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Misguided Pain Guidelines?

When Strong Claims Follow From Weak Evidence

An Arduous Process

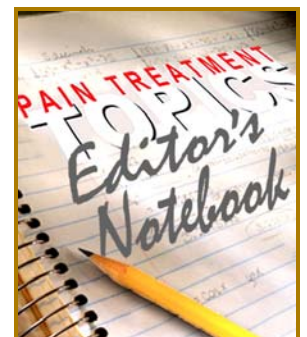
The development of clinical medical-practice guidelines is a difficult, arduous process. Typically, experts in various disciplines volunteer many hours of their time for medical research reviews and analyses, meetings with fellow guidelines-panel members to reach a consensus, and painstaking writing and revisions of the final report. However, as we noted in the previous edition of this *e-Briefing* newsletter [2008;3(1)], there are concerns about the quality of current medical research. As critics have proposed, “many wrong, or at least unreliable, therapeutic answers are being generated due to biased studies, representing small numbers of patients, and using inappropriate analyses” [Altman 2002]. A next logical question is how this affects the quality of clinical practice guidelines.

When, due to inadequate or weak evidence, guidelines are strongly influenced by value judgments, organizational preferences, or personal opinion are they still valid for application in everyday clinical practice? Or, are such guidelines to at least a certain extent misguided?

Some Concerns About Guidelines

Clinical practice guidelines are systematically developed statements intended to assist health-care providers with decisions about appropriate care for specific patient circumstances [Tricoci et al. 2009]. Guidelines are supposed to be just that, *guides*, not rules [Shaneyfelt and Centor 2009].

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Guidelines are intended to assist with decisions about patient care; they are ‘guides’ not ‘rules.’

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According to some commentators, there are simply too many guidelines, often on the same topics, and too many are of questionable quality, delivering directive rather than assistive statements for everyday clinical practice. Consequently, guidelines are not always adhered to by healthcare providers even though, once published, the guideline recommendations cannot be ignored [Shaneyfelt and Centor 2009; Sniderman and Furberg 2009].

Guidelines are expected to be based on evidence rather than opinion. However, it has been suggested that, “Most current articles called ‘guidelines’ are actually expert consensus reports” [Shaneyfelt and Centor 2009]. At that, the experts sometimes have biases affecting their opinions, which are rarely made fully transparent to the reader. Gaps often exist in available evidence, so judgements may be influenced by the previously held positions of panel members; in effect, “what is to be decided is often already decided with the selection of the deciders” [Sniderman and Furberg 2009].

The process of formulating guidelines is essentially unregulated, and any group of individuals can designate itself as a guideline-development panel. Different panels often examine the same disease condition or topic of concern and reach significantly disparate conclusions [Shaneyfelt and Centor 2009]. Furthermore, guidelines usually derive their authority from the sponsoring organization and the prestige of the journals in which they are published. Once issued, those organizations become promoters and defenders of the guidelines, and panel members become stakeholders in the uncontested acceptance of their recommendations [Sniderman and Furberg 2009].

Following are several examples of recent guidelines developed for clinical pain management practice that demonstrate various reasons for concern.



Opioid Rx Guidelines in Search of Evidence

Clinical practice guidelines from the American Pain Society and the American Academy of Pain Medicine (APS/AAPM) were published in February 2009, following 2 years of work and a review of 8,000 studies [Chou et al. 2009a]. The guidelines panel provided 25 recommendations on the safe and effective chronic (long-term) use of opioids for carefully selected patients with chronic noncancer pain (CNCP). The recommendations were wide-ranging, broadly addressing patient selection and risk stratification, informed consent and opioid management plans, initiation and titration of opioid therapy, management of breakthrough pain, monitoring of patients, dose escalation and high-dose opioid therapy, use of methadone, prevention and management of opioid-related adverse effects, indications for opioid rotation or discontinuation of therapy, driving and work safety, identifying a medical home for patients and when to obtain consultation, and chronic opioid therapy during pregnancy.

The APS/AAPM guidelines panel was both exuberant and exemplary in its thoroughness and transparency; in addition to the 17-page guidelines document itself [Chou et al. 2009a], there are 285 pages of supplemental documentation explaining the details of study methodology and consulted resources, as well as describing extensive gaps and deficiencies in available evidence [APS 2009; Chou et al. 2009b, 2009c]. Panel members also were intellectually honest in conceding that they were hindered by an overall lack of evidence and the poor quality of what was available. In fact, the panel did not rate any of its recommendations as supported by high-quality evidence and only 4 recommendations were viewed as supported by even moderate-quality evidence — yet, all but 3 carry a “strong recommendation” designation.

