    h. Physical therapy / Occupational therapy
    i. Regenerative therapies: platelet rich plasma, prolotherapy, stem cells
    j. Stimulators: peripheral, spinal, deep brain
    k. Surgeries
    l. Trigger point interventions
    m. Ultrasound
2. Psychological Approaches / Pain Behavior Therapies
    a. Acceptance and Commitment Therapy
    b. Cognitive Behavioral Therapy
    c. Behavioral therapies
    d. Pain education
3. Treatment of certain underlying medical conditions
    a. Acute pain conditions
    b. Diabetes
    c. Gastrointestinal conditions
    d. Psychological conditions
    e. Rheumatologic conditions
    f. Sleep-related conditions
    g. Strategic deprescribing

Opioids

The judicious use of opioids may provide functional (the primary goal) and analgesic (the intermediate goal) advantage to patients. Benefit in both ways is well-established for short-term acute, including postoperative, pain[65,66,67]. In acute contexts, though, non-opioids may perform as well as or better than opioids[68,69]. Even when the condition in which opioids are used is reasonable, the amounts prescribed are often far greater than is necessary and should be limited[70]. Prescribers are well advised to keep abreast of the researched recommendations relevant to the pain conditions they treat.

Far more controversial - appropriately so - is the use of opioids long-term for chronic pain conditions. While it is true that there are no prospective, placebo-controlled studies involving opioids for a year or more, it is also true these studies will never be performed to answer the controversy definitively because it is unethical to allow patients to remain on a placebo for a long duration of time while experiencing disabling pain. There are, however, open-labeled studies that suggest that some patients may have long-term benefit[71,72,73,74], though the methodology of the research can be called into question.

If and when a decision is made to use an opioid, then the question is which one, as all opioids are not the same. Each opioid moiety has differential effects on the opioid receptors mu, kappa, delta, and nociceptin. These receptors have differential effects on analgesia and adverse effects[75,76] due to variable affinity, intrinsic activity, and potency, though the mu receptor is generally the most important. It is useful to consider which opioid worked best in the past; however, a patient's insistence on a particular opioid is very likely to indicate problematic use, if not addiction. With respect to efficacy and potential adverse effects, genetics at some point in the future may have predictive value, though today that value has not been realized[77,78]. On the other hand, initial opioid selection can be based in part on presence of certain co-existing non-pain medical conditions or concerns (data limited), though relative safety in one domain may be risky in another (Table 1). Opioid selection otherwise is based on more practical considerations: cost, coverage, formulary, prior authorization requirements, and availability.

Table 1

Opioid Selection Considerations based on Medical Condition

+ Constipation [79,80,81,82]
  - Worse: Methadone, Morphine
  - Better: Buprenorphine TD, Fentanyl TD, Oxycodone CR, Tapentadol
+ Renal Disease [83,84,85,86,87]
  - Avoid: Morphine, Codeine, (also avoid NSAIDs)
  - Safer: Buprenorphine, Methadone, Fentanyl
+ Hepatic Disease [87,88,89,90]
  - Avoid: Methadone, Codeine, (also avoid NSAIDs, APAP)
  - Safer: Fentanyl
+ Serotonin syndrome risk more likely: Tramadol, Tapentadol
+ Depression less likely: Buprenorphine
+ Respiratory depression less significant: Buprenorphine, Tapentadol, Tramadol [80,89,91]
+ Hypogonadism less likely: Buprenorphine, Tapentadol [80,91]
+ Addiction liability lower: Buprenorphine, Tapentadol, Tramadol, Methadone, Abuse Deterrent Formulations [92,93,94,95,96,97,98]

On follow-up, in general the goal is to achieve a 30% improvement in both pain[99] and function[100]. This should be assessed on each patient encounter to ensure durability of benefit over time. If efficacy is not found or if gains are lost over time, a change in therapy is indicated. The presence (or not) of adverse reactions should be elicited – first in an open-ended fashion, then direct inquiry about constipation (the most common side effect at 40%[101]), nausea ± vomiting (experienced by 30%[71] yet usually resolves spontaneously), dyscognition, sedation, psychomotor impairment, respiratory function, mood decrements (PHQ-2 → PHQ-9 for depression, GAD-7 for anxiety) – all of which should be specifically listed in the Review of Systems if not already documented in the History of Present Illness section.

