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The Quest for Rational Chronic Pain Pharmacotherapy

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Kroenke, Krebs and Bair are to be commended for providing a comprehensive and critical review of chronic pain pharmacotherapy. As they explain, chronic non-cancer pain is extremely common, causes widespread suffering and disability, and prompts a great deal of health care utilization. Psychiatrists see many patients with chronic pain due to the high rates of comorbidity between mental health, substance abuse, and chronic pain disorders. Furthermore, the pharmacotherapies used to treat these types of disorders overlap considerably. Therapies prescribed for one of these types of disorder may augment or may disrupt therapies for the other disorders. It is therefore important for psychiatrists to be aware of the full array of options for chronic pain pharmacotherapy.

Health care systems (such as the Veterans Administration) and accreditation bodies (such as the Joint Commission on the Accreditation of Health Care Organization, JCAHO) have urged greater attention to pain through initiatives such as “pain as the fifth vital sign.”[1] But in outpatient settings, there has been little guidance about how to follow improved monitoring of pain with improved therapy for chronic pain.

The past two decades have seen large increases in the use of long-term opioid therapy for chronic pain. High potency DEA Schedule II opioids have shown the largest increases.[2] Opioid therapy is more common, more prolonged and more potent in patients with mental health and substance abuse disorders, even though these patients have been excluded from randomized trials as ‘high risk.’[3] Prescription opioid abuse is now the fastest growing form of drug abuse. As many teenagers start non-medical use of prescription opioids as start cannabis.[4] Prescription opioids are now also the number one cause of accidental drug overdose.[5] It is therefore timely and important to review the full range of options for the pharmacotherapy for chronic pain so that the effectiveness and adverse effects of opioids can be compared to those of other pharmacotherapeutic agents.

An important shortcoming to highlight about all randomized trials of pharmacotherapy for chronic pain is their short duration. Medications that will be used by patients for years have been evaluated in trials that last weeks to months. There are scientific, monetary and ethical reasons for the short duration of randomized trials. It is difficult to prevent crossover from placebo to the active treatment or complete dropout from a long randomized trial. Long trials are expensive and the FDA has not required them of pharmaceutical companies. Finally, it is ethically dubious to deprive patients of effective treatments over the long term simply because they were randomized to placebo. It is therefore necessary to extrapolate long-term clinical effectiveness from short-term clinical trials. The validity of this extrapolation may be especially doubtful in the case of long-term opioid therapy where issues of tolerance, physical and

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psychological dependence, and opioid-induced hyperalgesia still need to be sorted out. There is a real possibility of “analgesic failure” with long-term opioid therapy.[6]

Kroenke, Krebs and Bair are to be commended for the stepped-care approach that they recommend. Too often, acute pain management with opioids drifts into chronic pain management with opioids without any explicit consideration of alternatives. Among the alternatives, the authors place tricyclic antidepressants and tramadol in their second step, immediately following the simple analgesics, acetaminophen and NSAIDs (Table 3). I think this ranking is consistent with the available evidence base, but it is not consistent with my clinical practice. In the older and medically-ill patients I treat, the serotonin-norepinephrine reuptake inhibitors (SNRIs) are much easier to use and appear to be as effective.[7] My clinical experience also suggests more abuse liability for tramadol than has appeared in the literature. Topical analgesics can be useful for the small group of patients with clearly localized neuropathic or arthritic pain.

In Table 4, the authors summarize the evidence base for non-opioid pharmacotherapy of chronic pain. Neuropathic pain has the clearest pathophysiology of the pain types listed, and the most well-proven non-opioid treatments. Though opioids have been shown to be effective in neuropathic pain, there are proven alternatives that should be tried first. There are also good alternatives to opioids for fibromyalgia. The only opioid shown to be effective in fibromyalgia is tramadol. The vast majority of chronic pain falls into the last two categories, osteoarthritis and low back pain, where the effectiveness of non-opioid analgesics is less proven. There are published and forthcoming trials suggesting that tricyclics and SNRIs are effective for low back pain and osteoarthritis.[8,9]

