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A White Paper

Principles for Patient-Centered Opioid Prescription Guidelines

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ABSTRACT

Many knowledgeable professionals and informed patients believe that the CDC Guidelines were deeply influenced by anti-opioid bias on the part of writers on the CDC Working Group which authored it. Even more damaging have been revelations that medical evidence assembled in support of the work was manipulated to discredit opioid reliability and to over-magnify opioid risks. As one group of medical professionals aptly phrased the issues, the CDC Guidelines are "neat, plausible, and generally wrong." Inarguably, so also is most of the dominant public narrative on opioids and chronic pain. As phrased in a widely viewed TED Talk on U-Tube, "Everything You Think You Know About Addiction is Wrong."

1. Introduction

This paper is updated from an April 2017 article published by the National Pain Report. [1] It was reprinted with permission by *The Journal of Medicine* [2] and introduced by *Pain Week* under the feature title "What if Prescribing Guidelines Were Patient Centered?"[3]

A CDC Guideline for prescribing opioids to adults in chronic non-cancer pain was published in March 2016. [4] It has since become clear that this Guideline is generating horrendously negative outcomes for chronic pain patients and their doctors. [5] [6] Many doctors are choosing to leave pain management rather than face possible prosecution by State authorities or the US Drug Enforcement Agency, for "over-prescription" of pain relieving opioids.[7] Tens (if not hundreds) of thousands of patients are being summarily discharged without referral and sometimes without management of opioid withdrawal. There are increasing reports of patient suicides.[8] [9]

Many medical professionals have published sharply critical reviews of the problems of the CDC Guideline.[10] [11] Also of deep concern are proposed 2019 rule changes by the US Centers for Medicare and Medicaid, which make the Guideline a mandatory standard for insurance reimbursement and place sharp limits on the duration of opioid treatment for acute pain.12

Many knowledgeable professionals and informed patients believe that the CDC Guidelines were deeply influenced by anti-opioid bias on the part of writers on the CDC Working Group which authored it. Even more damaging have been revelations that medical evidence assembled in support of the work was manipulated to discredit opioid reliability and to over-magnify opioid risks 13. As one group of medical professionals aptly phrased the issues, the CDC Guidelines are "neat, plausible, and generally wrong."14 Inarguably, so also is most of the dominant public narrative on opioids and chronic pain. As phrased in a widely viewed TED Talk on U-Tube, "Everything You Think You Know About Addiction is Wrong."15

Patient Perspective: It is now clear that US CDC Guidelines must soon be withdrawn for a major rewrite. Given the horrendous outcomes of the misapplication and misinterpretation of these Guidelines, this is the only

ethically and morally sound way forward.

US public narratives have become mired in an avalanche of hype, conflicting claims and financially self-interested posturing on the part of addiction treatment specialists, government prosecutors, insurance company partisans and pharmaceutical company marketers. Pending accomplishment of this re-write, alternative guidelines should be applied. These include the opioid prescription guideline of the Federation of State Medical Boards, and the European Pain Federation position paper on appropriate opioid use in chronic pain management (December 2016) [16]

Especially important in any rewriting process must be the inclusion of stakeholder voices that were largely unheard in the first writing of the Guidelines. Chronic pain patients or their advocates should be among this list, as should board certified pain management specialists active in community practice outside hospitals.

It is thus appropriate to ask what pain patients might write if they were tasked to revise prescription guidelines on their own behalf. The following White Paper offers principles and published data that may guide such an effort. This is not a "standard" of medical practice. Development of such standards requires a partnership between medical professionals, other stakeholders and patient advocates.

This summary of principles is instead, a good faith effort to capture both the state of medical evidence and the experience of many thousands of patients who support each other online and in social media -- too often in the absence of support from medical professionals and government policy communities.

2. Patient-Centered Guidelines

2.1. Cancer vs. Non-Cancer Pain - Distinctions Without Differences

Patient Perspective: There should be no distinction in principle between the objectives of treating pain, which is acute, chronic, or associated with advanced medical conditions assessed to be terminal. The objectives in all of these categories are to alleviate suffering, promote patient functioning and improve quality of life to the degree possible. In this sense, treatment of pain is always "palliative". To deny treatment of any form of pain when effective means exist to manage it, is a fundamental violation of human rights, as recognized by Human Rights Watch.

