

PAIN TREATMENT TOPICS

News/Research



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OTC pain relievers; Synvisc-One™ (sodium hyaluronate) injection; Avinza® (morphine sulfate); generic oxycodone; Ryzolt™ (tramadol ER); generic topiramate; antiepileptic drugs; botulinum toxin types A and B; Raptiva® (efalizumab).

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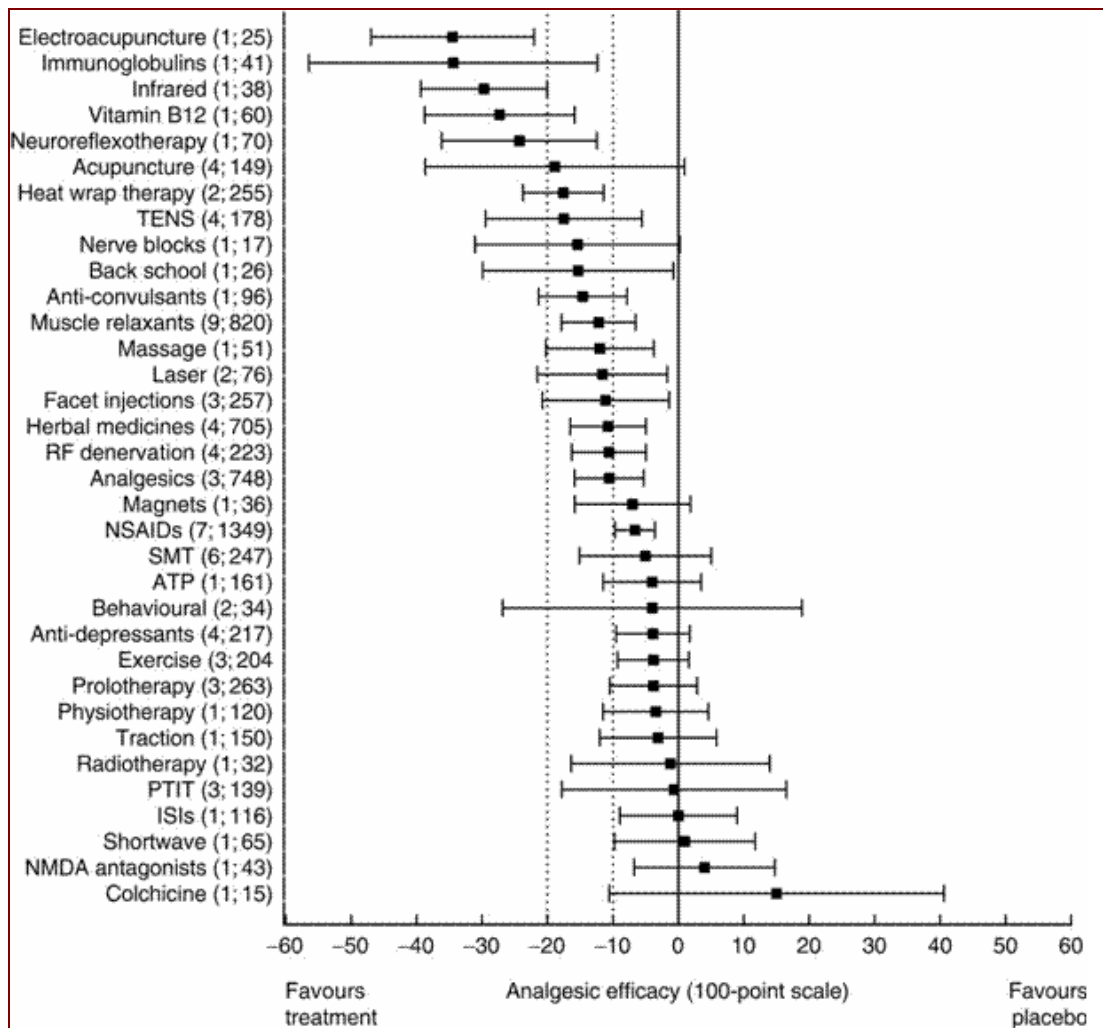


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Most Therapies for Low Back Pain Offer Little Pain Relief

Researchers at the University of Sydney, Australia, conducted a meta-analysis to estimate the analgesic effects of treatments for non-specific low back pain (NSLBP) reported in randomized placebo-controlled trials (RCTs). Their systematic search, which extended up to November 2006, uncovered 76 RCTs reporting on 34 therapies. Outcome measures comparing analgesic effects of the respective treatments with placebo were converted to a 100-point pain scale.

See **Figure** below. Only half of the investigated treatments had statistically significant beneficial effects, and most of these were small or moderate in size: 47% had point estimates of effect <10 points on the 100-point pain scale, 38% had point estimates from 10 to 20 points, and only 15% had point estimates of >20 points. Overall, this meta-analysis revealed that the analgesic benefits of most treatments for NSLBP are small and they do not significantly differ in populations with acute versus chronic NSLBP (not shown in figure). However, the analysis was hindered by a lack of sufficient evidence in many cases to arrive at reliable and valid conclusions (discussed below).



Abbreviations in the figure: ATP = adenosine triphosphate; ISIs = intradiscal steroid injections; NMDA = N-methyl-D-aspartate; PTIT = percutaneous thermocoagulation intradiscal techniques; RF = radiofrequency; SMT = spinal manipulative therapy; TENS = transcutaneous electrical nerve stimulation; "Analgesics" were undefined but probably represent opioids.