If side effects are present, they should be addressed. Dose reduction can be considered but unlikely to help constipation for which other options are available[102,103]. End-of-dose failure (increased pain before the next scheduled dose) can be managed by decreasing the interval between dosages, since in research or by clinical experience individuals may experience limited duration of action for various opioids: oxycodone short-acting (2 hours), oxycodone controlled release (6 hours), morphine extended release (6 hours), hydromorphone (2 hours), methadone (6 hours), fentanyl transdermal (48 hours), and buprenorphine weekly patch (6 days)[104,105,106]. Breakthrough pain - separately defined[107] - may be incident (environmentally prompted) or spontaneous (no obvious trigger) in type and can be addressed with short-acting opioids[108,109,110] (no more than 8 per month recommended) and better yet non-opioid

options[111]. Opioid inadequacy can also be addressed by switching (rotation) to a different opioid, which can be successful in half or more of patients in research primarily involving single rotations[112,113,114,115,116,117,118,119]. Research on multiple sequential switches was found in only one poorly designed study[120] and should be reserved to prescribers highly experienced.

Continued opioid therapy, however, is not always appropriate. Opioid use in some patients can become a source of pain due to central hypersensitization (opioid-induced hyperalgesia)[121,122]. This paradoxical response was first suggested by Lord Albutt in 1870: "Does morphia encourage the very pain it pretends to relieve?"[123] However, the phenomenon is still poorly understood, is caused by multiple neuropharmacologic mechanisms, and should be suspected when opioid efficacy declines when the underlying pain condition has not progressed. Management primarily involves opioid tapering as opposed to that for opioid tolerance which responds favorably to opioid dose increases[124,125,126].

In fact, because it is difficult to discern evolving loss of benefit and/or advancing adverse reactions (*e.g.*, subtle dyscognition), it is prudent to offer opioid tapering to *all* persons on long-term opioids. Such an offer does not mean forced reductions[127], however, unless clear-cut respiratory compromise is identified. Indeed, voluntary tapering can be very successful and often result in improvements in pain and function[128,129]. Even if complete discontinuation is not achieved, the least necessary dose can be established, providing a better safety profile for the patient. In the absence of severe opioid side effects like respiratory compromise, there is plenty of time to taper. Because ultimate success is more important than rapid failure, initiating the taper by a small amount (*e.g.*, by 5 mg of hydrocodone) is preferred for a few reasons. Patients are concerned prescribers will "throw them under the bus" with brisk dose decrements, and maintaining a therapeutic alliance is enhanced by a slower trajectory. Patients need to know the medical provider is "all in" on addressing their pain, so sequential trials of non-opioid approaches simultaneously are important. Small initial reductions can be adjusted up or down according to the individual's response. Here, patients should lead the shared decision-making because it is their expertise – their lived experience – which is most relevant in the tapering progression.

Some circumstances call for abrupt discontinuation rather than tapering, though. Identification of major opioid-related aberrancies - for example, a forged prescription, obvious impairment, or diversion - necessitates this. It is also quite unlikely that individuals with Opioid Use Disorder (OUD) will be able to taper due to the craving they experience. Depending on the circumstances, discontinuation should be paired with the use of withdrawal medications, such as outlined in Table 2.

Table 2
Withdrawal Medications: Basic Recommendations

Pain	Naproxen	220 mg	PO	qid prn	#20
Back Spasm	Cyclobenzaprine	10 mg	PO	qid prn	#20
Abdominal Cramps	Hyoscyamine	0.125 mg SL	SL	qid prn	#20
Shakes, Sweats	Clonidine[5-8]	0.1 mg	PO	qid prn	#20
	Lofexidine [9,10]	0.1 mg	PO	2 tid	#36 or #96