2.2. Opioids in Current General Practice

In the practice of general medicine, prescription opioid analgesics are not drugs of first choice in the control of long-term pain. Opioids are more frequently used with moderate to severe acute (short term) pain associated with injury, surgery or dental procedures, for situations where pain is expected to resolve in a few days as the underlying disease or disorder itself resolves. When prescribed for periods over 30 days, opioids are most often used for pain that is found by a physician to be unresponsive or intractable to other therapies.

Patient Perspective: In the context of chronic pain and palliative care for terminal conditions, managed access to opioid prescriptions is indispensible at the current state of medical knowledge. This is also true in non-life-threatening chronic pain conditions, despite a general perception and much public commentary to the effect that opioid analgesics can be dangerous if misused. Likewise of great concern is that the majority of medical schools and in the US and Europe presently lack mandatory courses in pain management. This deficiency must be corrected on a priority basis in the near term.

2.3. Minimum Effective Opioid Dose and Duration in Acute Pain

For opioids as with any other medications, widely accepted best medical practice is that treatment should be accomplished with the minimum dose that is effective and for the minimum duration appropriate to the intended purpose. In acute pain associated with injury, surgery or dental procedure, initial prescriptions tend to be limited to a few days. However, there is wide variability of pain intensity between different acute medical conditions and wide variation in individual sensitivity to medication. A hip replacement in a 70-year-old patient does not compare to extraction of a wisdom tooth in a 21 year old.

Patient Perspective: Doctors must be free to prescribe both opioid and non-opioid analgesics for durations and in doses that they deem adequate for the patient to sleep and to function in daily life while acute conditions are resolving. Primary effects in pain reduction must be balanced against negative side effects or hazards in the individual patient. As noted during January 30 2018 public hearings of the FDA Opioid Policy Steering Committee[17], detailed standards for prescribing are most appropriately developed by medical professional societies and specialized certification Boards familiar with conditions of medical practice, rather than by legislation or regulation by State regulatory authorities.

2.4. Principles for Extended Opioid Prescribing

Patient Perspective: The experience and training of physicians are centrally important in determining appropriate types and strengths of all prescribed medications. Provision must also be made for integrating patient reports, particularly when pain control is experienced as inadequate. When opioids are to be used in high doses for prolonged periods, consultation with a Board Certified specialist in pain management is recommended.

Extension of an opioid prescription originally written for acute pain must take into account, progress - or lack thereof - toward resolution of the medical issues which prompted the prescription. When pain is refractory to therapy, physicians must be particularly careful to avoid assignment of stigmatizing labels such as "drug seeking" in both direct patient interactions and documented medical records. Care must also be taken not to falsely attribute patient reports of emerging chronic pain as an indication of substance abuse issues. Several useful patient-centered survey tools are available for identifying patients in whom past inappropriate opioid use may comprise a risk.[18]

Large scale analysis of medical insurance records demonstrates that incidence of chronic opioid prescribing in populations of non-surgical patients is on the order of 0.136%.[19] "Chronic" in this context is taken to mean 10 or more opioid prescriptions in a year or continuous prescribing for 120 days or more. When records of surgical patients were analyzed after 11 common surgical procedures, it was found in four of these procedures that incidence of chronic prescribing remained unchanged after surgery. In the remaining seven procedures, chronic prescribing was observed in a maximum of 0.7% of post surgical patients. This maximum was associated with total knee replacement, a procedure known to be associated with development of treatment-resistant chronic pain.[20] [21] It is plausible that much of the increase seen in chronic prescribing reflected emergence of chronic pain conditions, some of them due to failure of surgical procedures to correct underlying medical problems. This analysis demonstrates beyond any reasonable contradiction that simple exposure to medically managed opioids among opioid-naïve patients is not a significant factor in initiating patterns of chronic opioid use.