[COMMENTARY: The above **Figure** is a forest plot, reproduced from Machado et al. (2009), representing analgesic efficacy of treatments for acute or chronic NSLBP, listed from most effective (at the top) to least effective (toward the bottom). In parentheses are the number of trials; total number of participants. Squares represent combined estimates of effect for multiple trials or means for single trials. Error bars are 95% confidence intervals. Negative values favor treatment — the dotted lines define the magnitude of pain-reduction effects: large (>20), moderate (10–20), or small (<10).

This plot of results is both telling and instructional. Treatments reported to have the largest benefits (>20 points) had been investigated only in single trials and enrolling relatively small numbers of patients — so, the results cannot be trusted as reliable and valid at this time. Also, the smaller the number of patients studied the wider the confidence intervals; meaning there is a wide range of actual effects possible (high variation) in the populations studied, and when there is considerable overlap of confidence intervals across treatments they are not statistically different from each other. Surprisingly, for a condition as common as NSLBP, the number of total studies investigating potentially beneficial therapies is relatively small.

NSAIDS, represented by 7 RCTs enrolling 1,349 patients, have been the best studied and there is a narrow range of effect variation; yet, the <10-point benefit is rather disappointing. “Analgesics” (ie, opioids) were found more beneficial than NSAIDS, but there is overlap in their confidence intervals, so the differences may not be significant. Other treatments, such as muscle relaxants (9 RCTs; 820 subjects) appear to offer greater promise (>10-points); however, the confidence interval for this class of drugs also overlaps that of NSAIDS, so there may not be statistically significant differences between the two treatments. For many therapies, including exercise (which is often recommended for NSLBP), the confidence intervals actually cross into the “favors placebo” zone, indicating that positive pain-relief benefits in select patients are possible but statistically unlikely to occur.

Still it must be remembered that statistical significance, or lack thereof, portrayed in an analysis of this sort may not translate into clinical significance for individual patients. Clearly, more and better research is needed to fully evaluate treatments for NSLBP, and the authors concede that there may be benefits that are more important than pain relief alone, such as improved functionality, and that certain subgroups of patients may benefit more than others. There also is a problem with analgesic-therapy RCTs in the selection of placebos; it is important that the placebo intervention does not share beneficial components of the treatment intervention, which is not always the case. For example, as the next item (below) demonstrates, placebo (fake) acupuncture can produce effects nearly identical to true acupuncture therapy. — SBLJ

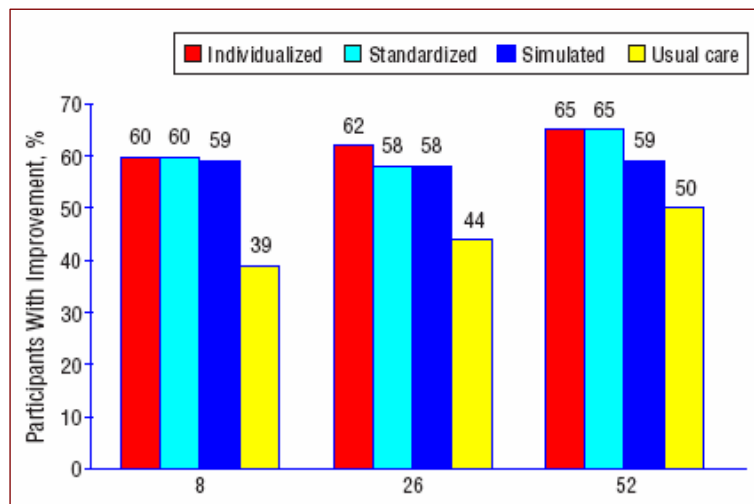
Source: Machado LAC, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. *Rheumatology* 2009;48(5):520-527.

Acupuncture – Real or Fake – Tops Usual Care for Back Pain

Three types of acupuncture therapy — an individually tailored program, standard therapy, and a placebo simulation involving toothpicks at key acupuncture points — appear more effective than usual care for chronic low back pain, according to a report in the May 11, 2009 issue of *Archives of Internal Medicine*.

Researchers at Group Health in Seattle and Kaiser Permanente Northern California in Oakland compared the 4 different types of treatment in a randomized clinical trial involving 638 adults (average age 47) with chronic low back pain. During the 7-week treatment period, **(a)** 157 participants received 10 acupuncture treatments in a manner individually prescribed by a diagnostic acupuncturist; **(b)** 158 underwent a standardized course of acupuncture treatments considered effective by experts for low back pain; **(c)** 162 received 10 sessions of simulated acupuncture in which practitioners used a toothpick inside of an acupuncture needle guide tube to mimic the insertion, stimulation, and removal of needles; and **(d)** 161 received usual care. Participants reported changes in their symptoms and in the amount of dysfunction caused by their back pain after 8, 26, and 52 weeks.

Compared with usual care, either of the acupuncture therapies had more beneficial and persisting effects on chronic back pain (see **Graph** adapted from Cherkin et al. 2009). At the 8-week follow-up, 60% of the participants receiving any type of acupuncture (individualized, standardized or simulated) experienced a clinically meaningful improvement in their level of functioning, compared with 39% of those receiving usual care. At the one-year follow-up, 59% to 65% of those in the acupuncture groups experienced an improvement in function compared with 50% of the usual care group. (Improvement was defined here as at least a 3-point increase on the Roland-Morris Disability Questionnaire scale.)