Risk Management

The recommendations above assume that patients use these agents safely, which is not the case for a significant proportion of those exposed to opioids. Central to this concern is the nonmedical use and OUD. Studies vary widely[130,131,132,133], but in a systematic review, Vowles *et al* found the prevalence of opioid addiction in pain populations prescribed opioids to be 8-12%[134]. Identification of and managing this is critical in and of itself, but also because opioid addiction characteristics have been seen in 80-95%

of those who die of an opioid-related overdose[135,136]. Consequently, clinicians should carefully attend to risk management as well as pain management. The following steps are recommended[137,138]:

1. Risk Screening (Table 4)
2. Risk Stratification (Table 4)
3. Risk Mitigation (Table 5)
4. Risk Monitoring (Table 6)
5. Aberrancy Management (Table 7)

Risk Screening and Risk Stratification

Risk Screening ideally should begin prior to the first office visit contact with a new patient through the review of the patient's medical records. Among the risk factors that predict poorer outcomes (Table 3), eliciting responses to the following are especially important: 1) Personal and family history of Substance Use Disorder (SUD), 2) Personal history of psychiatric or mood problems, and 3) Personal history of trauma.

Table 3

Factors Associated with Opioid Nonmedical Use, OUD, Opioid-Related Overdose

1. Personal / Family history of Substance Use Disorder – especially OUD[135,139,140,141,142,143,144,145,146]
2. Personal history of psychiatric or mood problems[144,145,147,148,149]
3. Personal history of trauma[150,151,152]
4. Male gender[143,153,154]
5. Younger age[143,147,155]
6. Legal problems[142]
7. Specific opioid prescribed: fentanyl, morphine, methadone[145]
8. High dose opioid prescribing[142,144,147,156,157,158]
9. History of medication-related aberrancies[141,159,160]
10. Multiple prescribers or pharmacies[161,162]
11. Respiratory / pulmonary disease, including COVID[145,149,163,164,165,166,167]
12. Co-prescribed respiratory depressants, notably benzodiazepines[145,149,168,169,170,171,172,173]
13. Cardiac disease[149]
14. Certain circumstances with cancer[1]
15. Impaired renal or hepatic function[145,146]
16. Certain infectious diseases, *e.g.*, HIV, hepatitis[174,175,176]
17. Lower educational achievement[177]
18. Not married, divorced[175,178]

There is a range of approaches that are effective in determining and managing safe controlled substance prescribing, which are best employed in a multi-faceted manner[179,180]. To being with, all patients – not just those for whom controlled medications are or might be prescribed – should be screened for the use of addiction-prone substances through the use of the screening portion of Screening, Brief Intervention, and Referral to Treatment (SBIRT) [181,182,183,184,185]. This is no more complicated than to ask, "Do you currently or have you ever used [tobacco, alcohol, cannabis, illicits; stimulants, benzodiazepines, opioid for reasons other than prescribed]?" A "yes" answer to any one specific substance should be secondarily screened for problems with tobacco (Fagerström Test[186]), alcohol (Alcohol Use Disorder Identification Test [AUDIT][187]), cannabis (Cannabis Use Disorder Identification Test [CUDIT-R][188]), illicit drug use (Drug Abuse Screening Test [DAST-10][189]). If problematic use is identified through these screeners, the presence (or not) of addiction should be determined and addressed accordingly. If prior but not current use is found, inquiry as to why a substance was discontinued is

important as the person may have discontinued use due to difficulties or addiction, which are still risks even when problems are remote.

"Trust, but Verify"
Because some individuals may not be honest about addiction-prone substance use[190,191], additional approaches are indicated. When available, information provided by family and others associated with the patient can be useful. Though imperfect[192,193], review of the online prescription database (specific name varies by state) can determine 1) Which controlled prescriptions were filled, 2) How many prescribers prescribed them, and 3) How many pharmacies dispensed them[194,195]. Enhancements within these databases differ by state, but can be helpful in determining other worrisome circumstances, such as high daily morphine milligram equivalents (MMEs) of opioids received. Risky prescribing/dispensing has been associated with opioid-related overdose[196], and use of the online prescription database can limit inappropriate prescribing[197,198,199,200,201], as well as opioid-related overdose deaths[202]. It is recommended that review of prescription databases be performed prior to any controlled substance prescribing – *i.e.,* for both acute and chronic pain.

