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A White Paper

Prescription Opioids and Chronic Pain

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ABSTRACT

The March 2016 “CDC Guidelines for Prescribing Opioids for Chronic Pain” for adult, non-cancer chronic pain must be withdrawn and rewritten. CDC and all government agencies must recognize both the indispensable role that opioids play in chronic pain management, and the central role of physicians to assess and prescribe medications, as patients require.

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1. Main Points

1.1. There are over 116 million chronic pain patients in the US (Institute of Medicine)

Chronic pain is defined as pain lasting longer than 90 days or otherwise exceeding medically expected recovery times. Once diagnosed, many chronic pain patients will have debilitating severe pain for the rest of their lives. For many, pain is resistant (refractory) to a wide range of therapies.

For millions of people, management of severe pain has for years included prescription opioid medications as a key element. Opioid medications frequently make a life-or-death difference in quality of life. However, at present, patients with severe pain are being made scapegoats for a perceived – and largely false -- “epidemic” of opioid addiction and overdose deaths, which have been misattributed to prescription analgesics.^{1 2 3 4}

There are presently no reliable replacements for opioids.⁵ Due to underfunding of research on treatments for pain, there are no significant prospects for new treatments in the foreseeable future.

1.2. March 2016 CDC Chronic Pain Guidelines

In March 2016, the Centers for Disease Control released updated guidelines for prescription of opioids in adult, non-cancer chronic pain. Outcomes of these guidelines have been horrific for millions of patients. The CDC guidelines⁶ recommended that general practitioners should perform an analysis of risks and benefits before prescribing more than 90 Morphine Milligram Equivalent Daily Dose (MMEDD). Although originally phrased as voluntary, the Guidelines became a statutory requirement on the Department of Veterans Affairs, three months before CDC published its final guideline. Non-VA Hospitals and doctors across America quickly interpreted the Guidelines on safety review as a mandatory maximum dose standard.^{7 8}

Fearing sanctions by the US Drug Enforcement Agency or State authorities if they prescribe opioids to people who need them, doctors are leaving pain management practice in droves.⁹ Availability of pain management specialists is dropping in most areas of the US and Canada. Pharmacies are limiting inventories of opioid medications, and challenging doctors’ prescriptions on grounds of corporate policy. Patients with legitimate prescriptions are being turned away.¹⁰

The US Centers for Medicare and Medicaid estimate that approximately 1.6 million older citizens are presently maintained on opioid doses at

levels above 90 MMED.¹¹ US CDC has estimated that over 19 million prescriptions were written in 2016 for “high dose” (over 90 MMED) opioids for all purposes – acute, chronic, or palliative care treatment.¹² However, among doctors who remain in pain management practice, many are discharging high-dose patients or coercing them to quickly taper down to levels below 90 MMED – levels that are ineffective in hundreds of thousands of patients. Many high-dose patients are being discharged without management for withdrawal symptoms.¹³

Effects of CDC Guidelines are compounded by restrictive legislation in several US States, which are imposing limits on dose levels, the number of days a prescription may extend, and/or the number of renewals allowed. Tens of thousands of patients are being driven into outright agony, with significant suicide risk.^{14 15} Among patients treated by the Veterans Administration, hundreds of suicides have been confirmed.¹⁶

1.3. Weak evidence for CDC Guidelines

Medical evidence underlying the CDC Guidelines is extremely weak, absent or biased.

The Core Experts writing group that authored the CDC Guidelines included no practicing Board Certified Pain Management specialists who had experience managing patients in community settings. Psychiatrists in addiction management dominated the group. There was no representation by the CDC’s own medical ethics group.

The majority of the published studies that the CDC used as evidence in the writing of the Guidelines were evaluated as “Type 4” – “Subject to significant limitations and uncertainties”.¹⁷ Significant studies, which contradicted assumptions of the writers group, were omitted.¹⁸ Four studies quoted by CDC to justify risk thresholds for opioid daily dose were mutually contradictory and inconsistent.¹⁹ Methodology for comparing different opioids (Morphine Milligram Equivalent Daily Dose) is founded upon opinion and pseudoscience.²⁰

The four studies used by the Guidelines writers do show an increased risk of apparent overdose death associated with high dosing. However, the absolute annual risk of dying with doses greater than 100 MMED 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%.²¹

Even if we accept the questionable methodology of some of these studies without challenge, it still seems reasonable to compare their estimated risks of death to outcomes of other drug therapy. Consider, for instance, medical conditions like atrial fibrillation, for which thousands of patients are treated every year. Atrial fibrillation is very common in older patients, as is deep venous thrombosis and associated pulmonary embolism.