Clinical Perspectives: The authors conclude: “For clinicians and patients seeking a relatively safe and effective treatment for a condition for which conventional treatments are often ineffective, various methods of acupuncture point stimulation appear to be reasonable options, even though the mechanism of action remains unclear. Furthermore, the reduction in long-term exposure to the potential adverse effects of medications is an important benefit that may enhance the safety of conventional medical care.” However, the authors also observed that, despite apparent benefits of acupuncture for many patients, the treatments received by subjects cost up to \$1,200 and were not offset by overall cost savings to the healthcare system during the year of the study.

[Comment: *The authors concede that their findings raise questions about acupuncture’s purported mechanisms of action. They write, “It remains unclear whether acupuncture or our simulated method of acupuncture provide physiologically important stimulation or represent placebo or non-specific effects.” Even superficial stimulation of acupuncture points may activate physiological processes that result in reduced pain and improved function. Alternatively, the improvement may be due to another aspect of the treatment experience, such as interaction with the therapist or a belief that acupuncture will be helpful.*

In this study, the qualities of “usual care” for back pain were not well-defined and it is possible that such care was suboptimal for many patients. It also should be noted that the maximum NNTs (numbers-needed-to-treat) for true acupuncture were 5 at two months (100/[60-39]) and about 7 at one year (100/[65-45]); that is, clinically speaking, 1 out of 5 to 7 patients would benefit from acupuncture over standard care for chronic low back pain. Similarly, we previously reported in these Pain-Topics UPDATES that an even larger study in Germany (Haake et al. 2007) found that patients with low back pain receiving either sham or true acupuncture experienced a 20% greater response rate (NNT=5) compared with those in the conventional therapy group. — SBL.]

Sources:

Cherkin DC, Sherman KJ, Avins AL, et al. A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain. *Arch Intern Med.* 2009;169(9):858-866.

Haake M, Muller HH, Schade-Brittinger C, et al. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med.* 2007;167(17):1892-1898.

See: http://pain-topics.org/news_research_updates/issue11.php#True

NOTE: Other studies have found that acupuncture is also beneficial for migraine and tension headaches. As above, however, researchers found that both real and ‘fake’ acupuncture offered benefits. For summaries of these studies, see: http://pain-topics.org/news_research_updates/issue19.php#Migraines_Tension_Headaches

Elastic Lumbar Belt Eases Lower Back Pain

Researchers from hospital rehabilitation centers in France evaluated the effects of a lumbar belt on functional capacity, pain intensity, and medication consumption in patients with subacute non-specific low back pain (NSLBP). Patients (n=197) with NSLBP lasting 1 to 3 months and under usual care by a family practitioner were randomized to either a group using an elastic textile lumbar belt or a control group without a belt. Clinical effectiveness criteria were measured during a 3 month period, including **a)** functional recovery using the EIFEL scale (the French version of the Roland-Morris disability scale), and **b)** change in pain intensity using a 100 mm visual analog scale (VAS). One additional assessment was patient use of analgesic, anti-inflammatory, or muscle-relaxant agents.

Patients in the lumbar belt group were wearing the support 5 days per week on average at day 30 (mean = 8 hours/day), 4 days/week at day 60 (mean = 6 hours/day), and 3 days per week at day 90 (mean = 5 hours/day). Results showed significant EIFEL score improvements in the lumbar belt group compared with the control group for baseline to day 30 (p=0.022) and baseline to day 90 (p=0.023). Similarly, differences in VAS pain intensity scores in the lumbar belt group showed significant reductions for baseline to day 30 (p=0.038) and baseline to day 90 (p = 0.002) compared with the control group. Also, at study's end, fewer patients using the lumbar belt required medication for symptom relief when compared with patients in the control group (mean 60.8% versus 40%; p=0.029).

Clinical Concept: The researchers concluded that lumbar belt wearing allows patients with subacute low back pain "to improve significantly the functional status, the pain level, and the pharmacologic consumption." They further suggest that an elastic lumbar belt offers a safe option for complementary nonpharmacologic therapy in combination with standard drug treatment in patients with low back pain.

[Comment: *The calculated NNT (number-needed-to-treat) for medication-free symptom relief is approximately 5 [100/(60.8 – 40)]. That is, for every 5 patients using a lumbar belt, 1 additional*

*patient (beyond what would be normally expected) had significant symptom relief without the need for medication after 3 months. So, while this is a noninvasive and relatively inexpensive intervention, patients should be advised of realistic expectations for its effectiveness. It also should be noted that research on the routine or prophylactic use of lumbar support products to **prevent** back pain or injury has not been conclusive.*

Outcomes in this study may have been dependent on the specific elastic lumbar support belt that was used, which was made by a French company and does not appear to be available at medical suppliers in the United States. Several American companies produce potentially similar elastic lumbar back support products, such as Breg, Inc. at:

<http://www.breg.com/spine-bracing/lumbar/elastic-lumbar-support.html>. — WD, SBL.]

Reference: Calmels P, Queneau P, Hamonet C, et al. Effectiveness of a lumbar belt in subacute low back pain: an open, multicentric, and randomized clinical study. *Spine*. 2009(Feb 1);34(3):215-220.