When considering opioid prescribing for chronic pain or for acute pain when concerned, drug testing should be performed for additional verification (or not) of reported substance use[203,204,205,206]. In-office point-of-care urine drug *screening* has advantages in that it is inexpensive and results are immediate but is fraught with false positives and false negatives[206,207,208]. Such immunoassays are good "conversation starters" but should not be relied upon for major clinical decisions[206]. Definitive - also termed confirmatory or quantitative - *testing*, on the other hand, will identify those substances to which a patient has been exposed with certainty, using Gas Chromatography with Mass Spectrometry (GC-MS) or High Performance Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS) techniques[203-208]. Definite identification, however, does not clearly indicate the reason for the presence of a particular substance. For example, a "morphine" result may be due to morphine *per se* (prescribed or not), codeine (prescribed or not), poppy seeds (variable individual results), or heroin[209,210]. Validity testing by various means is important as well in order to determine if the patient has attempted to adulterate, dilute, or substitute the sample provided for analysis[206].

A valid definitive test that shows only the prescribed agents is termed "expected". The presence of non-prescribed substances or the absence of prescribed medications are "unexpected" or "potentially inappropriate"[211] and necessitates a discussion with the patient, and possibly a change in plan[206]. Research demonstrates this process of initial as well as follow-up drug testing using either urine or oral fluid matrices improves identification of inappropriate substance use[201,212,213] and improves the safe use of prescribed medications by patients[214]. Skill in the interpretation of drug testing is best accomplished through establishing a basic knowledge, selecting a testing vendor[215] with whose laboratory scientist can provide guidance, and experience over time.

Opioid-related overdose is primarily related to respiratory compromise[145,149,163-167]. Of particular concern are those to whom other respiratory depressants – especially benzodiazepines – are currently prescribed or being considered[145,149,168-173]. The STOP-BANG questionnaire is useful in identifying those at risk for obstructive sleep apnea[216]. Those on opioids or might be and have pulmonary conditions can be evaluated by screening with overnight nocturnal oximetry and/or testing with formal sleep studies[217,218]. Though less prominent lately, methadone is over-represented among opioid-related overdose deaths[219] not only because of its effect on respiration, but also because it can cause QT prolongation that can result in *torsades de pointes,* a life-threatening arrhythmia[220]. For that reason, baseline and periodic EKGs are indicated when methadone is prescribed[221].

When opioid prescribing is considered, determining the risk for unsafe use in the future is helpful. Many screeners have been developed, though many have limited validation. Among these, perhaps the best validated as predictive is the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) now available in a shorter 12-item form[222,223,224], rising above other screeners in comparative studies[225]. More recently developed, the Risk Index for Overdose or Serious prescription Opioid-induced Respiratory Depression (RIOSORD), unlike many other screeners includes elements regarding clinical conditions and the opioids themselves (*e.g.*, MMEs, methadone). It has been validated in veterans and commercial populations[226,227,228] and could be used on follow-up if changes in the measured elements occur. The Opioid Risk Tool (ORT) has been used widely but has limited validation[229].

Although the above description is complex, Risk Screening is outlined more succinctly in Table 4. It is medical judgement then applied to screening data that stratifies an individual patient's risk as low, intermediate, or high[230,231,232]. For those at high risk, non-opioid options are clearly preferred. The estimated level of risk helps determine the kind and frequency of risk monitoring on follow-up.

Table 4
Risk Screening and Stratification

ASK

- Personal History of Substance Use Disorder
- Family History of Substance Use Disorder
- Personal History of Psychiatric or Mood Issues / Diagnoses
  PHQ-2 → PHQ-9 if affirmative for depressed mood; GAD-7 if affirmative for anxiety
- Personal History of Trauma: ACE questionnaire
- Risk for future opioid-related aberrancies: SOAPP-R (alternatives: RIOSORD, ORT)
- Personal History of Addiction-Prone Substance Use: Screening Portion of SBIRT
  Do you or have you ever used _____
  - Alcohol affirmative → AUDIT screener
  - Cannabis affirmative → CUDIT-R screener
  - Tobacco affirmative → Fagerström Test
  - Drug affirmative → DAST-10 screener
- Current opioid amount: Practical Pain Management Opioid MME Calculator

