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Expert Opinion

A Practice Guide for Continuous Opioid Therapy for Refractory Daily Headache: Patient Selection, Physician Requirements, and Treatment Monitoring

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Objectives.—To provide a guide to the use and limitations of continuous opioid therapy (COT, or daily scheduled opioids) for refractory daily headache, based on the best available evidence and expert clinical experience.

Background.—There has been a dramatic increase in opioid administration over the past 25 years, with limited evidence of efficacy for either pain reduction or increased function, and increasing evidence of adverse effects, including headache chronification. To date, there has been no consensus on headache-specific guidelines for selecting patients for COT, physician requirements, and treatment monitoring.

Methods.—A multidisciplinary committee of physicians and allied health professionals with extensive experience and expertise in the administration of opioids to headache patients, undertook a review of the available evidence from the research and clinical literature (using the PubMed database for articles through December 2009) to develop headache-specific treatment recommendations. This guide reflects the opinions of its authors and is not an official document of the American Headache Society.

Results.—The guide identifies factors that would qualify or disqualify the use of COT, including, determination of intractability prior to initiating COT, requisite experience of the prescriber, and requirements for a formal monitoring system to assess appropriate use, safety, efficacy, and functional impact. An appendix reviews the available evidence for efficacy of COT in chronic headache and noncancer pain, paradoxical effects (opioid-induced hyperalgesia, medication overuse headache, opioid-related reduction in triptan and nonsteroidal anti-inflammatory drug efficacy), other adverse effects (nausea and constipation, insomnia and sleep apnea, respiratory depression and sudden cardiac death, reductions in sex hormones, issues during pregnancy, neurocognitive functioning), and issues related to comorbid psychiatric disorders.

Conclusions.—Only a select and very limited group (estimate of 10-20%) of refractory headache patients who meet criteria for COT respond with convincing headache reduction and functional improvement over the long-term. Conservative and empirically based guidelines will help identify those patients for whom a COT trial may be appropriate, while protecting their welfare and safety.

Key words: continuous opioid therapy, refractory daily headache, guidelines

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The last 25 years have witnessed a reversal of the historic and traditional reluctance to administer opioids chronically for the treatment of chronic pain. The dynamics and machinations behind this reversal are numerous and largely beyond the scope of this document but include both growing eagerness to provide effective pain control to those who require it and heavily funded marketing and "educational" strategies by opioid manufacturers to alter the attitude toward opioid usage. These strategies included generous funding initiatives for physician advocates and professional society educational programming, and funding to liberalize the views of physicians, state medical board members, and government agencies.

Dramatic Increase in Opioid Administration.— The success of these efforts is evident. Of long-term opioid therapy, 90-95% is now prescribed for chronic noncancer pain (CNCP).[1] Based on data from the National Ambulatory Care Survey, the prevalence of opioid prescriptions for chronic musculoskeletal pain doubled from 1980 to 2000 (from 8% to 16%), with no corresponding increase in the frequency of office visits for musculoskeletal pain.[2] Prescriptions for more potent opioids (hydrocodone, oxycodone, morphine) increased from 2% to 9% of visits. The prevalence of visits on a national level where opioids were prescribed by primary care physicians increased by 44% in the decade between 1992 and 2001.[3] In at least one state (Arkansas) the cumulative yearly dose of opioids increased by 37-38% between 2000 and 2005, for both commercial and Medicaid insurance patients, primarily due to the number of days opioids were prescribed.[1] Between 1997 and 2003 the retail distribution of methadone in the USA rose by 824%; for oxycodone the increase was 660%.[4] Recent review of a large medical insurance claims database found that 19% of the chronic opioid therapy prescriptions (greater than 180 days/year) were for headache,[5] despite growing evidence that chronic use of opioids promotes the progression rather than control of the primary process related to headache (see later).

Abuse and Diversion.—The Partnership for a Drug Free America in 2009 published its Partnership Attitude Tracking Study report, which evaluated 6518 teenagers in the USA, grades 7 through 12. Among the key findings were: 61% agree that prescription drugs are easier to get than illegal drugs; 41% believe that abuse of prescription and over-the-counter drugs is less dangerous than abuse of illegal drugs; 30% believe them to be nonaddictive; 20% have abused prescription drugs to get high; and 10% admit to abusing prescription pain killers.[6] Reported abuse of narcotics other than heroin by 12th graders has remained relatively constant (above 9%) since it was first measured in 2002 through the most recently available data (2008): one in 10 report nonmedical use of Vicodin, and slightly more than one in 20 (5.3%) report recreational use of Oxycontin in the past year.[7] Among persons age 12 and older who used prescription pain relievers for nonmedical purposes in the past year, 55.7% reported that the drug source for most recent use was a friend or relative, and received the drug at no expense – in those cases, 80.7% reported that the friend or relative had obtained the drugs as a prescription from only one doctor.[8]

Opioid-Related Deaths.—The Centers for Disease Control in 2009 reported poisoning deaths involving methadone increased from 790 to 5420 from 1999 to 2006.[9] Fatal poisoning involving all opioid analgesics rose from 4000 to 13,800 fatalities during the same period, and involved nearly 40% of all poisoning deaths in 2006. Though cocaine and heroin remain responsible for many of the fatalities, the increase seems mostly to involve opioids, including methadone, Oxycontin, and Vicodin. Drug deaths now kill more people than auto accidents in 16 states, and counting.[10] According to the National Drug Policy report released in May 2009, prescription opioid-related deaths increased 114% from 2001-2005.[11]

Limited Efficacy Data.—The startling escalation in administration of opioids for CNCP has occurred in the face of little evidence of long-term efficacy. In fact, evidence that daily opioid administration (*continuous opioid therapy* or *COT*) is efficacious is lacking and does not appear to justify the aggressive advocacy and administration. Only a minority of those who participate in randomized, controlled trials of scheduled opioids appear to sustain benefit over the long term.[12,13] For chronic daily headache (CDH), only 15-26% of patients showed significant benefit 3 years

or longer after initiating treatment.[14] Moreover, patient claims of global improvement were significantly elevated above that supported by the medical record,[14] and a substantial number of patients who reported over 50% improvement in pain continued to report significant functional impairment.[15] Meta-analytic reviews of evidence from long-term (6 months or longer) outcome studies of COT for chronic noncancer pain (CNCP) provide weak evidence of efficacy at best.[16] In the case of chronic back pain, data failed to show efficacy over placebo or other control conditions, and in some cases, failed to show pain reduction from baseline.[17]