Guideline for Low Back Pain Interventions, Surgery, & Rehab

In the May 1, 2009 edition of the journal *Spine*, the American Pain Society (APS) issued a new clinical practice guideline for low back pain emphasizing the use of non-invasive treatments over interventional procedures or surgery, as well as shared decision-making between provider and patient. To develop the guideline, a multi-disciplinary APS panel, augmented by experts on interventional therapies, reviewed 3,348 abstracts and analyzed 161 relevant clinical trials. Based on their data, the panel recommends:

1. Against the use of provocative discography (injection of fluid into the disc in order to determine if it is the source of back pain) for patients with chronic nonradicular low back pain.
2. The consideration of intensive interdisciplinary rehabilitation with a cognitive/behavioral emphasis for patients with nonradicular low back pain who do not respond to usual, non-interdisciplinary therapies.
3. Against facet joint corticosteroid injection, prolotherapy, and intradiscal corticosteroid injections for patients with persistent nonradicular low back pain, and there is insufficient evidence to guide the use of other interventional therapies.
4. A discussion of risks and benefits of surgery and the use of shared decision-making with reference to rehabilitation as a similarly effective option for patients with nonradicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms.
5. There is insufficient evidence to guide recommendations for vertebral disc replacement.
6. A discussion of the risks and benefits of epidural steroid injections and shared decision-making, including specific review of evidence indicating lack of long-term benefit, for patients with persistent radiculopathy due to herniated lumbar disc.

7. A discussion of the risks and benefits of surgery and use of shared decision-making that references moderate benefits that decrease over time for patients with persistent and disabling radiculopathy due to herniated lumbar disc or persistent and disabling leg pain.
8. Discussion of risks and benefits of spinal cord stimulation and shared decision-making, including reference to the high rate of complications following stimulator placement, for patients with persistent and disabling radicular pain following surgery for herniated disc and no evidence of a persistently compressed nerve root.

Clinical Perspective: In a press release, lead author and director of the APS Clinical Practice Guideline Program, Roger Chou, MD, noted that randomized trials are still limited for generating evidence-based recommendations for a number of commonly used interventional procedures, and the guideline also highlights the need for more research. “We have advocated strongly in many of our recommendations for physicians to use shared decision-making [involving patients] because of the relatively close trade-offs between potential benefits relative to harms, costs and burdens of these various treatment options,” Chou noted.

While a number of diagnostic tests, interventional therapies, and surgeries are available to treat low back pain, and their use is increasing, in some cases evidence for the use of these interventions is mixed, sparse, or not available. Chou and colleagues reaffirm previous recommendations that all patients with low-back pain stay active and talk honestly with their physicians about self-care and other approaches. “In general, non-invasive therapies supported by evidence showing benefits should be tried before considering interventional therapies or surgery,” said Chou.

Source: Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. *Spine*. 2009;34(10):1066-1077.

Arthritis Stems Activity in Adults With Heart Disease

Most people with heart disease (HD) can benefit from a program of physical activity, usually providing the potential to lower blood pressure, reduce low-density lipoprotein levels, and improve physical function overall. To learn more about the barriers to physical activity in patients with HD, investigators at the Centers for Disease Control and Prevention (CDC) evaluated data from the 2005 and 2007 Behavioral Risk Factor Surveillance System (BRFSS) for adults with self-reported heart disease and physician-diagnosed arthritis. (The BRFSS is an annual random-dialed telephone health survey of adults in all 50 states and several U.S. territories; the final sample for this investigation included more than 750,000 respondents.)

For the 2 years combined, just over 57% of adults with heart disease were affected with arthritis as a comorbid condition, compared with 27% of adults with arthritis alone in the general population. Persons with HD and arthritis were 30% more likely to be physically inactive as compared with those having HD without arthritis.

Clinical Concept: The survey results suggest that arthritis may be an important barrier to physical activity in persons with heart disease, and the authors note that these findings are consistent with other research in this area. Healthcare providers should consider potential arthritis-related

barriers to physical activity in their HD patients and encourage them to seek appropriate moderate-intensity aerobics and muscle-strengthening exercises.

[Comment: An editorial note following the report recommends several self-management interventions that are appropriate for adults with both conditions, such as the Arthritis Foundation Aquatics Program and others that are available in many communities. The CDC offers a guide to self-management programs for patients with arthritis; nationwide locations are included in some program listings at: <http://www.cdc.gov/arthritis/intervention/index.htm> — WD.]

Reference: Arthritis as a potential barrier to physical activity among adults with heart disease—United States, 2005 and 2007. *MMWR Morb Mortal Wkly Rep.* 2009 Feb 27;58(7):165-169.

 See full-text article at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5807a2.htm>

Low-Dose Naltrexone Eases Pain, Fatigue of Fibromyalgia

According to a pilot study published in the journal *Pain Medicine*, low doses of naltrexone may ease fibromyalgia symptoms. Researchers at Stanford University found that the drug reduced the severity of fibromyalgia symptoms — primarily pain and fatigue — by almost a third compared with placebo.