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There are too many guidelines, often on the same topics, and too many are of questionable quality, delivering directive rather than assistive statements.

The APS/AAPM opioid-prescribing guidelines panel was hindered by an overall lack of evidence and by the poor quality of evidence that was available.

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According to the authors, a “strong” recommendation was based on the panel’s assessment (value judgements) that “potential benefits of following the recommendation clearly outweigh potential harms and burdens.” However, the benefits in terms of improved patient outcomes and the validity for everyday practice of *strong recommendations based on weak evidence* must be questioned.

For example, the panel noted that several patient-screening instruments exist and are recommended for predicting potential prescription opioid misuse or abuse; however, they concede that clinical evidence for the external validity of these tools and their benefits for everyday patient care are still lacking. Similarly, other researchers examining the needs of family physicians for guidance in this area observed, “No well-tested, easily administered screening tool exists for detecting drug-seeking behaviors in primary care patients” [Gianutsos and Safranek 2008]. The American Pain Society, itself, had earlier noted that when it comes to identifying patients exhibiting “drug seeking behavior” there “are no diagnostic behavioral criteria or accepted medical definitions” [Paice 2007].

As another example, although panel members recognized that opioids theoretically have no maximum or ceiling dose, they still concurred that a reasonable definition for high-dose opioid therapy is >200 mg/day of oral morphine (or equivalent). This was based on low-level evidence and the panel acknowledged that there actually is no standardized definition for what constitutes a “high” dose. Still, this 200 mg/day threshold was designated as a trigger for strongly recommending increased patient monitoring and other precautionary measures, potentially including discontinuation of opioid therapy.

This is not the first time that a somewhat arbitrary opioid-dose ceiling has been proposed in a guideline. In 2007, the Washington State Agency Medical Directors’ Group [AMDG 2007] suggested in their guidelines that opioid doses greater than 120 mg/day of oral morphine or equivalents should rarely be given and, if necessary, only prescribed after consultation with a pain management expert. Yet, in a recent editorial titled “Unintended Harm from Opioid Prescribing Guidelines,” Fishman and Webster [2009] observe, “It is remarkable that the 120 mg guideline was confirmed without access to sufficient scientific evidence. Nowhere is it shown that the recommendation contributes to greater safety or diminished harm.” Furthermore, it implies that doses below that threshold level are inherently “safe.”

Surprisingly, the American Academy of Pain Medicine and the American Pain Society, had formally objected to the AMDG guidelines, believing that any such restrictions would not resolve problems associated with chronic opioid prescribing [AAPM 2007; Paice 2007]. Yet, two years later, without significant additional evidence, the AAPM/APS guidelines recommend 200 mg/day as defining a high-dose level of concern.

At face value, all of the recommendations in the new APS/AAPM guidelines appear to make common sense for prudent medical practice when it comes to opioid therapy. However, the panel acknowledged that, at present, clinical decisions regarding the use of opioids for chronic noncancer pain must be based on weak evidence. A most important concern is that very little research supports whether or not the panel’s recommendations will favorably impact therapeutic outcomes. All of this seems to suggest that the promulgation of guidelines in this area might have been premature; perhaps, the findings of the APS/AAPM panel would have served the field better by establishing a direction for further investigations to fill in the critical research voids that were uncov-

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Benefits for patients and the validity of strong recommendations based on weak evidence must be questioned.

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ered by their very thorough examination of long-term opioid prescribing for chronic noncancer pain.

Other guidelines on this subject had been developed in the past. In an online publication, Washington and Fanciullo [2008] examine 8 earlier documents; however, only half actually use the term “guidelines” in their titles; the others designate their documents as “management strategies,” “recommendations,” or “model policy,” which more appropriately connote that the contents are suggestions rather than rules. Yet, in all of those documents, the lack of randomized controlled trials for analysis was acknowledged as problematic, and there were strong discrepancies across guidelines in methods for evaluating the strength of the evidence presented and in topics of concern that were included or excluded.



ECG Screening in Methadone Patients Challenged

In March 2009, the *Annals of Internal Medicine* published cardiac safety guidelines for physicians prescribing methadone for pain or as opioid-addiction therapy [Krantz et al. 2009]. The authors included some, but not all, members of a panel that had been convened by the U.S. Center for Substance Abuse Treatment (CSAT) to examine available evidence regarding problems of methadone-associated arrhythmia and develop government-endorsed guidelines.