Other Risks and Harms.—Beyond opioid-related death as detailed above, other opioid-related adverse effects are highly prevalent, reported by as many as 77% of patients receiving COT for CNCP.[18] The most commonly reported and easily identified include nausea and constipation.[12,19] Less easily identified, but insidious and under-recognized, is the phenomenon of opioid-induced hypersensitivity to pain, often referred to as opioid-induced hyperalgesia (OIH). This apparent paradox, where even brief periods of opioid administration can activate pronociceptive mechanisms, including the release of pro-inflammatory cytokines, which may eventually override the analgesic effects. Endocrine changes,[20,21] anxiety and depression,[22-24] neurocognitive impairment in some patients,[22,25] sleep disturbance[4,26,27] (with associated daytime sleepiness[27]), respiratory depression,[19,28] and sudden cardiac death[29] are among other significant adverse consequences that are often overlooked as associated with opioids. In November 2006, the United States Food and Drug Administration issued a Health Alert for health professionals on risk of death, cardiac arrhythmias (eg, QT interval prolongation), and narcotic overdose associated with methadone.[30] It should be noted for balance that opioids spare the liver and kidneys – a significant advantage over some other simpler analgesics, such as the nonsteroidal anti-inflammatory drugs and acetaminophen.

Evidence for Opioid-Induced Illness Progression.—Enhanced by advances in neuroimaging and neuroscience research, there exists an increasing understanding of the physiological pathways shared by various chronic pain conditions and the potential adverse influence that chronic opioid therapy has on pathophysiological mechanisms, ultimately leading to progression of the illness rather than its control, particularly in the domain of headache disorders. In the spectrum of chronic pain disorders, headache occupies a unique position, with a long-standing recognition of problems associated with frequent acute treatment usage, initially referred to as *ergot or analgesic* rebound.[31-34] As far back as 1983, Saper proposed that the chronic use of medicine for acute headache *exceeding 2-3 days of use per week, week after week*, represented the threshold to establish the progressive dynamic.[33] Clinical evidence implicating frequent use of opioids as a significant contributor to the chronification and treatment resistance of migraine is mounting and compelling. Recent epidemiological studies have identified the frequent use of opioids and opioid-combination drugs as a significant risk factor for the progression from episodic migraine to CDH, with an odds ratio of 2.3 (1.3-3.9).[35] The critical level of exposure is around 8 days a month, with a more pronounced effect for men,[36,37] a level of use somewhat below the current MOH criterion for opioids of 10 or more days per month in the International Classification of Headache Disorders, 2nd Edition (ICHD-II).[38]

Lack of Headache-Specific Guidelines.—Recent guidelines for COT promulgated by the American Pain Society and American Academy of Pain Medicine identify headache as one of 4 common CNCP conditions (along with back pain, osteoarthritis, and fibromyalgia) where COT might be considered, but the guidelines do not address the unique aspects of headache, such as balancing the risk of MOH against the potential benefit of scheduled opioids.[39]

In this context and with the growing concern and involvement of government and the health care professions in this matter, the American Headache Society (AHS) encouraged an expert panel to develop a guide for the identification of headache sufferers who might be appropriate candidates for COT, with recommendations for patient selection, physician preparation, and monitoring requirements. It should be noted, however, that this guide does not represent an official position paper of the AHS. This

practice guide is based on empirical evidence where available (see *Appendix*) and on the consensus of clinical experience from a multidisciplinary panel of senior and scholarly clinicians with COT experience in the treatment of headache. We anticipate that these recommendations will be subject to further peer review and modification based on the accumulation of the clinical experience of headache specialists and additional outcome research.

A GUIDE FOR CONTINUOUS OPIOID THERAPY FOR HEADACHES: SELECTION OF PATIENTS, PHYSICIAN REQUIREMENTS, AND GENERAL MONITORING RECOMMENDATIONS

Goal and Scope of the Guide.—Most experts in headache believe that continuous administration of opioids for chronic headache should be restricted to a small subset of cases and not administered to a majority of patients who have difficult-to-control headaches. This guide was developed to assist clinicians in identifying those patients who might be appropriate candidates and to recognize patients who may not qualify for opioid therapy. It also provides guidance in the monitoring and management of patients prescribed opioids.

Because there is a strong demand for direction in this area but an absence of sufficient data, the guide was developed as a *consensus document* based upon the existing evidence, expert opinion, and experience. A multidisciplinary group of senior, scholarly headache specialists (physicians, psychologist, physician assistant, nurse practitioner), each with many years of experience in the use of opioids in the treatment of headache, comprised the panel. Among the experts who either contributed to the development of the guidelines or who approved them subsequently are those with public advocacy positions for the liberal use of opioids in the treatment of chronic nonmalignant pain disorders, as well as those who have publicly expressed a cautionary note.

The Practice Guide (Modified with Permission from Saper and Lake)[15]

A. All of the following (1-5) are required

1. The patient is an adult over age 30.
2. Moderate to severe, pain, and functional compromise occurring more that 20 days/month.
3. A history of reliable and compliant medication usage and related behavior.
4. Prescribing physicians have at least 4 clinical visits over months of time in which there are personal, direct treatment encounters with the eligible patient prior to administration of opioids. (Physicians must know the patient and have a reasonable understanding of the level of intractability, compliance, maturity, and psychological makeup.)
5. The prescribing physician has competence, knowledge, and experience in the use of the scheduled opioid.