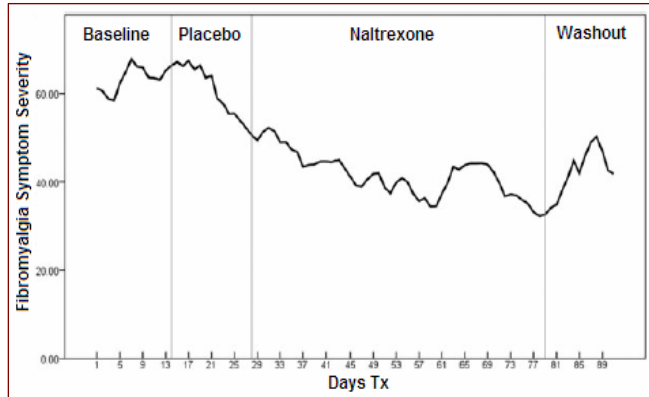
Study participants included 10 women with moderately severe fibromyalgia in whom baseline measures were taken for 2 weeks, followed by 2 weeks on placebo, followed by 8 weeks of naltrexone therapy (4.5 mg/day), followed by a 2-week washout period (no drug therapy). Thereby, each subject served as her own placebo control in this single-blind, crossover design trial. Each day, subjects recorded their symptoms on a handheld Palm computer. Four patients (40%) had been taking medication prior to the study — pregabalin, duloxetine, and gabapentin (1 patient), fluoxetine and nortriptyline (1 patient), or cyclobenzaprine (2 patients) — and these were continued throughout the trial.

During naltrexone therapy, participants reported 32.5% lower daily fibromyalgia symptom severity overall on a visual analog scale compared with baseline ($p=0.0005$), whereas the reduction was only 2.3% during the placebo phase compared with baseline ($p=0.003$). Looking at individual symptoms, low-dose naltrexone most significantly improved pain, fatigue, and stress.

Six of the 10 patients were substantial “responders,” having a 30% or greater reduction in symptom severity on naltrexone compared with placebo. In these persons, baseline levels of erythrocyte sedimentation rate were higher and strongly correlated with response to low-dose naltrexone; interaction effects of other drugs taken by 4 of the subjects during the study were not noted. Naltrexone was well tolerated, with side effects (eg, vivid dreams in 2 women) reported as mild. Patients actually reported greater tolerability with the drug than placebo, mimicking the long history of naltrexone’s safe use in treating opioid addiction.

Clinical Perspective: The authors conclude that low-dose naltrexone may be an effective, highly tolerable, and inexpensive treatment (less than \$40/month) for fibromyalgia. However, more research is needed in much larger trials and naltrexone is not FDA approved for this application. The authors also observed that fibromyalgia sufferers with higher sedimentation rates (indicating general inflammatory processes) had greater symptom reduction, so this therapy may be of most benefit for a particular subset of patients; however, this needs further exploration.

*[Comment: See **Graph** from Younger and Mackey, 2009 — Of interest, reductions in symptom severity began during the placebo phase, continued to a significantly greater extent during naltrexone therapy, and persisted somewhat during the washout period. It is unknown if symptom improvements would have continued with longer administration of placebo, or would have returned to baseline during a longer followup (washout) period. This highlights the importance of having separate placebo and treatment groups with longer followup periods.*



Due to the crossover design (with all patients receiving both placebo and naltrexone) and the large number of repeated (daily) observations, this study had high internal statistical power to detect naltrexone effects. However, the very small number of subjects cannot be assumed to validly depict the larger population of fibromyalgia sufferers; therefore, much larger, randomized, placebo-controlled trials will be necessary. — SBL]

Source: Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Med*. Published online ahead of print: April 22 2009.

NOTE: An early report of this study was mentioned in the *Pain Treatment Topics* paper — *Opioid Antagonists, Naloxone & Naltrexone – Aids for Pain Management* — which discusses research on the benefits of these agents within a larger context. This evidence-based report is available for free download at:

 http://pain-topics.org/clinical_concepts/innovations.php#antagonists

Patients Hide Use of Complementary & Alternative Medicine

To examine patients' self-care use of complementary and alternative medicine (CAM), investigators at the University of Western Ontario in Canada conducted an observational study among patients being treated in 3 orthopedic clinics for osteoarthritis. The 373 adult patients (\geq age 16) who met inclusion criteria were given a specially-designed and pretested questionnaire prior to practitioner consultation for osteoarthritis.

In addition to other data, the survey asked patients about the specific type of CAM therapy being used, their reasons for using CAM, how they believed CAM was helping them, and whether their practitioner was aware of their CAM use. Results showed that 43% of patients were using one or more CAM therapies and more than 40% admitted that their practitioners were unaware of this CAM use. The top 3 reasons for failing to disclose the information included: **1)** it was not important (30%), **2)** the practitioner would not be interested (14%), and **3)** the practitioner would not know about CAM therapies (8%).

Clinical Concept: It is important to note that almost 8% of study participants were taking alternative medicines that could interact with their blood pressure medication, nearly 29% were taking anticoagulant/antiplatelet medication along with an alternative medication that could interact, and 6% were taking conventional pain medications with a CAM product that had the potential to interact. While the authors acknowledge some limitations of the study (patient self-reporting and a

predominantly white population), they conclude that patients who do not share their CAM use with their healthcare providers are at increased risk of an adverse event or drug interaction. The authors recommend that practitioners make it part of their consultation to inquire about CAM use during each patient visit.

[Comment: The National Institutes of Health, Office of Dietary Supplements, provides a website offering brief descriptions of common dietary herbs and supplements, including information on known warnings and interactions. For more information, see:

http://ods.od.nih.gov/Health_Information/Information_About_Individual_Dietary_Supplements.aspx — *WD.]*

Reference: Marsh J, Hager C, Havey T, et al. Use of alternative medicines by patients with OA that adversely interact with commonly prescribed medications. *Clin Orth Relat Res*. 2009(Mar 3); [Early online publication prior to print].