The authors recommended in their guidelines that clinicians inform patients of arrhythmia risk when they prescribe methadone, and ask about a history of heart disease. They also recommend that *all* patients have pretreatment and follow-up electrocardiography (ECG) at 30 days and annually thereafter. Possible actions if the rate-corrected QT interval on the ECG exceeds acceptable limits include discussion with the patient of methadone’s risks and benefits, more frequent monitoring, dose reduction, or stopping methadone therapy entirely. Finally, clinicians are instructed to learn about interactions between methadone and other drugs that can prolong the QTc interval or slow elimination of methadone.

While attention to the cardiac health of patients prescribed any strong opioid medications would be prudent medical practice, the most controversial aspect of this guideline is the requirement for repeated ECG monitoring of all patients prescribed methadone. There are many irregularities in how the authors conducted their investigation and published their findings that raise important questions regarding the validity of this guideline. For one thing, Krantz and colleagues failed to use quality assessment tools for selecting and grading the evidence they considered. In fact, the authors state that they “did not pre-specify critical appraisal criteria” and the term “quality” does not appear anywhere in their document. This is contrary to commonly accepted standards requiring guidelines to include a quality grading system such as that described by the U.S. Preventive Services Task Force [Guirguis-Blake et al. 2007; Sawaya et al. 2007].

In a rebuttal editorial accompanying publication of the guidelines, Marc Gourevitch, MD, of New York University stresses that, overall, the recommendation for ECG screening presented in the guidelines “ventures well beyond the evidence presented.” He raises many cogent points of contention [Gourevitch 2009]:

- While it is evident that methadone can affect cardiac electrical conduction in certain circumstances, “how often patients treated with methadone develop arrhythmia is not clear.”
- The panel members presented no clinical trials or decision models to explain the relative benefits and harms of ECG screening.

While attention to the cardiac health of patients prescribed strong opioids would be prudent medical practice, the most controversial aspect of this guideline is required ECG monitoring in all patients who are prescribed methadone.

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- Rather than using their literature review to frame a process for acquiring missing data, the panel members went ahead in developing a clinical practice guideline, which was drafted and completed in only a 2-day meeting.
- Although other analyses of this topic specifically did not recommended routine ECG screening [Cruciani 2008; Methadone Mortality 2007; Pearson and Woosley 2005], the panel members do not explain why they reached a contrary conclusion.
- Many medications can cause QT prolongation; however, there are no published trials documenting that arrhythmia and sudden death can be averted by baseline ECG screening.
- The panel members provide no evidence to justify their recommended ECG screening frequency, or whether this is more critical for persons with existing cardiac risk factors.

Gourevitch concludes that "...plausible arguments can be made for and against routine ECG screening in methadone treatment. But before guidelines are implemented, research methods, such as decision analysis, should be brought to bear to permit clear appreciation of the tradeoffs, benefits, and harms of alternative screening strategies."

There also are concerns about how these guidelines were published that cast a cloud of doubt over their probity. The guidelines article first appeared in December 2008 prior to print at the *Annals of Internal Medicine* website under the title, "QTc Interval Screening in Methadone Treatment: the CSAT Consensus Guideline." This implied official CSAT approval and, although this was *not the case*, some readers were understandably misled and erroneously started putting the guidelines into clinical practice. Following protests to the journal's editor by concerned parties, the article was withdrawn; however, it soon reappeared at the journal's website without mention of CSAT in its title.

Furthermore, after no conflicts of interest had been declared by authors in the originally withdrawn article, readers of the reinstated prepublication HTML version of the article at the journal's website in late December learned that 2 of the authors and another member of the CSAT panel did indeed have financial conflicts of interest due to support by Reckitt Benckiser, the producer of buprenorphine, which is methadone's main competitor for opioid-addiction therapy [Bart 2009]. This also was indicated in the online version of the final article in mid-March 2009, but the printed version once again indicated, "Potential Financial Conflicts of Interest: None disclosed." One of the authors with a conflict of interest had also widely published case studies and commentary promulgating increased risks of arrhythmia with methadone and thus may have had a vested interest in the panel's conclusions. Furthermore, for unstated reasons, 2 of the 11 original panel members declined to be acknowledged in the final version of the guidelines paper, which raises question about the consensus process.