B. At least one of the following (1-5) must also apply

1. Convincing refractoriness to aggressive, advanced, comprehensive treatment, which should include:
   a. Treatment of MOH (if present) – see Appendix I for MOH criteria per 2004 IHS classification
   b. Appropriately aggressive pharmacotherapy
   c. Cognitive-behavioral pain management
   d. Interventional treatment, if indicated
   e. Diagnostic review to rule out organic and pathological disturbances
2. The presence of convincing, serious adverse effects from otherwise appropriate medications, thus severely limiting available treatments.
3. Older individuals (eg, >65 years old) where other treatments are ineffective or pose safety concerns (Note that relative risk of respiratory depression rises significantly with age, and that seniors may reach efficacy with significantly lower doses).
4. Individuals with significant medical comorbidities in whom other options for treatment are not available or contraindicated.

C. Any of the following (1-6) would generally disqualify

1. Significant severe Axis I DSM-IV diagnosis, or multiple diagnoses of moderate severity (exception – some patients with mood disorders attributed to their medical condition may

experience significant improvement in depression with pain relief).
2. Past or present *true addictive disease* (exception – nondrinking, rehabilitated alcoholic).
3. Any evidence or legal encounters regarding prescription drug abuse or surreptitious multisourcing.
4. Axis II Cluster B personality disorders (significant antisocial, borderline, histrionic, or narcissistic traits).
5. Presence of moderate to severe somatoform features.
6. Active psychosis or Axis II Cluster A personality disorders (paranoid, schizoid, schizotypal).
7. Family environment with known substance abuser due to risk of unintended diversion (exception – history of long-term sustained remission following treatment participation).

D. A formal monitoring system for appropriate use, safety, efficacy, and functional impact must be in place (see Part 2 for further details and tools)
1. Written, signed, and witnessed pretreatment agreement and informed consent
   a. Compliance expectations
   b. Collateral discussions with family member or significant other
   c. Collateral discussions with other treatment professionals
   d. Agreement and plan for safe withdrawal from COT in the event the prescribing physician or patient believes that discontinuation is in patient's best interest
   e. Compliance with the principle of one prescribing physician and one dispensing pharmacy for opioids
2. Pretreatment and ongoing urine drug screens.
3. Regular office visits every 1-2 months, including periodic contact with family members or significant others to assess efficacy, functioning, and adverse effects.
4. Periodic psychological consultation to assess compliance, efficacy, functioning, psychological benefit or adverse effects, adherence to self-help and cognitive-behavioral pain management techniques.
5. Accurate calculation of dose and pill counts coordinated with frequency of visits.
6. Formal assessment of efficacy and functional impact at each visit (this requires formal documentation on the chart).
7. Periodic communication with all treating professionals.
8. Pretreatment and periodic updates (through state registries, when available) of all scheduled drugs that a patient has been prescribed and filled in the past year.

APPENDIX—CONTINUOUS OPIOID THERAPY FOR CHRONIC DAILY HEADACHE AND CHRONIC NONCANCER PAIN: EVIDENCE FOR EFFICACY AND ASSOCIATED ADVERSE EFFECTS

Portions of the Appendix were previously published in *Headache* in January 2008,[15] updated here with references to published articles from the PubMed database through December 2009.

RESULTS OF LONG-TERM OBSERVATIONAL STUDY OF CONTINUOUS OPIOID THERAPY FOR REFRACTORY CHRONIC DAILY HEADACHE

In 1992, Saper and colleagues initiated a formal COT program for carefully selected, refractory patients with CDH (predominantly chronic migraine), with a plan to carefully monitor outcomes over the long term. All enrolled patients had been in a multidisciplinary practice for at least 2 years prior to starting COT, and failed to sustain benefit from available evidence-based prophylactic pharmacotherapy and behavioral intervention. Preliminary data, as reflected in published abstracts,[40-43] were encouraging in regard to efficacy. In a later published abstract, Rothrock also reported "good improvement" with 15 of 30 patients with COT (methadone), and "modest improvement" in 10.[44] However, when Saper et al assessed outcomes at 3 years or longer for 160 consecutively enrolled patients, 74% either failed to benefit or were discontinued for clinical reasons.[14]

Although 26% of the initially enrolled patients might be classified as good responders – based on

50% or better improvement in an index of severe headache activity compared to the 2-year baseline – this did not correlate with the type of global report of improvement on which physicians may often rely to justify continuing COT. Patients reported significantly higher levels of global improvement attributed to the opioid program (mean = 70% on a visual analog scale or VAS) than was actually supported by the medical record (mean = 46%, $P < .00001$). In fact, there was no statistically significant correlation between global reports of improvement on the VAS and the ostensibly more objective medical record data.[14] In a later article, Saper et al estimated that only 10-20% (16-32) of the initially enrolled patients (160) actually experienced meaningful sustained improvement from COT, when functioning and other collateral sources of data (eg, significant others) were included in the assessment.[15]

Furthermore, global reports of pain improvement attributed to COT did not necessarily correlate with meaningful improvement in functioning. The published report in 2004 was based on 160 patients who had started COT at least 3 years previously – the intent-to-treat group, of which 70 remained on COT for 3 years or longer. An overlapping group (n = 155), including those in the published study and additional patients enrolled in the COT program for less than 3 years, completed the Pain Disability Index (PDI),[45-47] a standardized set of rating scales ranging from 0 ("no disability") to 10 ("total disability") on 7 functional dimensions. Although some patients improved in functional outcomes, a substantial percentage of those who reported at least 50% improvement attributed to opioids on the VAS continued to report substantial functional impairment on the PDI, including occupation (38%), family and home responsibilities (31%), self-care (17%), and basic activities of daily living (10%).[15]

Saper et al believe that some of this reported disability may be due to decreased motivation directly related to frequent opioid use.[15] The lack of evidence for increased functioning was one reason COT was discontinued for many patients. Although not quantified, they encountered a number of patients who discontinued opioids under protest and then later volunteered how glad they were to be off opioids – that they had not realized the extent of opioid-related impairment, lack or motivation, or anhedonia they had experienced while on COT.