VERIFY

- Medical Record review
- Reports of family, others
- Online Prescription Database: Specific name varies by state
- Definitive Urine Drug Test: GC/MS or LC/MS-MS
- If already on opioids:
  - Oxygenation studies to determine respiratory safety
  - EKG to determine QTc if methadone is prescribed or considered

STRATIFY

Estimate risk for controlled substance use based on the screened information

- LOW risk for controlled substance use
- INTERMEDIATE risk for controlled substance use
- HIGH risk for controlled substance use

Risk Mitigation

Mitigation, as used here, means those strategies that are employed to limit future risks with opioid prescribing and should be initiated prior to prescribing. The focus is safety and that concern should be clearly communicated to patients. The approaches are listed in Table 5.

Table 5
Risk Mitigation

- Establish realistic goals: Pain and Functional improvement 30% [99,100]
- Use of alternatives to opioids – caution: they have risks too [11-64]
- Consider opioids with lower risk of addiction: buprenorphine, tramadol, tapentadol [80,89,91]
- Calculate and address morphine milligram equivalents (MMEs) [142,144,147,156-158]
- Prescribe naloxone + provide overdose rescue instructions [233,234,235]
- Avoid co-prescribed respiratory depressants, notably benzodiazepines [145,149,168-173]
- Provide informed consent: Risks, Benefits, Alternatives [236,237,238,239,240,241,242,243,244,245]
- Provide, explain, and have the patient sign a Controlled Substance Agreement (CSA) [242,243,244,246,247,248,249,250,251,252,253]
- Provide instructions for secure storage and safe disposal [254,255,256]
- Plan for drug testing and online prescription database review based on assessed level of controlled substance risk [192-210]
- Assessment of respiratory status: oxygenation status, underlying conditions [257,258,259,260]

Managing expectations through setting realistic goals is important. Pain improvement by 30% means that a typical patient with 7/10 pain severity can expect to achieve a reduction to 4/10 making it possible to also achieve functional goals s/he establishes and not press for higher opioid dosages to try and move to zero pain which is more unsafe. Keeping tabs on the total MMEs is important in this context as well. Prescribing naloxone to all patients on opioids regardless of dose and providing rescue instructions to their significant others can be life-saving[233-235]. Plans for monitoring by means of prescription database review, drug testing, and evaluation of oxygenation status as discussed above should be done.

Patient education and discussions begins with the first visit and continues at subsequent clinical contacts. Fundamentally, informed consent is not a document to be signed but a process of communication about the risks, benefits, and alternatives of and to opioid use as well as how to use these medications properly and safely. It is central to medical practice that shared decision-making involve engaging patients about the uncertainties of specific therapeutic interventions to optimize outcomes[236-244]. With the initial prescription, verbal delivery of information, responding to questions and concerns, and directing patients to obtain the Medication Guide - the plain language section of the Prescribing Information - from their pharmacist. On follow-up, specific topics should be addressed more in depth and then documented: "Informed consent given with emphasis on _____".

Although informed consent information may be included in the CSA[,244], the latter differs from the former. The term "agreement" is used rather than "contract" since a contract implies a definite consequence to a violation and agreement makes room for flexibility, an important and practical approach in clinical medicine. Found effective[246-250], this document describes in plain language[251] expected and prohibited behavior; patient authorization for consults, prescription database reviews, drug testing; and potential responses to medication-related aberrancies[252,253]. Specifically, the use of alcohol and illicits should be prohibited. Prescribers have to decide if cannabinoids might be allowed under certain conditions (not recreational) and for certain patients but only if those prescribers have adequate knowledge base about cannabinoids[53-55]. Clear instructions on secure storage – a safe (combination preferred) *not* in the bathroom – and safe disposal through reverse distributors[254-256].

It is recommended that the written CSA be provided at the first patient encounter and that the patient have an opportunity to review at their leisure between visits with the expectation of addressing questions and obtaining the patient's signature at the second clinical contact. In that way, the patient should be truly informed about its contents before agreeing to them.