2.5. The Role of "Fail First" or STEP Therapy

Patient Perspective: Insurance companies have placed increasing emphasis on STEP (fail first) therapy as an alternative to opioids or surgical interventions and as a means of cost control or risk management. However, the potential benefits of such therapy must be explicitly weighed in each patient, against the risks of disease progression or the development of even more intractable pain.

In this context, a deep professional expert review is needed of the outcomes of interventional surgeries and injections, to better establish for which conditions such procedures are most likely to be effective and with what long-term medical risks to patients. There is evidence that some interventional surgeries may harm as many patients as they help. The US Agency for Healthcare Research Quality may be an appropriate organization to conduct and publish such a review.

Acknowledging reservations concerning non-analgesic interventions, it is still medically appropriate to evaluate patient responses to therapies other than opioids, as a first step in addressing chronic pain. The World Health Organization "Three Step Analgesic Ladder for Pain Treatment" offers an established and recognized framework for accomplishing this evaluation. Multiple medical professional associations have also published guidelines. Notable among the latter are the April 2017 Guideline of the Federation of State Medical Boards and the European Pain Federation position paper on appropriate opioid use in chronic pain management [22] [23]

2.6. Is Opioid Abuse a Consequence of Managed Medical Exposure?

Patient Perspective: Treatment of pain in America takes place in a social environment where addiction to illegal opioids and overdose deaths involving them as contributing factors are major public health and policy issues. There is widespread concern that unmanaged or casual availability of opioids might lead many people to become addicted. While increased availability of prescription opioids before 2010 might have contributed to their diversion to recreational use, evidence from multiple sources suggests that risk of addiction in patients who have no previous history of opioid use is very small – less than one percent. [24] [25]

Opioid overdose deaths in 2016 were dominated by street drugs (heroin, fentanyl illegally imported from China and Mexico, methadone diverted from Medication Assisted Treatment programs). [26] In 2016, 15,000 people died of prescription drug overdose (possibly as little as one third of which involved prescriptions by physicians for the affected patient), and 35,500 died of illicit opioid overdose.

Likewise, recent large-scale analysis of insurance records of post-surgical patients confirms that incidence of later diagnosis of opioid abuse disorder among patients who are prescribed opioids after surgery is less than 0.6%. [27] Given the current hostile regulatory environment, it is plausible that actual risk of patient opioid abuse from managed medical exposure may be significantly lower than 0.6%. Some doctors mistake the emergence of post-surgical chronic pain for evidence of increasing risks of opioid abuse. Others may be rendering the diagnosis out of personal discomfort and concern for being sanctioned by State authorities or the US Drug Enforcement Agency. Many general practitioners lack deep training in the assessment of opioid use disorder, and lack routine exposure to the DSM-5 behavioural criteria that define it.

It is now known that short-term exposure to medically managed opioids creates only a low risk of continuing involvement.[28] Different biochemical processes are involved in drug dependence (characterized by withdrawal symptoms when drugs are tapered down rapidly) versus drug addiction (defined by a spectrum of obsessive and self-destructive drug seeking behaviours). Opioid use disorder in medically managed patients is extremely uncommon.

2.7. Risk Factors for Addiction vs. Chronic Pain

The most reliable risk factors associated with addiction are status as a male adolescent or young adult, a history of family trauma, and/or long term unemployment.[29] None of these factors is affected by restriction of opioids prescribed to patients in pain.

Patient Perspective: There is no evidence that restriction of opioid medications for patients reduces overdose deaths. To the contrary, it is clear that reformulation of OxyContin in 2010 to reduce its abuse potential was accompanied by a sustained increase in overdose deaths involving heroin and other street drugs.[30] There is also evidence that the restriction of prescription opioids since 2010 is actually contributing to the opioid crisis by driving patients in desperate pain to the streets.[31]

The demographics of Chronic Pain are significantly different from those of addiction. The typical chronic pain patient (by a ratio of 60/40 or higher compared to males) is a woman in her 40s or older with a history of one or more painful medical disorders including fibromyalgia, complex regional pain disorder, failed back surgery or neuropathy.[32] Women whose lives are sufficiently stable that they can see a doctor repeatedly for such medical issues are only rarely found to be addicted.