Problem drug behavior (dose violations, lost prescriptions, multisourcing) occurred in 50% of the 70 patients who remained on COT for 3 years or longer.[14] These issues were typically uncovered through detailed chart audits, collateral contact with significant others, or with other physicians. They were not necessarily revealed during standard clinical visits with experienced physicians, nurses, and psychologists. In most cases, compassionate confrontation on the problem behavior was sufficient to reset treatment on a level course, although problems often continued until identified and confronted.

EFFICACY OF CONTINUOUS OPIOID THERAPY FOR CHRONIC NONCANCER PAIN (CNCP)

Meta-Analyses and Randomized Placebo-Controlled Trials.—At the time of this writing, the most recently available meta-analysis of randomized controlled trials (RCTs) that assessed the efficacy and safety of opioids for noncancer pain is a report by Furlan et al who searched MEDLINE, EMBASE, and CENTRAL databases through May 2005 for RCTs of any opioid administered by oral or transdermal routes or rectal suppositories for CNCP (defined as noncancer pain for longer than 6 months). They found 41 trials involving 6019 patients: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis, or back pain), 12% neuropathic pain (post herpetic neuralgia, diabetic neuropathy, or phantom limb pain), 7% fibromyalgia, and 1% mixed pain. They found that 90% of the trials were either funded by or had one or more co-authors affiliated with the pharmaceutical industry. They found no trials of transdermal or rectal routes of administration, nor opioid infusion programs for chronic pain. There were no studies limited to headache patients.[12]

The mean duration of treatment was 5 weeks (range 1-16), well below the expected duration of treatment for scheduled opioids in clinical practice. Despite the relative shortness of the trials, one-third of the participants abandoned treatment. Dropout

rates averaged 33% in the opioid groups and 38% in the placebo groups. Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. However, in head-to-head comparisons with opioids, other drugs produced significantly better functional outcomes.[12]

Kalso and colleagues analyzed all available randomized, placebo-controlled trials through September 2003.[7] Fifteen trials met inclusion criteria, including 11 studies (1025 patients) comparing oral opioids with placebo. Mean pain relief with opioids was about 30%, with only a minority appearing to benefit from long-term treatment. In one study only 20% of patients still had relief with oral morphine after one year. Five studies found no significant difference between opioid or placebo treatment. Despite some benefit from short-term use of opioids, only 44% of 388 patients who were offered continued COT elected to remain on opioids for periods ranging between 7 and 24 months.[13] Others have subsequently noted that "The evidence base for this type of pain management is meager because the needed randomized controlled trials, *which ideally should last for several years*, have not been performed" (italics added).[48]

There is expected overlap between the cumulative Furlan meta-analysis[12] and the earlier Kalso meta-analysis.[13] Furlan compared the efficacy of opioids vs placebo in the 20 randomized controlled trials published through 2002 with the additional 8 trials published in 2003 and 2004. Opioid efficacy was comparable and stable; the additional trials did not change the conclusions.[12] A 2009 meta-analytic review comparing studies of COT that either allowed or prohibited the use of short-acting opioids as rescue medication found no evidence that rescue medication with short-acting opioids for breakthrough pain affected the analgesic efficacy of COT or the incidence of common opioid-related adverse effects (nausea, constipation, somnolence) in CNCP patients.[49]

There have been several systematic reviews of opioid efficacy for various subtypes of CNCP. Eisenberg found 9 articles assessing mu-opioid efficacy for treatment of evoked neuropathic pain, but only on the short term (24 hours, n = 7) or intermediate term (4 weeks, n = 2), and concluded that opioids can reduce the intensity of dynamic mechanical allodynia and perhaps of cold allodynia in peripheral neuropathy, with the 2 intermediate term studies showing greater efficacy for opioids than placebo.[50] In a systematic review of opioids for chronic back pain, Martell et al culled several databases for studies from 1966 through the end of 2004 or the first quarter of 2005.[17] Meta-analysis of the 4 studies assessing the efficacy of opioids compared to either placebo or nonopioid control failed to show reduced pain with opioids compared to the control conditions. Meta-analysis of the 5 studies that compared the efficacy of different opioids failed to show a significant reduction in pain from baseline. Aberrant drug-taking behavior ranged from 5% to 24%. Long-term efficacy (16 weeks or more) was unclear.

A randomized 12-week placebo-controlled trial by Katz et al used a withdrawal methodology to assess the efficacy of oxymorphone extended release tablets for opioid-naïve patients with chronic low back pain.[51] Sixty-three percent of the intent-to-treat population successfully titrated to a stabilized dose of oxymorphone, most within one month, with 18% dropping out during titration due to adverse events. Patients were then randomized to continued oxymorphone or placebo. Placebo patients discontinued treatment significantly earlier due to lack of efficacy than those who continued on opioid, and pain levels increased significantly more in the placebo group.

Most of the RCTs of opioids for CNCP have focused on relatively short-term outcomes. Noble and others published a meta-analysis of long-term efficacy and adverse events for CNCP patients treated with opioids for at least 6 months, including open-label studies. In a search of 11 databases through April 7, 2007, 17 studies (3079 patients) met inclusion criteria. They concluded that weak evidence suggests that oral and intrathecal opioids reduce pain long-term for patients who benefit short-term with minimal adverse effects. There were insufficient data from transdermal studies to quantify pain relief. They also found high dropout rates due to adverse effects (32.5% for oral opioids) or insufficient pain relief (11.9%, for oral opioids).[16]

Functional Outcomes.—Kidner et al reviewed functional outcomes for 1226 consecutively admitted patients with a chronic disabling occupational musculoskeletal disorder entering a functional restoration program.[52] Of this group, 596 were using opioids on admission, and 630 were not. The program required opioid tapering and discontinuation as part of the treatment. Those with a higher post-injury dose of opioids were significantly less likely to complete the program, and were less likely to return to work or remain in the work force. One year after treatment, patients in the group reporting the highest opioid use on admission were 11.6 times more likely to be receiving Social Security Disability income when compared with those who were not using opioids at the time of entering the program. High opioid use was also associated with higher health care utilization.