Tips for Preventing Methadone Analgesia Overdose

The April 2009 edition of *FDA Patient Safety News (#85)* focuses on a report from the Institute for Safe Medication Practices (ISMP) that lists several reasons for the serious and sometimes fatal overdoses that have occurred with methadone to treat moderate to severe chronic pain. ISMP points out that methadone differs from other opioids in a number of ways. For example, methadone remains in the body long after its analgesic effect has worn off. A patient may not experience the full analgesic effect of methadone until 3-5 days of use, so it must be titrated more slowly than other opioids. And, a high degree of tolerance to other opioids does not eliminate the possibility of methadone overdose.

Errors also have been reported because of confusion between methadone and other drugs with "look alike" names. In one report, a patient with a traumatic brain injury received 25 mg of methadone BID instead of methylphenidate and suffered respiratory arrest. Another serious problem can be confusion between mL and mg doses. In one case, a patient had been taking 13 mg/day of methadone, which was prepared in the community pharmacy using a 1 mg/mL methadone concentration. When the patient was hospitalized, the attending physician assumed that the hospital carried the same concentration and prescribed 12 mL of methadone without specifying the dose in mg. The order was filled with a stock solution containing 10 mg/mL — a nearly tenfold larger amount. Fortunately, the patient vomited most of the medication and survived.

ISMP recommends a number of steps to help prevent life-threatening methadone-related adverse events, including:

- When prescribing methadone for pain, avoid concomitant use of other opioids, benzodiazepines, and sedatives.
- Prescribe oral liquid doses of methadone in mg amounts, never in mL alone, since several concentrations exist.
- On the prescription, include the indication for use when prescribing methadone to avoid confusion with methylphenidate.
- Specify the exact time(s) for administration on the prescription. If a dose is missed, patients should be instructed to check with the physician before taking it later than originally scheduled.

- Remind patients to take methadone exactly as prescribed. Instruct them not to start or stop taking any other medications or dietary supplements without talking to their prescriber, because methadone interacts with many other drugs.
- Instruct patients on methadone to seek medical attention if they experience symptoms of overdose, such as slow or shallow breathing and extreme sleepiness, or symptoms of arrhythmia.

Ref: FDA Patient Safety News, #85, Apr 2009. Preventing Overdoses when Using Methadone to Treat Chronic Pain.

Trial Supports CR-Oxycodone for Herpes Zoster Pain

Although acute pain in patients with herpes zoster can be severe and has a substantial impact on health-related quality of life, there have been no randomized clinical trials of oral medications specifically for its ongoing treatment. In such a trial, investigators studied 87 patients with herpes zoster (aged ≥ 50 years) within 6 calendar days of rash onset and with severe pain in the prior 24 hours. Patients were treated with famciclovir in combination with 28 days of either controlled-release (CR) oxycodone, gabapentin, or placebo. The researchers evaluated subjects for adverse effects of treatment, acute pain, and health-related quality of life.

Treatment with oxycodone significantly reduced the average worst pain during days 1 to 8 and days 1 to 14 compared with placebo; results for days 1 through 28 were favorable but not statistically significant (pain resolved in most subjects by day 28). Treatment with gabapentin did not yield statistically significant reductions in pain relative to placebo for any of the 3 time periods.

The results showed that CR-oxycodone and gabapentin were generally well tolerated. Discontinuing participation in the trial, primarily associated with constipation, occurred more frequently in subjects randomized to CR-oxycodone (27.6%) compared with placebo (6.9%). However, only 69% of patients on CR-oxycodone in the trial used a laxative.

Practice Pointer: The results of this trial may provide a foundation for evidence-based treatment for acute pain in herpes zoster. In a published interview, lead investigator Robert Dworkin, PhD, from the University of Rochester Medical Center, New York, acknowledged a hesitation on the part of some within the medical community to treat acute pain of this nature with opioids. "There is a whole lot going on at the Food and Drug Administration on this topic right now, but the evidence supports the safety and efficacy of opioids when used appropriately for carefully selected patients," he said. "Although it can be expected that a generic extended-release oxycodone would also be efficacious," Dworkin continued, "it is impossible to know whether our results can be extrapolated to other opioid analgesics, for example, hydrocodone or morphine."

Reference: Dworkin RH, Barbano RL, Tying SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;1429(3):209-217.

Briefly Noted...

NOTE: Some of the entries below also were published earlier via our **e-Notification** e-mailings providing timely [Pain-Topics.org](http://pain-topics.org) news and updates. Register for a free subscription to receive e-Notifications, at: <http://pain-topics.org/registration/>

◆ Opioids Favored for Pain in Elderly

In early May 2009 the American Geriatrics Society (AGS) released new guidelines addressing the pharmacological management of persistent pain in older persons. These guidelines will be officially published in the August issue of the *Journal of the American Geriatrics Society*.

The newly revised guidelines include 27 recommendations focusing on seniors 75-years and older, as this group tends to be more frail and suffers from multiple chronic illnesses. Persistent pain is common among older people, especially those suffering from degenerative spine conditions, arthritis, nightly leg pain, or pain as a result of cancer. When ongoing pain is ignored or incorrectly treated, this can cause adverse outcomes including falls, disruptions in sleep, depression, and anxiety — adding to an increase in unnecessary health care costs.