2.8. Patient Education and Management

There is general consensus among physicians who treat chronic pain, that before starting opioid treatment for chronic pain, clinicians and patients should mutually establish treatment goals and expectations for pain and function. Criteria and a transition plan should be established for how opioid therapy will be discontinued if observed benefits do not appear to justify risks or disabling side effects. [33]

Periodically during opioid therapy for chronic conditions, clinicians should discuss with patients known risks and realistic benefits of opioid therapy as well as patient and clinician responsibilities for managing therapy. Patients should be reminded of their responsibility for controlling access to powerful opioid drugs by friends or family members who have not been prescribed them. Likewise, patients should be reminded that opioid prescriptions should not be obtained from multiple doctors.

Patient Perspective: However, opioid therapy should not be discontinued or refused in the absence of evidence that the underlying disorder is resolving, or that side effects of treatment outweigh benefits in the individual patient. There is no medical evidence for a need to taper down patients who are otherwise stable at *any* dose level, absent changes in their medical profile. Discharge of a patient solely because they have a history of high-dose opioid prescription is medically and ethically inappropriate.

2.9. Managing Persons with Addiction in Chronic Pain Practice

Physical dependency on opioids for pain control may cause withdrawal symptoms when medications are suddenly reduced. However, drug dependency is not the same medical entity as addiction. In patients for whom resolution ("cure") of underlying medical conditions is deemed unlikely, dependency may be an acceptable and manageable side effect in maintaining the best possible quality of life, in the absence of effective non-opioid therapies. When dependent patients are withdrawn from opioids for whatever reason, physicians are ethically required to provide assistance with managing withdrawal symptoms.

Clinicians should not dismiss patients from their practice solely because of a suspected or confirmed substance use disorder. Such action can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity to initiate potentially life-saving interventions.

Patient Perspective: It is important for the clinician to collaborate with the patient regarding their safety, to increase the likelihood of successful treatment. Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with both pain and substance use issues require ongoing pain management that maximizes benefits relative to risks. Consultation with an addiction treatment specialist is in order for general practitioners and others who lack current training in the specialty or who are not appropriately licensed.

2.10. Variability in Patient Metabolism

Multiple physiological and genetic factors influence choice and dose of opioid provided to the individual patient. These factors include the types and causes of pain being treated, physical weight of the patient, issues of renal or hepatic insufficiency, [34] patient's history of previous opioid exposure, any history of alcoholism or drug abuse, and the individual's ability to metabolize opioids or non-opioid medications and the genetics of the mu-1 opioid receptor. When pain is unresponsive to initial prescription of opioids, genomic testing may be useful, to investigate whether the patient is a poor metabolizer of opioids. However, genomic testing is still at an early stage of practice. Research is needed to assess the reliability of opioid-related genomic testing and to reduce its costs.

Although it seems plausible that higher opioid dose levels might be associated with higher risk of dependency or addiction in some patients, medical evidence is presently inadequate to generalize any specific numerical threshold on opioid dose levels that should be considered dangerous. Published data in large-scale studies suggest that risk of developing opioid use disorder is only weakly sensitive to dose levels between 20 and 120 MMED. [35]

The significance of "relative risk" of untoward outcomes versus opioid dose level should also be evaluated in the context of *absolute* risk. The four studies used by the CDC Guidelines writers show an increased risk of apparent overdose death associated with higher dosing. [36] [37] [38] [39] However, overall risk of overdose death across all dose levels was on the order of 0.05% or lower. For doses greater than 100 MMED, the absolute annual risk of dying was estimated at 0.21 to 0.25%/year. In a related study by one of these authors, the annual risk of overdose death with a MMED of greater than 400 was 0.5%.[40]

These outcomes are precisely comparable to the risk of fatal haemorrhage with medical conditions like atrial fibrillation, for which thousands of patients are treated with anti-coagulants every year. Atrial fibrillation is very common in older patients, as is deep venous thrombosis and associated pulmonary embolism. Medication related mortality rates among patients treated for these conditions with blood thinners are on the order of 0.25 to 0.5% per year. Among many chronic pain patients, a maximum fatality risk of 0.5% per year would be considered trivial in comparison to the certainty of daily agony.