These findings are consistent with a study by Volinn et al using multivariate statistical techniques to explore associations between opioid therapy for back pain and work loss, reviewing workers compensation claims for nonspecific low back pain.[53] Compared with the no opioid reference group, odds for chronic work loss were 6 times greater for claimants with schedule II opioids, and 11-14 times greater for claimants with opioid prescriptions of any type during a period of 90 days or longer. The costs of claimants with schedule II opioids averaged $19,453 more for those taking schedule II opioids than the no opioid group. They conclude that "for most workers opioid therapy did not arrest the cycle of work loss and pain."

Although the direction of influence is unclear (some might argue that the opioid-using patients were more seriously injured or painful, and "required" higher doses of opioids), what does emerge from both of these recent studies is consistent with what was reported by Saper et al in the previously discussed long-term outcome study of COT for refractory headache patients.[15] In a national epidemiological study of noncancer pain in Denmark,[54] opioid usage was significantly associated with reports of higher pain levels (moderate/severe or very severe), poor self-rated health, unemployment, greater use of the health care system, and a lower quality of life, as reflected on all items on the SF-36. As with all cross-sectional epidemiological research, causal relationships cannot be established. However, the authors note that "it is remarkable that opioid treatment of long-term/chronic noncancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity."[54] Despite patient reports of subjective pain relief from frequent or daily opioid therapy, improved functional capacity – one of the primary goals of chronic pain management – remains elusive for many if not most of these patients, and may paradoxically move in the direction of greater impairment.

Age and Efficacy.—Individual differences in response to opioids have long been recognized, but few studies have attempted to identify predictors of response. In a retrospective chart review of 206 patients with CNCP, Buntin-Mushock et al found that only adults over age 60 showed a significant reduction in visual analog pain scores from the start of opioid therapy until discharge from the clinic, with a daily dose 54% lower than younger patients. However, the amount of change was modest, from 6.9 ($\pm$0.3 on a 10 point scale) to 5.3 ($\pm$0.3, $P < .01$).[55] We have been unable to find any published studies to date of the efficacy – or long-term safety – of frequent opioids for children, adolescents, or young adults. Opioid tolerance, and therefore receptor alterations, appears to develop more much more rapidly in younger patients,[55] a finding supported by experimental studies on age-related tolerance in animals.[56] A review by Riley and Hastie found younger age to be a risk factor for opioid abuse, although it was also associated with greater opioid efficacy.[57]

PARADOXICAL EFFECTS OF OPIOIDS

Opioid-Induced Hyperalgesia.—The paradoxical enhancement of nociceptive sensitivity following chronic opioid administration – *opioid-induced hypersensitivity to pain* – has been identified in both human and animal studies.[58-60] In a systematic review of OIH and related terms (opioid-induced abnormal pain sensitivity, opioid hyperalgesia, opioid-induced paradoxical pain, opioid-induced abnormal pain), Mitra concluded that despite initial skepticism and reservations, the phenomenon of OIH in humans is

now accepted as a clinical reality, and a challenge facing pain management in a variety of settings from maintaining posit-operative analgesia to chronic pain to palliative care.[61] OIH can occur with even brief periods of administration. For example, the intraoperative administration of fentanyl or remifentanil enhances the extent and duration of postoperative pain.[62] Recent studies have shown that neural plasticity associated with the development of opioid *tolerance* may activate a *pronociceptive* mechanism that could counteract the analgesic effect of opioids.[59] Studies with animal models suggest genetic variation as a significant factor contributing to differences in the propensity to develop OIH.[63]

Several factors have been identified as mediating OIH. Sustained morphine exposure increases activity of sensory neuropeptides (calcitonin gene-related peptide [CGRP] and substance P) and their downstream signaling messengers (prostaglandins, lipoxengenase metabolites, and endocannibinoids).[64,65] Whether OIH might be mitigated by CGRP antagonists currently under development is yet to be determined. Sustained morphine also increases NK-1 receptor expression in the spinal dorsal horn.[66] NK-1 receptor expressing neurons play a critical role in sustained morphine-induced neuroplastic changes, which underlie spinal excitability reflected as thermal and tactile hypersensitivity to peripheral stimuli, and to reduced antinociceptive actions of spinal morphine.[67] Opioid-induced activation of neuropeptide FF receptors has also been shown to play a critical modulating role in the OIH and associated opioid tolerance.[68]

Cholecystokinin (CCK) is upregulated in the rostral ventromedial medulla (RVM) during persistent opioid exposure. CCK is both antiopioid and pronociceptive, and activates descending pain facilitation mechanisms from the RVM. The neuroplastic changes elicited by opioid exposure reflect adaptive changes to promote increased pain transmission and consequent diminished opioid efficacy (ie, tolerance).[60,69] Opioids induce glial cells to release proinflammatory cytokines, including tumor necrosis factor, that play a role in compromised opioid analgesia and adverse effects including tolerance, dependence, and reward.[70-72] Opioids have also recently been implicated in immune response suppression, although the relationship between activity in the immune system and pain is not well understood.[73]

Using advanced psychophysical techniques, Ram and colleagues found a significant loss of diffuse noxious inhibitory control (DNIC) in chronic pain patients using opioids vs nonopioid patients, with the opioid dosage and treatment duration emerging as predictors of lower magnitude DNIC.[74] OIH is a pronociceptive process that is related to, but differs from, tolerance. Multiple neurobiological mechanisms are involved, including a central role for the excitatory neurotransmitter N-methyl-D-aspartate, along with spinal dynorphins and descending facilitation from the rostral ventromedial medulla.[75] Spinal NK-1 receptor expressing neurons mediate both OIH and antinociceptive tolerance by activating descending facilitory pathways.[67] The transient receptor potential vanilloid1 receptor (TRPV1), a molecular sensor of noxious heat, acts as an integrator of multiple forms of noxious stimuli and plays an important role in the development of inflammation-induced hyperalgesia following opioid exposure.[76]

Porreca has recently outlined a comprehensive understanding of OIH and the descending facilitation of pain.[77] The phenomenon occurs with multiple classes of opioids, and is not due to active metabolites. Opioids have both hyperalgesic and analgesic effects. On initial exposure the hyperalgesic impact is buried under a more potent analgesic effect, and emerges over time with continued opioid exposure. Morphine administration results in selective trafficking of TRPV1 to peripheral terminals. Morphine increases expression of inflammatory peptides (substance P and CGRP) in the dorsal raphe gray and spinal cord. Morphine induces changes in the trigeminal system, including dose-dependent facial allodynia. Morphine produces modest increases in substance P and CGRP expression in the trigeminal ganglion. Morphine induced CGRP expression in dural afferents – the apparent primary site of migraine-related nociception – is long-lasting. Morphine infusion can induce adaptive changes that render the recipient vulnerable to hyperalgesia when confronted with a stressor days or weeks later – long-lasting adaptive changes that can lead to "pain without injury."