In the final print-edition of the paper, there is a note from the editor clearly specifying, "This publication is not a federal guideline. A government agency has recently forwarded draft recommendations related to QTc interval screening in methadone treatment for field review prior to finalization." This, combined with the many other concerns surrounding this paper, raises an important question: "Why were these guidelines published at this time?"

Finally, in late March 2009, the American Association for the Treatment of Opioid Dependence [AATOD 2009] promulgated their own approach, titled "QTc Interval Screening – AATOD Policy and Guidance Statement." Relying on available best evidence and a consensus of the group's members, most of whom are experienced practitioners, AATOD recommended that ECG screen-

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"...plausible arguments can be made for and against routine ECG screening in methadone treatment. But before guidelines are implemented, research methods, such as decision analysis, should be brought to bear to permit clear appreciation of the tradeoffs, benefits, and harms of alternative screening strategies."

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ing should be reserved for methadone-treated patients having specific and significant arrhythmia risk factors. They also stress referrals for cardiac consultation in cases of known or detected cardiac conditions affecting heart rhythm, and the need to educate patients on cardiac-related symptoms to watch for. Whether or not these commonsense recommendations will be accepted as a standard of patient care remains unknown at present.



Fibromyalgia Guidelines Inconsistent

In a recently reported review, investigators in Germany compared and contrasted published guidelines for the management of fibromyalgia syndrome (FMS) published as of April 2008 [Häuser et al. 2009]. After a thorough search, 3 documents were identified, coming from several professional organizations: APS (American Pain Society, 2005), EULAR (European League Against Rheumatism, 2007), and AWMF (Association of the Scientific Medical Societies in Germany, 2008).

The guidelines steering committees and panels of the APS and AWMF comprised multiple disciplines engaged in the management of FMS and included patients, whereas the task force of EULAR included only physicians, predominantly rheumatologists. APS and AWMF ascribed the highest level of evidence to systematic reviews and meta-analyses, whereas EULAR credited the highest level of evidence to randomized controlled trials.

Both APS and AWMF groups assigned the highest level of recommendation to aerobic exercise, cognitive-behavioral therapy, amitriptyline, and multicomponent treatment. In contrast, EULAR assigned the highest level of recommendation to a regimen of pharmacotherapy. Although there was some consistency across the 3 guidelines in their recommendations for pharmacological treatments, significant other differences are likely to cause some confusion or lack of direction for healthcare providers. The investigators attributed the inconsistencies across guidelines as due to the dissimilar criteria used for evidence selection and inclusion, variable weighting systems used for evaluating the evidence, and the different composition of the guideline panels.

Conclusions: A Long Road Ahead

These examples of possibly “misguided guidelines” in the pain management field are not unique in all of medicine. A recent examination of the various cardiovascular practice guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) found that only 11% of more than 2,700 recommendations were supported by high-quality evidence, and roughly half had very limited scientific backing [Tricoci et al. 2009]. Instead, most recommendations were based on expert opinion — essentially, subjective viewpoints.

Tricoci et al. [2009] observe that, through the years there have been considerable increases in the number of guideline recommendations in the cardiology field, but these have not been uniformly supported by increases in the quality of evidence. And, they point out that the field of cardiology has an extensive pool of large-scale clinical trials to draw upon, which many other medical specialties are lacking. An implication is that, if achieving quality guidelines in a field like cardiology is problematic, it could be even more troublesome in the pain management arena, which has a less extensive and weaker foundation of high-quality evidence.

While some authors propose that their guidelines are non-binding — eg, “Clinical practice guidelines/recommendations are intended to enhance patient care and do not supplant clinical

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Although guidelines for treating fibromyalgia have inconsistencies regarding pharmacologic therapy, significant other differences are likely to cause some confusion among healthcare providers.

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judgment” [Krantz et al. 2009] — the recommendations often do become accepted as *standards of patient care* that are turned into performance measures used to critique the quality of health-care delivery [Shaneyfelt and Centor 2009]. As such, for example, they may be used to establish policies affecting insurance reimbursement for recommended therapies or procedures [Tricoci et al. 2009]. Furthermore, guidelines may be submitted in courts of law as evidence, and adherence or nonadherence to the implied standard of care may be alleged to portray either defensible or negligent performance, respectively, by a healthcare provider under scrutiny.

Much of what is officially published as practice guidelines, might better serve the pain management community if presented as “suggestions,” “strategies,” “advice,” or even “guidance.” Language can and does make a difference, and those latter terms denote helpful but optional treatment approaches rather than medically and legally binding standards of care.