An important criterion for evaluating risks and benefits among long-established patients is whether the patient has been on a stable opioid dose for a prolonged period, with minimal progression of underlying medical conditions which generate pain. Minimum therapeutic dose levels may vary widely – perhaps from 20 to1000 morphine milligram equivalent daily dose (MMEDD).[41] Likewise there are case reports of patients well maintained and stable on doses over 2000 MMEDD.[42]

Patient Perspective: Physical dependence on opioids is not a sufficient criterion to justify withdrawal of these medications from stable chronic pain patients, irrespective of dose. The Centers for Medicare and Medicaid Services have estimated that over 1.9 million older people are

managed on opioid doses exceeding 90 MMED in 2018.[43] However, there are no published data on risk of drug toxicity or overdose versus specific dose levels above 90 MMED. And there are no published data demonstrating that pain levels improve after coerced tapering down of opioids, as might be expected if "opioid induced hyperalgesia" was a real or reliable medical entity.

Physiological dependence is an expected and acceptable outcome of long-term use of opioids; when there is medical reason to taper down dose levels, the taper schedule must be tailored over weeks to months – not days. Physiological dependence on opioid analgesics is not permanent, nor is there evidence that it inevitably leads to addiction.

2.11. False Alarm Issues in Prescription Drug Monitoring Programs

All 50 US States have established Prescription Drug Monitoring Programs (PDMPs). The US Food and Drug Administration is considering program investments to integrate these databases in a common nationwide system.[44] However, it remains doubtful that such programs have saved any significant number of lives, despite contributing to a hostile regulatory environment and influencing physicians to reduce opioid prescribing. [45] To the contrary, "In ... analysis of states with PDMPs in operation for 5 or more years, the programs were found to be associated with significantly higher mortality rates in legal narcotics, illicit drugs, and other and unspecified drugs." Likewise, false indications of "doctor shopping" have been a basis for refusing timely renewal of prescriptions to significant numbers of patients, with attending negative consequences to pain management.[46] Important causes of false alarms include the lack of any accepted "universal identity record, and possibly HIPA restrictions which limit patient medical data disclosures."

Physician inability to use PDMP interfaces in a timely manner, integrated with existing Automated Medical Records systems, is a continuing concern in managing doctor workloads.[47] In States where PDMP use is not yet required by law, significant numbers of physicians have chosen not to use these systems. Full integration of PDMPs with automated record systems may require redesigns to multiple State PDMPs under a common Federal Data Standard and data exchange protocols. Utility of PDMPs might be enhanced were they to automatically signal prescribers jointly in the event of detection of concurrent opioid prescriptions.

Patient perspective: As a matter of principle, when a PDMP detects concurrent opioid prescriptions from different providers or there are indications that a patient has requested treatment by three or more doctors in a year, there is reason to review medical records with the patient. This process should assess circumstantial factors beyond the patient's control, before taking action to more closely monitor opioid access, alter treatment plans, or engage a substance abuse management specialist in coordinated treatment. Discharge of the patient as a "doctor shopper" or "drug seeker" is ethically inappropriate and comprises patient abandonment.

2.12. Problems with Opioid Analgesic Availability

There is evidence of shortages in opioid analgesics in US hospitals and clinics,[48] [49] [50] as well as increasing resistance by major pharmacy chains to stocking these medications.

Patient Perspective: US Government authorization for production and distribution of opioid medications should be optimized to ensure that all patients with legitimate medical needs receive their prescriptions in a timely manner. Automated measures should also be implemented to detect drug diversion in National distribution systems.

Pharmacists who believe that a prescription exceeds accepted medical practice should contact the prescribing physician's office immediately, to confirm the appropriateness of the prescription. In no instance should a patient be refused refill on a valid prescription solely on the basis of pharmacy corporate policy or the individual "comfort levels" of the pharmacist. Provision of adequate medical records to the pharmacist should be sufficient to assure filling of a prescription.