In clinical practice, OIH is often marked by allodynia and worsening pain despite increasing doses of opioids, a red flag. The patient may also experience a diffuse spreading of what was initially experienced as more focal pain, a common experience for many patients when episodic migraine transforms to medication overuse headache (MOH).

Medication Overuse Headache: Transformation from Episodic to Chronic Daily Headache, Improvement Following Opioid Withdrawal.—One of the great advances in the field of headache science was the discovery that the frequent use of certain medications – centrally acting analgesics, ergotamine, triptans, and butalbital-containing compounds – can contribute significantly to the transformation to CDH and intractability until the implicated drugs are discontinued.[78,79] Prospective epidemiological research has identified the *frequent use* of analgesics (*once a week or more*) as a significant risk factor for chronic pain 11 years later.[80] This relative risk (RR) is greatest for headache disorders, including chronic migraine (RR = 13.3) and chronic nonmigrainous headache (RR = 6.2). However, the RR is also significantly elevated for chronic neck pain (RR = 2.4) and low back pain (RR = 2.3). The RR for CDH predicted by analgesic *overuse* (ie, daily) was 19.6 for migraine and nonmigrainous headache combined.[80] Daily use of opioids for nonheadache conditions (eg, to control bowel motility in colectomy patients) increases the risk of episodic migraine transforming to CDH.[81] The frequent use or overuse of certain classes of analgesics and abortive medications (eg, opioids, barbiturate containing analgesics, triptans) may be the primary risk factor leading to CDH.[82] Recent epidemiological studies have identified the frequent use of opioids and opioid-combination drugs as a significant risk factor for the progression from episodic migraine to CDH, with an odds ratio of 2.3 (1.3-3.9).[35] The critical level of exposure is around 8 days a month, with a more pronounced effect for men,[36,37] a level of use somewhat below the current MOH criterion for opioids of 10 or more days per month in the ICHD-II.[38] However, the frequency of headache episodes, even in the absence of medication overuse, is also a predictor of the transformation to CDH.[83]

The terms to describe the overuse of acute treatment medication have evolved, from "rebound" and "drug-induced headache" to "medication overuse headache."[78,79] The definition of MOH continues to undergo revision. The ICHD new appendix criteria (2006) define MOH (when attributed to opioids) as use 10 or more days a month, but no longer require recovery to episodic headaches within a 2-month period after withdrawal in order to confirm the MOH diagnosis.[84] Research and clinical experience continue to highlight the benefits of withdrawal from overused medication and recovery of therapeutic responsiveness when the offending medications are discontinued, as well as the potential time frame for recovery – from 2 to 3 months or less[85] to perhaps as long as 10 months in some cases.[86] Evidence for headache improvement following withdrawal from frequent opioids continues to accumulate. Patients with opioid-related MOH who were withdrawn from opioids during comprehensive inpatient treatment (48% of 267 consecutive admissions who completed the program) were more likely to achieve moderate-significant headache improvement than other refractory headache patients who were not using frequent opioids on admission.[87] Studies published from 2007 to 2009 from multiple treatment settings continue to document headache improvement and enhanced treatment responsiveness after withdrawal from frequent opioids, in conjunction with both nonopioid prophylaxis and behavioral treatments.[88-97]

Even in cases of primarily nonheadache CNCP, *discontinuation* of opioids as part of comprehensive pain rehabilitation program can lead to significant improvement. In a longitudinal prospective study, Townsend et al assessed treatment outcome at discharge from a 3-week interdisciplinary program focused on functional restoration and at 6 months post discharge for 373 consecutive patients.[98] Over half (57.1%) were taking opioids daily at admission, and reported significantly greater pain severity and depression than the nonopioid group. Significant improvement occurred on all variables at both discharge and 6-month follow-up, regardless of pretreatment opioid status.

Long-term outcome studies have also identified high rates of relapse after drug withdrawal for

patients receiving pharmacological prophylaxis: 31% within 6 months of withdrawal, and from 21% (triptans) to 71% (analgesics) at 4 years,[85,99] although this may be mitigated by adding behavioral coping skills for pain management, such as biofeedback.[100,101] Negative prognostic indicators for relapse during the year after withdrawal include both a longer duration of drug overuse,[95] and a high frequency of use, eg, a pre-treatment intake of 30 or doses/month.[96]

Opioid-Related Reduction in Efficacy of Triptans and NSAIDs.—For years, clinicians have suspected that overuse of certain drugs rendered their patients refractory to other appropriate treatment. In the case of prophylactic medication, the evidence has suggested recovery of therapeutic responsiveness after withdrawal.[85,99] For migraine sufferers, even intermittent prior exposure to opioids may impede the efficacy of triptans[102] or nonopioid analgesics (eg, NSAIDs).[103] In studies of the treatment of moderate to severe migraine with rizatriptan (pooled n = 2068 individuals), 284 (13.7%) reported recent prior use of opioids. Recent prior use was associated with a reduced likelihood of freedom from pain 2 hours post-triptan, 34% vs 42% ($P < .013$). In the "Treat a Migraine Early" studies, recent prior opioid use was also associated with reduced efficacy, 41% vs 59% pain free at 2 hours ($P < .007$).[102] These findings are preliminary, but consistent with a report from Jakubowski et al, who found that between 64% and 71% of their subjects achieved freedom from acute migraine pain and allodynia within 1 hour of ketorolac infusion.[103] The only factor they uncovered to predict failure to respond to ketoralac was a history of opioid treatment in the nonresponders. The authors question whether opioids might contribute to long-term sustained headache intractability, even in nonactive opioid users – some of these patients had only used opioids intermittently in the past. However, it remains also possible that many patients with a prior opioid history had a more aggressive or refractory disorder than those who had not previously received opioids. Although further research on prior use of opioids and failure to respond to treatment is needed, these studies raise a yellow flag of caution.