This was the recent approach of a panel in the United Kingdom that convened to produce evidence-based guidelines for the management of cancer-related breakthrough pain in adults [Davies et al. 2009]. They found insufficient evidence for developing guidelines regarding individual interventions and appropriately avoided the term “guidelines” in their published paper. The group did arrive at 12 recommendations (as suggestions) regarding generic strategies considered as useful, but they clearly cautioned that those were based on low-level evidence (eg, case series, expert opinion).

Along those lines, Shaneyfelt and Centor [2009] strongly advance their view that, “If all that can be produced are biased, minimally applicable consensus statements, perhaps guidelines should be avoided completely.” They further propose that, unless there are improvements in the guidelines development process, clinicians and policy makers should reject calls for adherence to guidelines.

Recognizing the lack of high-quality evidence in many medical disciplines, last February (2009) the Obama administration and U.S. Congress budgeted more than \$1 billion to fund research comparing the effectiveness of various treatments in head-to-head comparisons. This was part of a larger strategy to eventually streamline healthcare costs; however, it is unknown how much of this will benefit the pain management field and, considering the vast number of studies to be done and the time required, this is but a worthwhile first step on a long road ahead.

References:

- AAPM. Position on the Washington State Agency Medical Directors’ Group (AMDG) published guidelines on opioid dosing for chronic noncancer pain. October 16, 2007.
- AATOD (American Association for the Treatment of Opioid Dependence, Inc.). QTc Interval Screening – AATOD Policy and Guidance Statement. 2009 (March). Available online at: <http://www.aatod.org/qt.html>. Accessed 4/2/09.
- Altman DG. Poor-quality medical research: what can journals do? *JAMA*. 2002;287(21):2765-2767.
- AMDG (Washington State Agency Medical Directors’ Group). Interagency guideline on opioid dosing for chronic non-cancer pain: an educational pilot to improve care and safety with opioid treatment. Olympia (WA): Washington State Department of Labor and Industries; 2007(Mar). Summary available online at: http://www.guidelines.gov/summary/summary.aspx?doc_id=12243. Accessed 3/25/09.
- APS (American Pain Society). Evidence review: guideline for the use of chronic opioid therapy in chronic noncancer pain. Glenview, IL: American Pain Society; 2009. Available online at: http://www.ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf. Accessed 3/15/09.
- Bart G. Passing guidelines on the OT [letter]. *Ann Int Med*. February 11, 2009 [rapid response to Krantz et al. 2009;150(6)]. Available at: <http://www.annals.org/cgi/eletters/0000605-200903170-00103v1#112636>. Accessed 3/19/09.

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- Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009b;10(2):147-159. Available at: [http://www.jpain.org/article/S1526-5900\(08\)00830-4/abstract](http://www.jpain.org/article/S1526-5900(08)00830-4/abstract). Access checked 3/15/09.
- Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009a;10(2):113-230. Available online at: [http://www.jpain.org/article/S1526-5900\(08\)00831-6/abstract](http://www.jpain.org/article/S1526-5900(08)00831-6/abstract). Access checked 3/15/09.
- Chou R, Fanciullo GJ, Fine PG, et al. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009c;10(2):131-146. Available online at: [http://www.jpain.org/article/S1526-5900\(08\)00832-8/abstract](http://www.jpain.org/article/S1526-5900(08)00832-8/abstract). Access checked 3/15/09.
- Cruciani R. Methadone: To ECG or not to ECG...that is still the question. *J Pain Sym Manag*. 2008;36(5):545-552.
- Davies AN, Dickman A, Reid C, Stevens A-M, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009;13(4):331-338.
- Fishman SM, Webster LR. Unintended harm from opioid prescribing guidelines. *Pain Med*. 2009;10(2):285-286.
- Gianutsos LP, Safranek S. Is there a well-tested tool to detect drug-seeking behaviors in chronic pain patients? *J Fam Prac*. 2008;57(9):609-610. Available online at: <http://www.jfponline.com/Pages.asp?AID=6636&issue=September%202008&UID=>. Accessed 3/15/09.
- Gourevitch MN. First Do no harm ... reduction? *Ann Intern Med*. 2009;150(6). Available at: <http://www.annals.org/cgi/content/full/150/6/417>. Accessed 3/17/09.
- Guirguis-Blake J, Calonge N, Miller T, et al. Current processes of the U.S. Preventive Services Task Force: refining evidence-based recommendation development. *Ann Intern Med*. 2007;147:117-122.
- Häuser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome - A systematic review. *Eur J Pain*. 2009(Mar) – Epub ahead of print.
- Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment: clinical guidelines. *Ann Intern Med* 2009;150(6):387-395. Available at: <http://www.annals.org/cgi/content/full/150/6/387>. Accessed 3/17/09.
- Methadone Mortality — A Reassessment. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment; 2007(Jul). Available at: http://www.dpt.samhsa.gov/pdf/Methadone_Report_10%2018%2007_Brief%20w%20attch.pdf. Accessed 3/18/09.
- Paice JA. Letter from president of the American Pain Society to the Washington State Agency Medical Directors Group (AMDG). July 19, 2007. Available at: <http://www.ampainsoc.org/enews/aug07/APSBoardResponse.htm>. Access checked 3/26/09.
- Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf*. 2005;14:747-53. [PMID: 15918160]. [Medline]
- Sawaya GF, Guirguis-Blake J, LeFevre M, et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. *Ann Int Med*. 2007;147(12):871-875. Available at: <http://www.annals.org/cgi/reprint/147/12/871.pdf>. Accessed 3/17/09.
- Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines. *JAMA*. 2009;301(8):868-869.
- Sniderman AD, Furberg CD. Why guideline-making requires reform. *JAMA*. 2009;301(4):429-431.
- Tricoci P, Allen JM, Kramer JM, Califf RM, Smith Jr SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301(8):831-841.
- Washington TA, Fanciullo GJ. Evidence-based guidelines for opioid therapy [online]. *EmergingSolutionsInPain.com*. 2008(Nov).