2.13. Urine Testing

There is presently no conclusive evidence that drug use "contracts" between patients and doctors or employment of urine testing actually reduce the number of hospitalizations for opioid toxicity or the number of overdose deaths. There is no accepted practice standard for "which patients to test, which substances to test for, how often to test, and how to act on the results." [51] Research investment appears to be needed to better characterize testing outcomes, lower costs and improve reliability (reduce false positive rates) of urine testing.

Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts have noted that there may be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). In addition, the costs of urine testing can be reduced by restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management. Before ordering urine drug testing, clinicians should have a plan for responding to unexpected results.

Patient Perspective: When a patient must travel more than one hour to attend medical appointments, use of short-notice urine testing should be implemented by local public health nurses or local clinics in the communities where patients live.

2.14. Prescription Drug Monitoring Programs vs. Pill Mills

Patient perspective: There is valid concern that some physicians licensed to dispense opioids have done so inappropriately or with inadequate patient oversight. However, the volume of opioids prescribed in a medical practice is not a one-size-fits-all criterion to justify confiscation of a doctor's medical records or imposition of sanctions prior to review by State medical boards or courts. Prescribing patterns must be assessed in

the context of the numbers of patients served, the nature of their underlying medical issues, and the area availability of practitioners and centers formally licensed to prescribe.

Prominent announcements of ongoing investigations, witness coercion and delays of court proceedings are too frequently used by prosecutors as a means of coercing doctors to sign consent decrees or face personal ruin. DEA confiscation of business or personal assets is used to deny skilled legal representation. These measures should be grounds for legal action for malicious and false prosecution.

There is reason to be more concerned with major corporate drug distribution companies than with individual doctors. Reports *by CBS 60 Minutes* and *The Washington Post* have identified patterns of drug shipments into rural zip codes, where shipment volumes could not possibly be justified by the numbers of medical practices and patient populations. DEA investigators have complained of being shut down or facing impossible hurdles to prosecuting the distribution companies, by their own legal counsels or by Department of Justice prosecutors. [52]

2.15. Research Needed on Biological Markers for Pain

Patient Perspective: A careful and non-stigmatizing distinction must be applied in the assessment of opioid risks and side effects among long-term pain patients. It is established that many if not most chronic pain patients do not get a euphoric "high" from opioid use. Nor do these patients commonly display the spectrum of compulsive and self-destructive drug seeking and escalating dose levels displayed by people with addiction. Some pain management specialists believe that neuro-chemical and genetic markers may identify patients in whom chronic pain has produced permanent changes in the brain. Such markers, if confirmed, may offer a stronger basis for discriminating between diagnoses of chronic pain versus substance abuse. Further research is needed to confirm the science and reduce such testing to common and affordable practice.

2.16. "Opioid Induced Hyperalgesia"

Despite many articles in the popular press and medical literature, there is little validated medical evidence for what is called "opioid-induced hyperalgesia" (increasing sensitivity to pain over time, requiring sharply increasing doses of opioids for effective pain control). There are no documented diagnostic protocols for this supposed medical entity in humans, and there is no generally accepted protocol for treatment, other than tapering down present medications and tapering up others. Some pain management specialists go so far as to suggest that if opioid-induced hyperalgesia exists at all, it may be associated primarily with constant exposure of the brain to opioids delivered by intra-thecal pain pumps. [53] [54]

Patient Perspective: Given these observations, when drug tolerance or increased pain is reported by patients, medical assessment is warranted for progression in underlying disease processes. Development of opioid abuse disorder should not be a default assumption. It is also well established that initial diagnosis of many chronic pain conditions is complex and frequently incorrect, creating opportunities for therapy failure. Arbitrary limitation of opioid dose levels in the face of increasing pain levels is ethically inappropriate.

2.17. Management of Dual Prescriptions

Opioids have both short term and long-term side effects that must be actively managed by the prescribing physician. These may include constipation, dry mouth, nausea, confusion, lethargy, sedation, suppression of sexual libido, situational or chronic depression, and anxiety. These side effects are highly idiosyncratic, varying from drug to drug and patient to patient. Drug interactions are also of concern in developing a pain management plan for the long term.