OTHER ADVERSE EFFECTS OF OPIOIDS

Prevalence of Opioid-Related Adverse Effects.—When all adverse effects were combined, 77% of 104 chronic noncancer pain patients receiving opioids at a National Health Service hospital pain clinic in London reported negative side effects. While 72.5% reported receiving some benefit, 86.5% had discontinued opioids at some point in their treatment, and 65% had done so permanently.[18]

Nausea, Emesis, and Constipation.—The most common adverse effect stemming from opioid administration is nausea, sometimes associated with emesis, occurring in 26% of 8855 patients in a retrospective cohort study of patients receiving short-term opioids in 35 community-based and tertiary hospitals.[19] In the Furlan meta-analysis of short-term RCTs noted above, only constipation and nausea were statistically significant.[12] Constipation and nausea can be difficult to manage, and in many cases tolerance does not develop over time.[104]

Sleep Disturbance: Insomnia and Apnea.—Mu opioid receptor agonists inhibit rapid eye movement sleep,[105] and limbic opioid receptors have been implicated in the generation of arousal and insomnia related to sleep deprivation-induced stress.[106,107] Sleep disturbance is common in patients receiving long-term COT for CNCP, with insomnia reported by 87% and combined insomnia with daytime sleepiness in 49% of a sample of 876 patients reported by Zgierska et al.[27] Opioid dose was associated with a slight tendency toward unrefreshing sleep and worse sleep maintenance, and use of long-acting opioids was associated with a trend toward increased napping. However, the strongest independent predictors of sleep problems were depression and pain severity. Only depression predicted daytime sleepiness or combined sleep/sleepiness problems. Reported sleep problems are also highly prevalent in chronic pain, regardless of medication regimen,[108-112] as high as 71% (sleep onset delay) to 78% (sleep maintenance problems) in a survey of 4269 chronic pain patients.[109] Some authors have suggested that effective pain control with opioids can improve sleep in various types of CNCP.[113,114]

An emerging literature since 2001 suggests that chronic opioid use is related to central sleep apnea,

occurring in approximately 30% of patients.[4] In a retrospective cohort study comparing 60 patients receiving COT with a cohort matched for age, sex, and body mass index, Walker et al found the apnea-hypopnea index was greater in the opioid group due to increased central sleep apneas, with arterial oxygen saturation in the opioid group significantly lower during both wakefulness and nonrapid eye movement sleep. There was a dose-response relationship between morphine dose equivalent and apnea-hypopnea, obstructive apnea, hypopnea, and central apnea indexes. Ataxic or irregular breathing during NREM sleep was also more prevalent in patients who chronically used opioids (70% vs 5%, $P < .001$) and more frequent (92%) at a morphine dose equivalent of 200 mg or higher (odds ratio = 15.4, $P = .017$).[26]

Webster et al performed polysomnography on 147 patients from a consecutive series of patients receiving COT for at least 6 months with a stable dose for at least 4 weeks. The apnea-hypopnea index was abnormal in 75%: 39% had obstructive sleep apnea, 24% had central apnea, 8% both types, and 4% with an indeterminate type. For patients on methadone, they found a direct relation between daily dose and both the apnea-hypopnea index ($P = .002$) and the central apnea index ($P = .008$), but no direct relation between dose and apnea for other around-the-clock opioids.[115] Opioid-associated central sleep apnea may be effectively managed with bilevel titration,[116] although servoventilation was found insufficient to manage opioid-related central apneas in other studies, and therapy with CPAP is usually unsuccessful.[117] Sleep-disordered breathing disturbance can improve following withdrawal from long-term opioid use.[118]

Respiratory Depression and Sudden Cardiac Death.—The most serious and potentially fatal opioid-related adverse effects in pain management are respiratory depression and cardiac arrhythmias.[28] In a study of 8855 CNCP patients receiving opioids (morphine, meperidine, or fentanyl), the overall rate of respiratory depression was 1.5%. When compared to adults age 45 or less, the relative risk for respiratory depression increased significantly with age: RR = 2.8 for ages 61-70, RR = 5.4 for ages 71-80, and RR = 8.7 for those over 81 years.[19] Early respiratory depression may manifest itself in drowsiness, yawning, or reports of difficulty breathing. In more significant cases, the patient may report confusion, with decreased pulse oxygen. The clinician should ask about early symptoms, evaluate further if there is reason for suspicion, and consider reducing the dose or discontinuing opioids.

In November, 2006, the United States Food and Drug Administration issued a Health Alert for health professionals on risks of death, cardiac arrhythmias (eg, QT interval prolongation), and narcotic overdose associated with methadone.[30] Methadone may pose a particular risk given its long half-life and accumulation in fat tissue over time.[119] During a 4-year period, Chugh and colleagues prospectively evaluated autopsy data from the medical examiner in the Portland, Oregon metropolitan area, for all consecutive investigations of sudden cardiac death. They compared deceased patients with a therapeutic blood level of methadone (<1 mg/L) and case comparison subjects with no identified methadone, excluding those with recreational drug use or any drug overdose. Based on a significantly lower rate of cardiac abnormalities in the methadone group (23%) than the comparison group (60%, $P = .002$), they concluded that methadone was "implicated as a cause of death, even at normal therapeutic levels." The most common indication for methadone use in the deceased patients was for pain control (55%).[29]