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Opioid Blockers Aid Pain Relief



INNOVATIONS

Special Reports from Pain Treatment Topics are designed to address specific questions or more thoroughly discuss topics of concern that are inadequately covered or neglected by other literature in the pain management field. These reports are based on current best evidence, with complete reference sources cited, and they undergo extensive peer review prior to publication and posting at Pain-Topics.org.

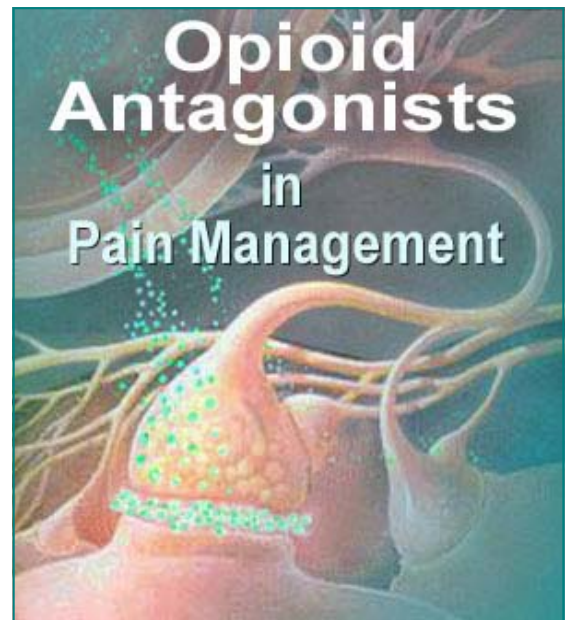
Achieving effective, durable, and safe pain relief, especially in patients with chronic and/or severe pain conditions, can be difficult. For many types of pain, prescription opioids are among the most effective analgesics. However, there could be concerns about the development of opioid tolerance or adverse effects. For certain difficult conditions, such as fibromyalgia or neuropathies, opioids alone are sometimes considered of limited effectiveness.

Healthcare providers interested in pain management must be alert to new or novel approaches that help to overcome deficiencies of opioids, such as treatment-limiting side effects, and as aids in relieving difficult-to-treat pain conditions. In this regard, there is a growing body of evidence suggesting potential benefits of opioid antagonists, particularly naloxone and naltrexone. This is unexpected because these drugs displace opioid molecules from their neuroreceptors, and block opioids from attaching to and activating those receptors.

In a peer-reviewed, evidence-based report for *Pain Treatment Topics*, Stewart B. Leavitt, MA, PhD, describes naloxone and naltrexone pharmacology and the theoretical foundations of opioid antagonists for pain management. Titled “**Opioid Antagonists, Naloxone & Naltrexone – Aids for Pain Management**,” the 16-page report includes summaries of 17 studies — case examples and clinical trials — investigating opioid-antagonist therapy in adult humans (see **Table** on next page).