Risk Monitoring

If and when the opioids are prescribed, ongoing monitoring (Table 6) is critical to help ensure continued safe use. Behavioral aberrancies are actions by patients which place them at risk, both those that may be reported by patients and those that might be observed by the practitioner at the time of clinical contact. Inquiry about and observation of specific items should be done with every clinical encounter, including those listed in the following documentation example for someone who is adherent in this case:

> Subjective section of the note for the patient encounter – *i.e.,* reported by the patient:
> "The patient reports taking opioids on a regular basis as directed, source here only, securely stored, and not ending up in other persons' hands. S/he reports not using alcohol, cannabis, or illicit substances."
>
> Objective section of the note for the patient encounter – *i.e.,* observed by the clinician:
> "Normal level of consciousness and orientation. No observed impairment, confusion, imbalance, slurred speech, track marks, alcohol or cannabis odor. Observed pain behavior is consistent with patient report."

The validated Current Opioid Misuse Measure[261,262] (COMM) is a questionnaire that may be used to elicit behavioral aberrancies as well. Every office visit should also track and address goal attainment and the opioid daily MME. MME calculators vary widely[263,264] and the Practical Pain Management Opioid MME Calculator is recommended, as it is based on the best available research.

Other monitoring should be done periodically based on stratified level of controlled substance risk and concerns identified at the time of clinical contact. Clinical experience suggests drug testing and prescription database review should be performed at a minimum of the following according to level of risk: low level (1-2 times per year), intermediate level (3-4 times a year), and high risk (5-6 times a year). Periodic random drug testing is useful[213,265,266] but a sample is not truly random if ordered on the basis of intuition and is probably better termed "surprise" testing. The inexpensive immunoassay is sufficient to begin a conversation about substance exposure, but the more-expensive definitive testing should be done at times unexpected by the patient even when there is no concern and, in addition, anytime misrepresentation is suspected[203-210].

The patient's clinical status may prompt other types of monitoring. Depending on clinical circumstances, re-evaluating oxygenation status can be considered when daily MME advances or there is new evidence of a developing respiratory problem[257-260]. An EKG should be obtained for QTc measurement annually or upon methadone dosage increase[220,221]. EKGs are also important when other medications that affect the QT are added or increased[267]. Counts of remaining product (pills, capsules, tablets, films, patches) can identify any mismatch with time dispensed and may have some utility[268]. Some prescribers will do this at every clinical encounter or periodically according to level of risk. Because of practical challenges, counts may be more useful when circumstances suggest problems or aberrancies. Patients have gamed this, however, by presenting look-alike pills (avoid by employing pill identification) or rent-back product previously diverted or overused[269,270]. In part, this can be obviated by requiring an on-demand count of a texted picture of the remaining prescribed product provided in real time by the patient.

Table 6
Risk Monitoring

At Every Clinical Contact

- Behavioral Aberrancies
  - Reported by the patient – Clinical Opioid Misuse Measure (COMM) useful
  - Observed by the medical provider
- Goal attainment
- Current opioid amount: Practical Pain Management Opioid MME Calculator recommended

Frequency According to Stratified Level Controlled Substance Use Risk

- Online prescription database review
- Drug testing with urine or oral fluid
- Counts of remaining product (pills, capsules, tablets, films, patches)
- Oxygenation status
- EKG for QTc if methadone is prescribed

Aberrancy Management

Aberrancies can be defined as violations of the CSA or somewhat more broadly as any activity by the patient that indicates unsafe or nonmedical use. Not all aberrancies are alike, and although not described in the literature, clinical experience suggests they can be ranked as low (Table 7), intermediate (Table 8), or high (Table 9) in terms of severity or concern. Research shows that 40-80% patients will exhibit opioid-related aberrancies, results varying by population studied, aberrancies measured, and duration of observation[213,266,271,272,273]. In one study 10% of low risk and 90% of high risk patients were aberrant[229]. Not all of these are of great concern. Lost or stolen prescriptions do occur, and patients might take an extra dose for severe pain (*viz.,* a medical aberrancy). These are problematic and not welcome, but do not necessarily forebode future aberrancies, addiction, and overdose death. Still, each must be addressed *and documented* along with the clinician's response. The clinician has the following options when faced an aberrancy or aberrancies:

1. Coach adherence / behavioral intervention + increased monitoring [274]
2. Specialist referral: Pain management, Addiction, Psychiatry [275]
3. Discontinue opioids and other addiction-prone prescriptions [274]
4. Discharge from the clinician's practice – last resort [275]

For low and intermediate level aberrancies, adherence coaching (warning, brief behavioral intervention) along with increased monitoring is often successful[274]. Recurrence may warrant exploration of the issues by specialty consultation[275]. "One strike and you're out" for lower level aberrancies is generally contraindicated as many patients may end up subsequently resorting to injudicious prescribers or street sources out of desperation. Even "three strikes and you're out", while catchy, is not evidence-based. Investigation on this issue is very sparse, and only two studies by the same research group were identified from 2007 and 2008. In that work, OUD was associated with one aberrancy involving cocaine but four or more of other types of aberrancies[276,277].

Pending other data, it may be reasonable to warn, monitor, and refer those presenting with up to three aberrancies, but just one in the case of stimulants. At that point, discontinuation of opioids (and other addiction-prone medications if relevant) rather than discharge from the practice is far preferable[275]. Just as in other areas of medical practice, ascertaining a new diagnosis does not mean release from care has to occur. The impetus to dismiss patients often has to do with their dishonesty: a violation of trust. Lying, however, is a symptom of the disease of addiction of patients trying keep the substances they

desperately crave available. These patients do not deserve to be shamed, but rather should receive evidence-based treatment, such as with Medication for Opioid Use Disorder (MOUD), formerly termed Medication Assisted Treatment (MAT).

On occasion, discharge from the clinician's practice is indicated, for example when forgery is identified, threatening behavior occurs, or non-compliance consistently recurs. However, it should be a last resort and done "therapeutically", *i.e.,* by reviewing why the aberrancies are problematic with the patient along with a referral to a known responsible prescriber who respectfully manages challenging situations. In doing so, it is important to follow the rules and guidance provided by the medical board in respective states to avoid abandoning the patient – typically, a registered letter indicating that the clinician will no longer be available to care for the patient after 30 days. Excepting for benzodiazepines whose discontinuation could result in life-threatening seizures[278,279,280], the clinician is not obligated to continue the same, reduced, or any opioids, though there is a responsibility of appropriate withdrawal management if opioids are tapered or discontinued altogether.

Table 7
Low Level Aberrancies

- Early refill x1
- Missed or late for appointment
- Self-directed dose increase x1
- Non-notification of mild adverse reaction(s)
- Low dose alcohol for a special occasion only
- Non-notification of other prescriber for a good reason x1
- Occasional problem-solving phone calls in lieu of clinical encounter (office or virtual)
- Non-participation in recommended non-opioid pain treatments for valid economic reasons

Table 8
Intermediate Level Aberrancies

- Early refill >1
- Lost / stolen prescription
- Unauthorized overuse >1
- Focus on specific opioid
- Unauthorized cannabis use
- Considers one's self to be addicted
- Limited interest in non-opioid approaches
- Not informing prescriber of significant adverse reaction(s)
- Non-opioid substance addiction slip, followed by return to abstinence
- Multiple problem-solving phone calls in lieu of clinical encounter (office or virtual)
- Non-participation in recommended non-opioid approaches for noneconomic reasons

Table 9
High Level Aberrancies

- Forged prescription
- Cocaine / Stimulant use
- Involvement in DUI / MVA
- **> 3 lower level aberrancies**
- Non-pain related opioid use
- Stealing controlled substances
- IV or IN route of administration

- Aggressive demands for opioids
- Active non-opioid substance relapse
- Refusal of non-medication approaches for pain
- Intoxication / Oversedation: Reported or observed
- Multi-sourcing: non-allowed prescribers / street / internet
- Reliance on problem-solving phone calls in lieu of clinical encounter (office or virtual)

Putting It All Together: Pain Management + Risk Management

Managing pain in clinical practice means managing the associated risks as well, particularly with opioid prescribing. As challenging as it is, this review attempts to adhere to Einstein's dictum to "make things as simple as possible…but not simpler" – see also Table 10. Each medical provider should become aware of one's biases – we all have them. Does one tend to over-trust or under-trust? Does one tend to over-prescribe or under-prescribe?