It is known that a significant fraction of patients who die from opioid-related overdose have also been prescribed benzodiazepine drugs. However, medical evidence for suppression of respiration due to combinations of opioids and benzodiazepines is very weak. Investigations suggesting an additive risk have been limited to case-control studies that have almost certainly suffered from diagnostic bias. The US Food and Drug Administration has published a Drug Safety Communication advocating for the continued co-prescription of benzodiazepines or CNS suppressants with opioids. [55]

Depression and anxiety are frequently co-morbid with chronic pain. Failure to treat depression may complicate treatment of pain itself. In line with the FDA Drug Safety Communication, physicians should carefully monitor dual prescription of Benzodiazepine drugs and opioids. Alcohol is also a major contributor in drug overdose and patients should be counselled on its dangers. Patient education must also emphasize that there are significant dangers in self-medicating, particularly with combinations of drugs.

2.18. Naloxone Therapy?

There is much public discussion of Naloxone as an interventional drug to counter the immediate effects of opioid overdose. Multiple US States are making this drug widely available to emergency medical technicians and police as an aid in saving the lives of drug overdose victims. [56]

However, there seems to be limited medical evidence that Naloxone can be used similarly to Methadone, to suppress cravings for other opioids over the long term. A few published reports have suggested that Naloxone therapy may merely postpone the decline and death of addicts who do not enter a more sustained program of community reintegration, community based treatment and supportive counselling. [57] Investment will continue to be needed in community programs of addiction treatment. There is no easy one-size-fits-all solution for addiction.

2.19. Non Pharmacological, "Non-Invasive" Therapies

There is also much public and professional discussion of non-opioid medications (e.g. corticosteroids, NSAIDS, anti-seizure medications, anti-depressants), non-invasive therapies (chiropractic, acupuncture, physical therapy), and behavioural therapies (rational cognitive therapy, operant

behavioural therapy, creative visualization, acceptance therapy, psychotherapy) as alternatives in chronic pain management. In December 2017, the Agency for Healthcare Research Quality (AHRQ) circulated a draft Systematic Review of published trials for over 20 types of alternate therapies in five classes of chronic pain. [58]

AHRQ reviewers discovered 4470 published trials from literature. After a rigorous quality review, only 205 of these trials were deemed of sufficient quality to be included in the outcomes review. Among these, AHRQ applied the evaluation "medical evidence weak" in over 100. Weaknesses that led to rejection of published trials were failure to follow patients for at least 30 days after completion of the trial, and failure to fully document protocols of "usual treatment", to which alternate therapies were frequently added. In many instances, usual treatment was almost certainly with NSAIDS or opioid analgesics. However the details of usual treatment were not clarified in the systematic review or the original trials reports.

From the AHRQ review data, it is apparent that non-opioid therapies may help some patients some of the time. However, detailed reading of the data reveals that the present state of medical evidence is too weak to generalize practice standards for the use of such therapies in preference to opioids. The gold standard test of an alternative therapy should be its value in enabling reduction of opioid dosage. No patient should be coerced to accept such therapies as replacements for opioids, particularly if the patient hasn't experienced improvement in pain during previous trials of the therapy.

2.20. Evidence for Medical Marijuana in Treating Chronic Pain

Due to its status as a Schedule I "narcotic", marijuana-related research has largely been stifled in the US, even as research continues elsewhere. In recent years, there has been an increasing trend toward legalization of medical uses and in some US States, recreational use. While much remains to be learned about the mechanisms and reliability of marijuana and its components (CBD oil, THC) as medical treatments, one fact is clear: there is no valid evidence supporting the designation of marijuana or its component products as a "gateway" drug for opioids or other addictive drugs. Moreover, data are emerging from States where medical marijuana has been legalized, suggesting that where marijuana is available, opioids are less often used both medically and recreationally. [59]

Immediate de-scheduling of marijuana is warranted to facilitate further medical research to investigate and quantify its potential benefits, reported by tens of thousands of chronic pain patients.

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"Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with pre-existing vulnerabilities...Older medical texts and several versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes."

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