Naloxone and naltrexone have been extensively studied in the past, and are FDA-approved for the treatment of alcoholism or opioid addiction (naltrexone) or opioid overdose (naloxone). A long-acting form of naltrexone for intramuscular injection also is approved for addiction therapy. These antagonists also are being used or tested as ingredients in specially formulated opioid analgesics to deter their misuse or abuse.

Leavitt notes, however, doses of naltrexone used in pain management are generally much smaller than in other applications; either in the 1 to 5 mg range, referred to as “low dose,” or less than 1 mg, in microgram amounts, designated as “ultralow dose.” In animal studies and human trials, very small concentrations of naloxone or naltrexone appear to enhance the pain-relieving efficacy of opioid-agonist analgesics, such as morphine, oxycodone, and others. Along with this, tolerance to and physiologic dependency on opioid analgesics, as well as certain opioid side effects, may be diminished. Furthermore, low-dose naltrexone has been successfully tested by itself as monotherapy for the management of several pain-related conditions, including Crohn’s disease, irritable bowel syndrome, and fibromyalgia.



Opioid antagonists like naloxone and naltrexone – which block opioid drugs from activating their receptors – may be surprisingly helpful in relieving difficult-to-treat pain conditions.

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Explanatory mechanisms of action behind the benefits of opioid antagonists in pain management are still under investigation. Essentially, appropriately low doses of opioid antagonists have been postulated to “reset” the opioid-receptor system for a period of time, which seems analogous to how rebooting a malfunctioning computer clears memory, refreshes the software, and often restores normal function. With opioid-agonist therapy, the body becomes better attuned to the beneficial effects of both external opioids, such as morphine, and naturally occurring internal opioids, such as endorphins.

Clinical research to date on low- or ultralow dose applications of opioid antagonists for pain management in humans has been limited. Still, the available evidence described in this report

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Opioid Antagonists for Pain in Human Trials/Cases

(See the full article for further explanation and references.)

Application	Antagonist Dose	Clinical Outcome
Naloxone (IV, Intrathecal, or Oral – as specified)		
Brief opioid detoxification for intractable pain.	0.6–1.2 mg IV (ca. 20 minutes).	Significant pain relief at lower opioid doses. Requires close monitoring.
+ Buprenorphine for postop breakthrough pain.	0.08–0.4 mg oral.	Effective, long-lasting analgesia
Monotherapy for acute postop dental pain.	0.4 or 1.0 mg oral.	Significant analgesia compared with placebo.
+ Pentazocine (60 mg) for dental pain.	0.4 mg oral.	Greater analgesia than monotherapy with pentazocine or 15 mg morphine.
+ PCA morphine postop.	0.00025 or 0.001 mg/kg/h steady infusion IV.	Reduced side effects and lower morphine consumption versus placebo
+ PCA morphine postop.	0.8 mg dose/IV bolus (= 0.38 mg/kg/h on average).	No benefit.
+ Nalbuphine (5 mg IV) postop.	0.2 mg IV.	Improved analgesia.
+ Intrathecal morphine (5 mg) for intractable chronic pain.	0.000050 mg/day intrathecal during followup.	Significantly improved ongoing pain relief.
+ Oxycodone (chronic noncancer pain; chronic back pain).	10, 20, 40 mg/d oral.	No loss of analgesia, improved bowel function at 2:1 oxycodone/naloxone ratio.
Naltrexone (Oral)		
Crohn’s Disease.	4.5 mg/day.	Favorable response in 89% of patients.
Irritable Bowel Syndrome (IBS).	0.5 mg/day.	Pain/symptom relief during first 2 months.
Fibromyalgia.	4.5 mg/day.	Unknown, but anecdotal reports favorable.
Neuropathic Pain (combined with methadone).	0.002 mg/day.	Improved analgesia at lower methadone dose.
+ Oxycodone (Oxytrex®) for osteoarthritis or chronic back pain.	0.002 mg/day.	Reduced opioid consumption and side effects, including resolution of opioid-induced constipation.
+ Hydrocodone (experimental).	0.25, 0.5, or 1.0 mg.	No beneficial effect.
+ Intrathecal morphine for chronic noncancer pain.	0.2 mg/day.	Reduced pain intensity, improved pain relief
Opioid (methadone) tapering.	0.125 or 0.250 mg in multiple doses/day.	Reduced withdrawal symptoms and opioid craving compared with placebo.