A risk of prescription opioid overdose of 0.25%/year is comparable to the risk of fatal hemorrhage with the best anticoagulants available for preventing stroke due to atrial fibrillation. The estimated risk of death from so-called “very high dose” opioids (0.5%/year) is comparable to the

risk of fatal hemorrhage with Warfarin for stroke prevention (0.38-0.5%/year). So why do we focus on the supposed “risk” of opioid overdose attending the treatment of severe chronic pain? This is a “risk” that many patients in agony would consider trivial. It is comparable to risks of other drug therapies.

Because of very high dropout rates among pain patients treated with placebos, there are few published randomized double-blind trials of the long-term effectiveness of opioids in chronic pain. However, the CDC writers misinterpreted the rarity of trials to assert that opioids are ineffective.^{22 23} The writers violated research standards of the CDC itself by failing to disclose that criteria for including trials of opioids were different and more stringent than those applied to non-opioid analgesics and behavioural therapies.²⁴

Although medical professionals often label patient reports “anecdotal”, many thousands report they have been stable on opioid medications for years and received substantial benefits in reduced pain, improved mobility, and better quality of life. Many of these patients are being discharged or coerced to taper down medications to less than therapeutic levels.²⁵

The term “opioid induced hyperalgesia” is sometimes seen in medical literature as a justification for claiming that opioid analgesics really aren’t effective. The claim is that due to some mechanism of the nervous system, opioids cause the body to become more sensitive to pain after a short period of exposure. However, no medical consensus exists on what this mechanism might be, or any criteria for confirming this unproven diagnosis. A search of the medical literature reveals no reports of patients whose pain improved with reduction in opioid dosage.

A label is not a diagnosis.

1.4. The confounding problem of individual metabolism

The CDC writers group also ignored well-established medical literature, which examines variations between individuals in their ability to metabolize (break down) opioid pain relievers.^{26 27} Six key liver enzymes are involved in metabolism for 90% of all medications. Due to genetic polymorphism, the expression of these enzymes can vary significantly between individuals. The result is that millions of patients are poor metabolizers of opioids, passing very low amounts of active breakdown products across the blood-brain barrier. Others are “hyper-active” metabolizers, in whom opioids pass through the body so rapidly that pain is reduced for only minutes rather than hours.

Both of these populations can potentially benefit from opioid therapy -- but not below the 90 MMED dose limits recommended in the CDC Guidelines. Some pain management specialists identify the range of “minimum therapeutic dose” for opioids as 20 to 1,000 MMED.²⁸ There are published case reports of “hyper-dose” patients who do well on dose levels over 2000 MMED, with no unacceptable side effects or observed symptoms of addiction.²⁹

The CDC Guidelines have had such horrific results that some of the writers in the Core Expert's group and outside reviewers of the document have disavowed it.³⁰ Additional medical professionals have directly opposed proposed changes in Medicare and Medicaid rules intended to implement CDC Guidelines as a mandatory standard of practice.³¹

2. Mythologies of Chronic Pain and Addiction

It is becoming clear that major implicit but mostly unstated assumptions of the CDC Guideline writers were inappropriate or outright fallacious.³² Among these assumptions is the claim that all opioid prescriptions should be regarded as immediate addiction risks for all patients exposed to them. We now know this assumption to be false.

2.1. Media Narrative

We've all heard media stories about young people who quickly became addicted after minimal exposure to medically managed opioids, descending into a spiral of drug seeking, life failure and eventual overdose death. Such stories are tragedies for the families that actually experience them.

Families grieve. They demand that government "do something." Their stories are very influential in our public conversation about substance abuse and overdose deaths. It is small wonder that government policy has focused centrally on reducing the availability of medical opioids.

2.2. Focus on Prescription Reduction

Is the present focus on reduction of medical supply appropriate? Almost certainly not! No matter how tragic these stories are, they are neither typical nor representative. As noted by Dr. Nora Volkow and Thomas A. McMillan, Ph.D. of the US National Institutes of Drug Abuse,

"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." (Emphasis - ATIP)³³

Even the statistics of the CDC itself have proven to be faulty, overmagnifying what has been called a "prescription opioid crisis". CDC has acknowledged that it has reported as "prescription opioid overdoses", deaths that were in fact due to illegally imported fentanyl and its analogs. They called their reported prescription opioid overdose rate "significantly inflated"³⁴ over several years. For 2016, this "inflation" amounted to nearly doubling the number of deaths attributed to prescription medications.³⁵

2.3. Large Scale Medical Studies

We also know from recently published, large-scale studies of surgical patients treated with opioids after discharge, that opioid abuse emerging from managed medical exposure is rare among patients who are profiled carefully before surgery. Millions of patients have such exposures every year.