A major change in this new guideline is the near elimination of recommending non-steroidal anti-inflammatory drugs (NSAIDs) in this patient population. Original guidelines recommended seniors use over-the-counter or prescription analgesics – NSAIDs or COX-2 inhibitors – before being prescribed an opioid drug. The AGS guidelines panel states that the risks of NSAIDs in older patients – which include increased cardiovascular risk and gastrointestinal toxicity – usually outweigh the benefits and has revised the guidelines to reflect recent findings. Based on newer clinical trials as well as clinical observation, the panel recommends that NSAIDs and COX-2s be considered rarely, and with extreme caution, in selected individuals. The new guidelines recommend that all elderly patients with moderate-severe pain or diminished quality of life due to pain should be considered for **opioid therapy**, which may be safer for many patients than the long-term use of NSAIDs.

Source: AGS news release, May 1, 2009.

 Access the AGS guideline at: http://www.americangeriatrics.org/education/pharm_management.shtml

◆ Topical NSAIDs for Osteoarthritis Reviewed

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) can provide pain relief similar to oral NSAIDs in some patients with osteoarthritis (OA), but with lower risks of systemic adverse effects. Rheumatologists from the David Geffen School of Medicine in Los Angeles reviewed the pharmacology, efficacy, and safety of topical diclofenac sodium 1% gel, salicylates, and capsaicin for symptom relief in hand and knee OA. Inconsistencies were encountered in published guidelines:

- Two European and International guidelines suggest a preference for topical NSAIDs over oral NSAIDs in appropriate patients with hand or knee OA of mild-to-moderate severity.
- Conversely, 2 American guidelines have not recommended topical NSAIDs (only topical methyl salicylate and topical capsaicin which have not shown benefits for OA treatment).

However, the American guidelines were written before the approval of diclofenac sodium 1% gel (Voltaren® gel) in the U.S. in late 2007. The authors review the clinical trial data that supports the use of this topical gel for pain relief in OA patients with hand or knee involvement.

Reference: Altman R, Barkin RL. Topical therapy for osteoarthritis: clinical and pharmacologic perspectives. *Postgrad Med.* 2009(Mar);121(2):139-147.

◆ Three Treatments for Knee Osteoarthritis Found Ineffective

Several new documents from the U.S. Agency for Healthcare Research and Quality (AHRQ) address treatments for osteoarthritis (OA) of the knee. There is a brochure for patients called *Osteoarthritis of the Knee: A Guide for Adults* and two reports for healthcare providers:

- *Three Treatments for Osteoarthritis of the Knee: Evidence Shows Lack of Benefit*
- *Treatment of Primary and Secondary Osteoarthritis of the Knee*

In these documents, several treatments are noted as NOT being helpful...

- Glucosamine and/or chondroitin usually do not reduce pain or improve knee movement.
- Joint lubricant shots (not the same as cortisone shots) usually do not reduce pain or improve knee movement.
- Arthroscopic knee surgery usually does not reduce pain or improve knee movement.

What does help? Staying active and losing weight are recommended, along with analgesics, primarily acetaminophen in most cases, for controlling pain and facilitating activity.



The AHRQ patient pamphlet and practitioner reports can be accessed at:
http://pain-topics.org/patient_resources/index2.php#kneeOA

[COMMENT: *Similar recommendations have been presented in other guidelines such as the “Guideline on the Treatment of Osteoarthritis (OA) of the Knee” from the American Academy of Orthopaedic Surgeons (AAOS 2008). These guideline authors recommend against using glucosamine and/or chondroitin sulfate or hydrochloride, needle lavage (aspiration of the joint with injection of saline), or custom made foot orthotics. For symptomatic relief of knee pain due to OA, acetaminophen (not to exceed 4 grams per day), non-steroidal anti inflammatory drugs (NSAIDs), or intra-articular corticosteroids (for short term pain relief) are recommended. Insufficient evidence was available to recommend for or against the use of bracing, acupuncture, or intra-articular hyaluronic acid.*

However, other guidelines, such as those from the Work Loss Institute (WLI) for knee/leg arthritis are contradictory. Glucosamine is recommended as providing effective symptomatic relief, and for modifying the progression of knee osteoarthritis over a 3-year period. Intra-articular (IA) injection of hyaluronic acid (eg, Synvisc) is suggested as decreasing OA symptoms. Furthermore, the guidelines suggest that total knee arthroplasties are reliable and suitable surgical procedures to return patients to function.



Both of these guidelines can be accessed at:

http://pain-topics.org/guidelines_reports/current_guidelines2.php#kneeOAguide — SBLJ

◆ Vitamin D Reports in Recent Journals

Last summer 2008, several evidence-based papers published at Pain-Topics.org described how inadequacies of vitamin D have been linked to various pain disorders. Research relating to this subject continues to be reported in various medical journals.

➤ 75% of patients may have inadequate vitamin D levels...

Vitamin D deficiencies among Americans are increasing, according to a large-scale comparison of data from 1988-1994 and 2001-2004 (total n=32,000). Between those time periods, average vitamin D (25[OH]D) serum levels decreased by 20% (from 30 ng/mL to 24 ng/mL), severe deficiencies of less than 10 ng/mL increased 3-fold (from 2% to 6% of the population), and at the latter time point 3 out of 4 persons had vitamin D levels below the minimally desired 30 ng/mL level.