But all pharmacotherapies have shown limited ability to increase the functional status of patients with chronic musculoskeletal pain. Therefore, pharmacotherapy alone cannot be recommended as sole treatment for these conditions. Some effort at reactivating patients must also be made.[10]

The authors summarize their opioid management strategy in Table 2. In general, I think this is a wise synthesis of available data and clinical experience. I will focus on the areas where I would supplement or revise what the authors have provided. “Maximize non-opioid analgesic strategies” is an important and reasonable first step. However, it can be difficult for clinicians to implement because patients are often exposed to opioids during an earlier “acute pain” phase of their illness. These patients can be reluctant to discontinue opioids in order to try alternative therapies.

Step two is to “inform subjects of risks.” This is an important step, but addiction is not the only risk that should be mentioned. First, it appears that the risks of iatrogenic opioid addiction are very low in patients without a personal or family history of substance abuse.[11] Addiction risk appears to arise in clinical practice because patients with prior substance abuse disorders are more likely to initiate and continue opioid therapy long-term.[12] Patients with past non-opioid substance abuse are also more likely to receive diagnoses of opioid abuse and dependence after receiving long-term prescribed opioid therapy.[13] Second, other less-explored risks of opioid therapy may be more important. Opioid-induced hyperalgesia is common among methadone maintenance patients and may be common among other patients receiving long-term opioid therapy.[14] Third, it is also important to give patients a proper sense of the benefit to be expected from long-term opioid therapy. The mean pain relief achieved for patients with chronic pain treated with opioids in the short-term randomized trials done to date is approximately 30%.[15] In my experience, patients and physicians are surprised that this figure is so low. Some patients will receive more relief, some less. It is perhaps the single most important fact in opioid treatment planning.

The third step in the authors' opioid management strategy is to "facilitate use of opioid agreements (contracts)." I agree that these contracts are very helpful and eventually timesaving. The stigma associated with these contracts largely disappears if they are implemented universally for all patients on long-term opioid therapy. I prefer to distinguish more common "opioid contracts" which specify only prohibitions and obligations for patients, from less common "opioid agreements" which also specify goals for therapy and obligations for the prescriber. Classical opioid contracts can intensify the adversarial atmosphere between doctor and patient, while a collaborative opioid agreement can establish a more collaborative atmosphere. I have developed a web-based training for primary care physicians, COPE: Collaborative Opioid Prescribing Education (available at: <http://depts.washington.edu/cme/online/course/EN0705>) that demonstrates how to negotiate and implement these agreements.[16]

Step four suggests follow-up at 2–3 month intervals with urine testing. I agree that urine testing is essential. You really don't know what your patients are taking until you look. I have been fooled many times. I think a 2–3 month interval is most viable in primary care clinics, and probably adequate for patients on stable doses of opioids. But those patients recently initiating opioids, those on increasing doses, or those otherwise high-risk patients need to be seen more frequently, generally each month. Step five suggests monitoring pain severity and functional impairment. This is crucial because functional impairment can easily persist or worsen without explicit attention. I find it worth the time to develop personalized functional goals with the patient which are then tracked over the course of therapy (details in the COPE training).

Steps 6 and 7 suggest a careful empiric attitude toward opioid initiation, escalation and continuation. This is very important and rarely done, probably because we do not have clear ways to measure the success of opioid therapy. Most patients don't like long-term opioid therapy and discontinue it. Other patients will request to continue opioid therapy, or even request to increase their dose, despite little effect on pain intensity and activity interference. These patients in effect deny that pain intensity and interference are the proper measures of the success of opioid therapy, explaining that opioids "take the edge off" their pain. Preliminary analyses of data from a large nationwide commercial health plan suggest that opioid therapy is more concentrated than any other prescribed therapy, with 5% of enrollees with chronic pain accounting for 70% of all the opioids consumed in a year. It also appears that a minority of patients discontinue opioid therapy after taking it for 90 days. These data suggest that "a careful empiric attitude" toward long-term opioid therapy has not yet been achieved.

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