A 2018 study reported in the British Medical Journal examined outcomes among more than 586,000 patients prescribed opioids for the first time after surgery.³⁶ Less than 1% continued renewing their prescriptions longer than 13 weeks. 0.6% were later diagnosed with Opioid Abuse Disorder during follow-up periods averaging 2.6 years between 2008 and 2016. Likelihood of diagnosis increased with the length of prescriptions, but rose only modestly as dose levels increased from under 20 to over 120 MMED.

It is quite possible -- even likely -- that the diagnosis of Opioid Abuse Disorder in many of these patients was incorrect. The diagnosis is typically made by treating physicians without recourse to accepted definitions of the disorder such as the American Psychiatric Association Diagnostic and Statistical Manual, 5th edition. Many doctors who diagnose patients with abuse are general practitioners who lack sufficient training in addiction and have little experience evaluating the behaviours that actually define drug addiction. Likewise, some physicians confuse patient reports of emerging chronic pain -- caused by failed surgery -- for potential opioid abuse.

During the period of the study, doctors increasingly became concerned with being sanctioned by law enforcement authorities for their use of opioid doses high enough to reliably manage pain. Thus they may have diagnosed drug abuse to protect themselves -- not their patients, who were often summarily discharged.

A 2016 study reported in the Journal of the American Medical Society³⁷ tracked long-term opioid prescriptions in non-surgical patients, and compared prescription rates to 642,000 patients who received one of eleven common types of surgery. Opioid prescriptions were defined as "chronic" when 10 or more scripts were written in one year or a prescription was renewed continuously for more than 120 days.

In this study, the rate for chronic prescriptions of opioid analgesics among millions of non-surgical patients was estimated at 0.136 percent. (Parenthetically, this finding strongly suggests that "doctor shopping" is not a significant source of opioids abused by people with addiction.) For 4 of the 11 surgical procedures studied, the same rate of prescriptions occurred after surgery as before. For the 7 remaining procedures, long-term opioid prescriptions rose by factors varying from 1.28 (0.174%) for caesarean delivery, up to 5.07 (0.69%) for total knee replacement.

The highest rate of post-surgical chronic prescriptions occurred for total knee replacement -- a procedure known to cause lingering pain in many who undergo it.^{38 39} It is likely that many on-going prescriptions after knee replacement reflected chronic post-surgical pain, rather than issues of opioid misuse. Although not examined in the study, this outcome may also be true of other procedures where long-term prescribing was observed.

These studies demonstrate beyond any reasonable contradiction that managed medical exposure does not by itself significantly raise risks of opioid abuse in surgical patients who are properly screened for previous opioid exposure. This outcome directly contradicts the false claim that addiction starts with just a few pain pills in any large number of people.

3. Addiction Risks

It may well be asked, what are the risks of opioid involvement or addiction among patients who have already experimented with drugs before they see a doctor? Volkow and McMillan offer us some insight on this question.⁴⁰ The CDC does not publish definitive statistics on this issue. But well-established demographics can offer general guidance. In the great majority of cases, the typical beginning addict and the typical chronic pain patient are different people.

3.1. The Demographics of Addiction and Chronic Pain

We now know that the most common beginning opioid abuser is an adolescent or early-20's male who has a history of family trauma, prolonged unemployment, and often mental health issues. This population is generally medically under-served. It is unusual for young males in economically distressed regions of the US to be seen by a doctor. When they are seen, it is unusual for them to be prescribed pain relievers for more than a few days. As noted by Volkow and McMillan, a few days are insufficient to cause drug dependency, much less addiction.

By contrast, the typical chronic pain patient (by a ratio of 60/40 or higher compared to men) is a woman in her 40s or older who has a history of traumatic injury, failed back surgery, neuropathic pain, fibromyalgia, or other disorders which generate prolonged severe pain.⁴¹ Among women whose lives are stable enough that they can see a doctor repeatedly, addiction to opioids is quite uncommon.

Clearly, "some" patients of any age may become physically dependent on opioids for pain relief, or later display the obsessive drug seeking and self-destructive behaviors which define Opioid Use Disorder. But equally clearly, the overlap between addiction and chronic pain occurs in a relatively small minority. To deal with our public health crisis constructively, public policy must centrally address the majority of people with addiction, before plotting excursions to help the outliers.