Table 10

Recommended Screening Tools for Pain and Opioid Risk Management

- *Acute Pain (short-term use): Initial Visit*
  - PEG-3 (Pain, Enjoyment, General Function)
  - Interview questions: personal and family history of substance use disorders
  - Screening Portion of Screening, Brief Intervention, and Referral to Treatment
  - Online Prescription Database (aka Prescription Drug Monitoring Program – varies by state)

- *Chronic Pain (long-term use): Initial Visit(s)*
  - PEG-3 (Pain, Enjoyment, General Function)
  - Screening Portion of Screening, Brief Intervention, and Referral to Treatment
    - Tobacco → Fagerström Test Alcohol → AUDIT Cannabis → CUDIT-R Drugs → DAST-10
  - Interview questions:
    - Personal and family history of substance use disorders
    - Personal history of psychiatric or mood problems
  - Adverse Childhood Experience questionnaire (ACE) for trauma
  - PHQ-2 → PHQ-9 if affirmative for depressed mood; GAD-7 if affirmative for anxiety
  - STOP-BANG for obstructive sleep apnea risk
  - Online Prescription Database (aka Prescription Drug Monitoring Program – varies by state)
  - Drug testing by definitive method: GC/MS or LC/MS-MS
  - Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R)
    - Alternatives: Risk Index for Overdose or Serious prescription Opioid-induced Respiratory Depression (RIOSORD), Opioid Risk Tool (ORT)

- *Chronic Pain (long-term use): Follow-up Visits*
  - Five A's: Activities (function), Analgesia, Affect (mood), Adverse Effects, Aberrancies
  - PEG-3 (Pain, Enjoyment, General Function)
  - Current Opioid Misuse Measure (COMM)
  - PHQ-2 → PHQ-9 if affirmative for depressed mood; GAD-7 if affirmative for anxiety
  - Online Prescription Database (aka Prescription Drug Monitoring Program – varies by state)
  - Drug screening by immunoassay, testing by definitive method: GC/MS or LC/MS-MS

- *For Other Conditions Suggested by History*

- Post-Traumatic Stress Disorder: PTSD Check List (PCL-C)
- Bipolar Disease: Mood Disorder Questionnaire (MDQ)
- Attention Deficit Hyperactivity Disorder: Adult ADHD Self-Report Scale (ASRS)
- Psychosis: Psychosis Screener (PS)
- Insomnia: Sleep Condition Indicator (SCI)
- Suicidality: Patient Safety Screener (PSS-3)

It is incumbent upon the pain provider to acquire and update one's knowledge, recognize her or his limitations, and access specialty consultation in those matters beyond one's ability or capacity, as well as when there is significant uncertainty as to diagnosis and treatment approach. It is not enough to have the knowledge: it needs to be applied. A thorough understanding of drug testing is pointless, for example, if it is not ordered.

All this should be reflected in the chart, including concerns that might not be communicated directly to the patient at any one time – a surprise urine drug test, for instance. Language that describes *both* actual pain management *and* risk management activities, discussions, and considerations should be recorded consistently in each SOAP section (or equivalent): subjective, objective, assessments, and plans for both of those domains. Guidelines are just that: guidelines, not rules, not laws – although clinicians are governed by those as well. They are typically reflective of best practices but also include the minimal standard of care elements that must be performed. Indeed, there are occasions when off-guideline prescribing is the best approach for the patient, and in that case the medical record should clearly state the rationale: "off-guideline prescribing because…" Doing so serves as a prompt for the practitioner to take a second look at the intervention(s) prescribed to make sure medical decision-making is sound as well.

This review, too, reflects best practice recommendations and is not meant to supplant sound clinical judgment for the individuals served - individuals whose conditions and treatment responses vary widely. These are persons, not cases, who deserve our attention to their lived experiences and struggles. Naomi Wolfe expresses well the challenge so many patients face with their medical providers:

"Pain is real
when you get other people to believe in it.
If no one believes in it,
pain is madness or hysteria."

Listen

Steven Wright, MD
Stader Opioid Consulting
July 27, 2021

Family Medicine
Addiction Medicine
Medical Pain Management

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