(Opioid Blockers for Pain... continued from page 10)

(summarized briefly in the preceding **Table**) suggests a number of possibilities that may be of interest to healthcare providers and their patients with pain, including:

- Brief detoxification using naloxone for difficult cases of opioid-unresponsive intractable pain, opioid tolerance, or suspected opioid-induced hyperalgesia.
- Ultralow-dose naloxone combined with various opioid agonists for managing postoperative pain.
- Ultralow-dose naltrexone (oral) or naloxone (intrathecal) as a component of intrathecal opioid analgesia for difficult cases of intractable pain.
- Ultralow-dose oral naltrexone combined with opioid agonists to provide an opioid-sparing effect, offering equivalent pain relief at lower opioid doses.
- Oral ultra-low dose naloxone or naltrexone combined with oral opioid analgesics to help prevent or reverse opioid-induced constipation and to potentially reduce other opioid side effects.
- Ultralow-dose naltrexone to help facilitate more comfortable opioid-agonist tapering.
- Low-dose naltrexone monotherapy for Crohn's disease, and possibly for fibromyalgia and short-term treatment of irritable bowel syndrome.

“Although further investigations to assess the safety and efficacy of these applications would be appropriate,” Leavitt suggests, “both of these agents have passed animal and clinical toxicity studies, and have been used for years in applications other than those described in this research report. Therefore, it is not surprising that they have exhibited favorable safety profiles when applied at low- and ultralow-dose levels, with few notices of adverse events or side effects at these doses when used individually as monotherapy or in combination with opioid analgesics.”

Naloxone and naltrexone are available today as generic, economically priced drugs, and it is important that practitioners become aware of the therapeutic options that these may provide for patient care. However, it must be understood that opioid antagonists are not yet FDA-approved for pain management purposes, so low- or ultralow-dose naloxone or naltrexone would need to be cautiously prescribed off-label for compounding at properly equipped pharmacies.



The contents of this report are for educational purposes and are not intended to endorse or promote the off-label prescribing of any drugs. Practitioners are advised to study the available evidence and use professional discretion in their prescribing decisions.

Opioid Antagonists, Naloxone & Naltrexone — Aids for Pain Management

An Overview of Clinical Evidence

By: Stewart B. Leavitt, MA, PhD, *Pain Treatment Topics*, March 2009.

This report is available for free download: <click on the URL link>

 <http://pain-topics.org/pdf/OpioidAntagonistsForPain.pdf> (260 KB, 16-pages)

This report also is reprinted and featured in the April 2009 edition (Vol. 9, No. 3) of the journal *Practical Pain Management*. To learn more about the journal and free subscription for healthcare providers, go to:

http://pain-topics.org/education_CME_locator/indexbkrv.php#practicalpain



Pain-Topics.org NEWS

Website-Rating Survey Results



During December 2008, we conducted an online survey asking visitors for their ratings of Pain-Topics.org on several dimensions. **Here are the results....**

- Overall, 89.4% rated Pain-Topics.org as better than other pain management websites they've visited (36.8% as "Far Better"; total favorable rating = 4.25 out of 5).
- 96.1% believed the site is above average in offering trustworthy information and education; 75% gave us the highest rating in this category (overall rating = 4.70 out of 5; none scored us as below 'average').
- 89.7% felt that Pain-Topics.org is 'useful (above average)' or 'very useful' to them (total rating 4.51 out of 5).
- 85.9% said it is 'easy' or 'very easy' to find what they are looking for at the site (total rating 4.23 out of 5).
- 94.8% of respondents said they will recommend Pain-Topics.org to others (the remaining 5.2% answered 'maybe').
- Of the 78 persons responding, two-thirds (66.7%) were healthcare professionals, 26.9% were patients, and 6.4% categorized themselves as 'other.' There were no significant differences in rating scores across the 3 groups.

There also was an area in the online survey form where respondents could insert comments or suggestions. Here is a selection...

- > I use your resources all the time. Very useful for the person down in the trenches with the pain patients. I have been recommending this website during pain lectures, and also for patients who attend our chronic pain classes. Thanks for being there!
- > Thank you for a website that is concise and very informative. I really appreciate all the information you have in one place.
- > I have already shared your website with the whole pharmacy department at the hospital I work at. I especially appreciate the guidelines section.
- > I appreciated recent comments on the prevalence of studies that are not well designed and your commitment to carefully scrutinizing studies for their inclusion on your website.
- > I refer pain patients to your website quite a bit.
- > I find your site quite helpful. I like the colorful visual format and also find it easy to navigate around the site.
- > Pain-Topics.org is a fabulous resource! As a patient AND a healthcare provider, it does NOT talk down to me nor does it make it impossible to follow.

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