3.2. More Misleading Statistics

A statistic often quoted in popular media is that over 70% of all people with addiction report that their first exposure to opioids was from prescription drugs. So how are these young men and women exposed to prescriptions? The answer is almost entirely through theft and diversion of unused medications left over after legitimate patients no longer need them. 75% of people with addiction who begin this way never saw a doctor for pain.⁴² Few are able to sustain a developing addiction from home supplies. They soon begin purchasing street drugs – either illegal drugs like heroin (often laced with illicitly-manufactured fentanyl), or safer, but diverted, prescription drugs that cost much more.

3.3. The role of self-administered poly-pharmacy

It has also become clear in recent years that overdose deaths only rarely involve a single prescription opioid given by a doctor to a pain patient. When the Commonwealth of Massachusetts did an extensive analysis of two years of overdose-related fatalities, they discovered that in only 9% of 1657 deaths did medical examiners detect an opioid in post-mortem examinations that could be tracked to the State Prescription Drug Monitoring Program.⁴³

The best predictor for overdose related death was self-administered poly-pharmacy, not a medically managed prescription. It can be credibly argued that such poly-pharmacy seems a plausible consequence of *undertreatment* of pain, rather than over-prescription. In 79% of 154 Massachusetts deaths where a prescription opioid was detected, the prescribed dose was below the 90 MMED threshold of risk identified in the CDC Guidelines. Likewise, two-thirds of the prescriptions were more than 30 days out of date, suggesting that some of those who died may have been cut off from pain management.

4. The Myth of Opioid Alternatives

Another mythology that greatly distorts our public conversation about opioid pain relievers is the idea that safer alternative therapies for pain exist and would be used if only they were covered by medical insurance. This assumption was explicit in recommendations of the CDC Guidelines. However, this idea is unfortunately naïve and largely unsupported by medical evidence.

4.1. AHRQ review of existing data

In December 2017, the US Agency for Healthcare Research Quality (AHRQ) circulated a draft "Systematic Review" of published trials data on non-pharmacological and non-invasive therapies for treatment of pain.⁴⁴ The yearlong review identified 4,470 published trials for techniques including Rational Cognitive Therapy, mindfulness, psychological counseling, acupuncture, massage, yoga, spinal manipulation and low-level laser therapy, among others. Five common types of pain were addressed: chronic low back pain, chronic neck pain, fibromyalgia, tension headache, and osteoarthritis.

After a rigorous multi-level quality review by medical experts, only 205 published trials were chosen for inclusion in the Systematic Review. The main reasons for study rejection were failure to follow patients for at least 30 days after trial, and failure to sufficiently document treatment protocols to establish repeatability of results. Among the surviving trials, AHRQ applied the assessment "Medical Evidence Weak" more than 100 times.

A further and potentially disqualifying weakness of the trials literature was that few investigators bothered to document the nature and protocols of "usual treatment" to which these non-invasive therapies were generally added or compared. In point of fact, "usual therapy" often comprises NSAIDs or opioid analgesics. But most trials reported in the literature do not establish the precise protocols that were followed under "usual

treatment”.

4.2. Alternative therapies may be no better than placebo

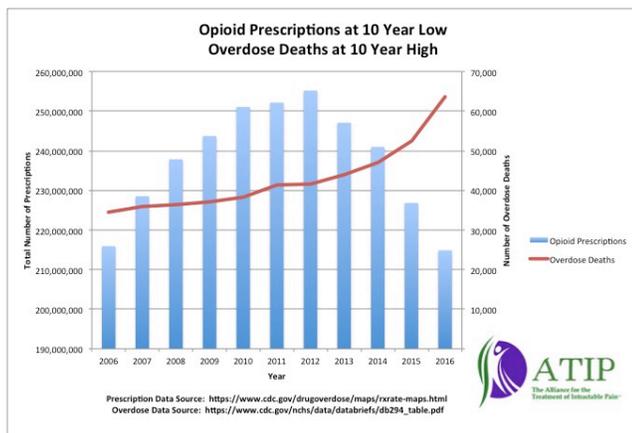
The AHRQ systematic review made an effort to dress up a pig in ballet tights, by claiming that at least a few of the trials they examined demonstrated measurable improvement in outcomes. However a detailed probe of details of the report brings us to a different insight. The most supportable conclusion that we may draw from the AHRQ systematic review is that non-invasive, non-pharmacological therapies can help some patients, some of the time – when applied as adjuncts to treatment with analgesics. But the present state of knowledge does not permit us to establish whether such alternative therapies are in fact any more effective than placebo.