Reductions in Sex Hormones.—Sustained opioids induce reductions in sex hormones in both men and women.[120,121] Sustained opioids can profoundly inhibit adrenal androgen production in both women and men, and significantly inhibit ovarian sex hormone.[121,122] Dehydroepandrosterone (DHEA)-dehydroepiandroisterone sulfate (DHEAS) deficiency is associated with fatigue, depression, weakness, and sexual dysfunction. In a study of nonhospitalized male and female patients using sustained action oral or transdermal opioids for nonmalignant pain, Daniell found DHEAS values to be significantly lower in opioid-users than nonopioid controls in a dose-related pattern. DHEAS was below age-specific norms in 67% of opioid uses vs 8% of controls, and below the lowest detection limit in 29% of opioid users vs 1% of controls. In contrast, adrenocorticotropic hormone (ACTH) levels

remained unaffected by opioids. The findings were unrelated to body mass index or concurrent hormonal replacement therapy.[122] Clinical correlates include reports of erectile dysfunction in men and hypogonadism,[120] although paradoxically 2 studies in the Furlan meta-analysis found that patients receiving COT actually reported improved sexual behavior on the PDI.[12] Clinically, we have seen false pregnancies, failure to menstruate, and galactorrhea in women, and breast enlargement in men. The National Institute of Health is currently undertaking a human study of opioid use and endocrinological changes.

Opioids During Pregnancy.—Although the occasional use of opioids for controlling severe pain during pregnancy may be relatively safer for the fetus than some other alternatives, there may be reason for caution in their use on a frequent or scheduled basis. Opioids can have neurotoxic effects on the brains of young animals, which are significant in perinatal administration.[123] A prospective study of 34 drug-exposed (opioids and nicotine) and 42 reference infants (nicotine only) one year after delivery found significantly lower scores on scales of locomotor development, hearing, speech, and intellectual performance, in addition to a higher incidence of neurological abnormalities in the opioid-exposed group.[124] These differences were independent of whether the child was living in a foster home or with the biological parents. A Norwegian study of post-natal development of children exposed to opioids *in utero* found significantly lower scores on the Bayley Scales at one year, and the McCarthy Scales at 4.5 years, with special weaknesses in the areas of visual-motor and perceptual abilities.[125] These children were reportedly raised under condition of "minimal postnatal social risk" with adoptive or foster parents.

Admittedly, extrapolation of these findings to mothers receiving COT for pain control only, under close medical supervision, must be approached with caution. For example, of the 34 mothers taking opioids in the first study, 12 were using without medical control and 22 were in a methadone maintenance program.[124] Nevertheless, such studies raise a flag of caution. Similar research is yet to be done with prospective mothers on COT for CNCP, and little is known of minimal dose levels at which possible delayed adverse effects on infant development may occur.

Neurocognitive Functioning.—Opioid treatment of patients with mild uncomplicated traumatic brain injury has recently been found to be associated with reduced learning.[22] Opioids seem to be more likely to worsen cognitive performance during the first few hours after a given dose, and during the first few days of use, particularly on timed performance in psychomotor tasks.[25] A prior review of the literature found inconsistent results regarding cognitive performance decrements in chronic pain patients receiving opioids for more than 3 days when compared with healthy volunteers. Relatively few differences have been found between pre- and post-opioid performance for chronic pain patients, or with the performance of a comparable pain population not taking opioids.[25]

COMORBID PSYCHIATRIC DISORDERS, OPIOIDS, AND CNCP

The presence of psychiatric comorbidities significantly increases the likelihood of a patient with CNCP receiving opioids. In a secondary analysis of data from the Health Care for Communities Survey, 1997-1998 (n = 9279), Sullivan et al found that the presence of major depression, dysthymia, panic, or generalized anxiety led to an odds ratio of 6.15 (95% confidence interval: 4.1, 9.1) for regular use of opioids ($P < .001$).[126] One possibility for this observation could be that more painful patients, who might "need" opioids, would also experience more psychiatric disturbance related to pain. However, the data suggest the opposite – that patients with depression or anxiety may be more likely to request opioids, or take opioids for their anxiolytic, soporific, or mood-enhancing effects. The presence of a psychiatric disorder only increased the odds for prescription opioids in patients with *low levels of pain interference* in their daily lives (OR = 3.15, $P < .001$), where opioid analgesia might not more efficacious than other alternatives. In contrast, for patients with high levels of pain interference, psychiatric disorders were not a significant factor influencing the physician's prescription decision. These observations from this initial study reported in 2005 continue as a trend in Sullivan's most recent report published in 2009: persons with CNCP and a

history of depression are more likely to receive long-term opioid therapy than those with no depression.[127] The presence of depression and other psychiatric disturbance (eg, somatization disorder) not only increases the likelihood of receiving prescription opioids for CNCP, but also increases the risk for prescription opioid abuse.[128,129] A comprehensive review by Riley and Hastie found the most consistent evidence for drug misuse and decreased opioid efficacy to be associated with patient depression and anxiety.[57]

In a study by Cicero et al investigating a large medical insurance claims database, headache diagnoses accounted for 19% of the chronic opioid prescriptions, defined as use of opioids >180 days/year (n = 3 726).[5] Patients receiving chronic opioids were more likely to have a mental health diagnosis (35%) than those taking opioids less than 10 days/year (15%) or no opioids (11%). The most predominant diagnoses in the chronic headache group were depression (22%) and anxiety disorders (11%).

In the outcome study of comprehensive inpatient treatment for refractory headache noted above, neither anxiety nor depression were predictive of opioid use on admission or outcome at discharge. However, presence of a personality disorder (PD) significantly increased the risk for opioid-related MOH on admission, from 38% of those with no PD to 62% ($P < .005$). Although less common than Axis I clinical syndromes, PDs were present in 26% of the patients on admission.[87]

Treatment of post-concussive patients with opioids has also been associated with increased depression, anxiety, and stress.[22] Respiratory depressive effects of the endogenous opioid system (and by extension, exogenous opioids) may play a role in triggering panic attacks associated with air hunger, by reducing the "suffocation alarm threshold."[24] However, studies in advanced cancer patients have shown reductions in depression and anxiety with opioid therapy (transdermal fentanyl), possibly due to enhanced pain control.[23]

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