The one true test of alternative therapies would be to test their efficacy in reducing opioid dosage in patients with pain severe enough to warrant chronic opioid management. Such a study has never been done. Thus, non-pharmacological therapies do not offer realistic “replacements” for analgesic treatment.

5. A Necessary Way Forward

Much public and government discussion of opioid addiction and overdose deaths is now focused on restriction of prescriptions to people in pain, and restriction of opioid supply overall. However, it is clear that this focus is miss-placed. The ‘war’ on drugs has become a war on pain patients.⁴⁵

Figure 1: Opioid Prescriptions vs Overdose Deaths



Even the most basic attention to overdose and prescription statistics must reveal that attempts to moderate the opioid “epidemic” by restricting supply have failed. According to the CDC, prescriptions are now at a 10-year low, but overdose-related deaths continue to escalate.⁴⁶

5.1. Review of CDC Data

It is also becoming clear that further restrictions on medical opioid supply will do nothing to moderate the trends revealed in Figure 1. There is evidence that restrictions may indeed be contributing to increased deaths, by driving chronic pain patients into the streets for pain relief - or otherwise - into decline, disability, and suicide.⁴⁷

5.2. A necessary first step

A necessary first step in correcting the horrid outcomes of the 2016 CDC Guidelines must be their formal withdrawal for a major re-write to correct multiple biases, errors and omissions. Board-Certified Pain Management physicians experienced in community-based, long-term treatment of chronic pain patients should lead such an effort.

This rewriting must be supported by a wide range of stakeholders, including providers from hospice, palliative care, cancer treatment, and patients or their advocates as voting members. Guideline development must be conducted using a publicly transparent process, supported by sufficient staff to process, analyze, and integrate external input.

5.3. Guideline Recommendations

Recommendations must be evidence-based, and guiding principles must include the following:

There is no one-size-fits-all patient or therapy. Medical professionals, responding to the needs of the patient, must tailor all pain treatment.

1. There can be no generalized single threshold of risk for Opioid Use Disorder versus opioid dose level or duration. There is no science to support such a threshold. Doctors must be able to trial their patients on different medications and dose regimes, perhaps combined with ancillary non-pharmaceutical therapies.
2. Medically managed exposure to opioid analgesics may create physical dependence without symptoms of addiction in patients treated long-term. Dependence, when it occurs, is an acceptable and physiologically expected outcome of effective pain treatment. Withdrawal symptoms can be managed with appropriately gradual tapering, if change or reduction of medication is medically indicated.
3. There is no medical evidence of benefit and ample evidence of needless harms in forced reductions of dose for patients who are medically stable and who benefit from existing dose regimes.
4. Risk of opioid abuse or protracted opioid prescription in properly screened, opioid-naïve post-surgical patients is significantly less than 1%. Doctors need training to distinguish between patients in whom prolonged need for opioid prescription is an indicator for development of chronic pain rather than an indicator of opioid misuse.
5. Patient screening for opioids should be oriented to identifying patients who have previous or present non-medical opioid exposure, in order to apply enhanced management protocols and make referral for drug abuse treatment where appropriate. The costs of urine testing are now outrageously high. False positives of urine testing are replete, and must be substantially reduced through better education and understanding of their results as they are often misused as grounds for patient dismissal.⁴⁸

6. A single deviation from an opioid management contract -- however minor -- is all too often viewed as adequate reason to discharge a chronic pain patient from care. However, best available medical evidence suggests that patients who “doctor shop” or “pharmacy shop” likely comprise less than 1% of all patients treated with opioid analgesics. Care must be taken to avoid patient stigmatization and false alarms in applying data from Prescription Drug Management Programs. Patient treatment contracts must recognize conditions and limitations of patient daily life before mandating arbitrary discharge or otherwise damaging the patient.
7. No physician who treats verifiable chronic pain should be subjected to disciplinary action or government sanction solely because of the gross volume of opioids that he or she prescribes. Without reference to the medical conditions and numbers of patients treated, volume of prescriptions is not a reliable indicator for drug diversion to opioid abusers or street markets.

A related step in avoiding further harms must be immediate direction from the US Congress to the Department of Veterans Affairs, to cease enforcement of the present VHA no-opioids policy. It is now well established that such policy is causing significant numbers of patient suicides in Veteran and non-Veteran populations.

Finally, pending issuance of a new CDC prescription guideline, all US States must stand down from efforts to impose further limitations on opioid prescribing for acute, chronic, or terminal pain. Enforcement of existing State limitations on dose level or duration should be suspended. If and when re-considered, such limitations must be grounded on published medical evidence of benefit and qualified by exceptions for chronic, intractable, or terminal pain conditions.

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