Source: Ginde AA, et al. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Archives of Internal Medicine*. 2009;169(6):626-632.

➤ Vitamin D₃ supplementation helps prevent painful bone/hip fractures...

A meta-analysis of controlled clinical trials (total n=42,000 patients) found that, in adults aged 65 and older, vitamin D supplementation reduced painful non-vertebral bone fractures by 20% and hip fractures by 18%. These significant benefits were only evident at doses of cholecalciferol (vitamin D₃) supplementation greater than 400 IU per day, and occurred with or without calcium supplementation.

Source: Bischoff-Ferrari HA, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency. *Archives of Internal Medicine*. 2009;169(6):551-561.

➤ Vitamin D has opioid-sparing effect in patients with chronic pain...

Investigators at the Mayo Clinic studied patients with chronic pain (n=267) admitted during 2006. More than a quarter of patients had vitamin D deficiencies (25[OH]D < 20 ng/mL). Among patients taking opioid analgesics, the morphine-equivalent amount required by vitamin-D-deficient patients was roughly twice that needed by patients with adequate vitamin D levels. The “deficient group” also was taking opioids 60% longer and had worse physical functioning than patients with chronic pain having adequate vitamin D levels. Thus, even when vitamin D supplementation does not help in ameliorating pain, other significant benefits still may be realized.

Source: Turner MK, et al. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. *Pain Medicine*. 2009;9(8):979-984.



Also see the Pain-Topics papers on *Vitamin D for Pain* at: <http://pain-topics.org/VitaminD>

◆ Fears Prevent Patients From Controlling RA Pain

Many patients with rheumatoid arthritis (RA) may have fears that hinder optimal management of their pain, a recent study by Canadian researchers suggests. McGill University investigators studied 60 patients with RA, all of whom were being treated by specialists. More than half of the pa-

tients (53%) described their pain as moderate to severe, while 47% reported mild or absent pain. Other than the regular use of nonsteroidal anti-inflammatory drugs and acetaminophen by a third of the patients, stronger analgesics or other modalities to reduce pain were seldom used.

A primary interest of the researchers was uncovering barriers that kept significant numbers of patients with RA from achieving optimal pain control. The top barriers found in study participants included:

- Worry about medication side effects (80%)
- Not wanting to take "too many pills" (63%)
- Concern about medication interactions (57%)
- Fear of addiction (35%)
- Fear of masking disease (27%)

More than half of the study participants (33 individuals) experienced at least 3 barriers. As might be expected, having more barriers was significantly associated with higher pain levels. The researchers conclude that people with rheumatoid arthritis should be questioned vigorously about their pain, and that clinicians should explore potential barriers to effective pain control.

Reference: Fitzcharles M-A, DaCosta D, Ware MA, Shir Y. Patient barriers to pain management may contribute to poor pain control in rheumatoid arthritis. *J Pain.* 2009;10(3):300-305.

◆ Adding Naloxone to Buprenorphine Fails to Deter Injection

Adapted from a summary provided by Andrew Byrne, MD, Redfern, Australia. Reporting on a Malaysian population of opioid-addicted patients being treated with buprenorphine, researchers from Yale University (Bruce et al. 2009) found no reductions in quantities of buprenorphine illicitly injected after the widespread change from pure buprenorphine (Subutex®) to the combination product with naloxone (Suboxone®). Even more concerning was a finding of increased needle sharing in the high proportion of subjects who reported withdrawal symptoms following the change in formulations.

In a group of 41 recruited illicit buprenorphine injectors in Kuala Lumpur, the researchers posed questions about injection of both the pure and combination products after a change in Government policy aimed at discouraging injecting. Pure buprenorphine was banned due to extensive abuse and replaced with the combination product containing naloxone. As in previous experiences reported long ago (Robinson 1993), a change to the combination product was not associated with a substantial reduction in abuse of the drug.

Half the sample (20 persons) reported experiencing withdrawal symptoms after the change, yet this had apparently not discouraged them from injecting; in fact, 44% increased the amount injected to compensate for reduced effects incurred by the naloxone component. Reported needle sharing was much more prevalent in those who also reported withdrawal symptoms (15 out of 20 or 75% of the 'withdrawal' subgroup), and the development of opioid withdrawal symptoms also was associated with increased benzodiazepine injection. Bruce and colleagues state that none of the subjects appeared to be using buprenorphine simply as a recreational drug but to maintain a functional level of opioids in their bodies.

References:

Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. *Am J Drug Alcohol Abuse*. 2009;35(2):68-72.

Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Dependence*. 1993;33;1:81-86.

Recent Drug or Device Approvals, Announcements, & Warnings

Following are news briefs on pain-management drug or device approvals or announcements, as well as items related to safety concerns for existing products. All brand names are registered trademarks of their respective manufacturers.

➤ **FDA Requires More Safety Warnings on OTC Pain Relievers**

The U.S. Food and Drug Administration announced a final ruling that will require manufacturers of over-the-counter pain relievers and fever reducers to include tougher safety warnings on their labels. Acetaminophen products must include warnings about the risk of liver damage. Makers of nonsteroidal anti-inflammatory drugs — including aspirin, ibuprofen, naproxen, and ketoprofen — will be required to warn users about the risks of stomach bleeding. Additional factors that increase the risk of serious adverse effects include: alcohol use, taking more than the recommended dosage, or using the drugs longer than directed. The FDA wants to increase consumer awareness on the safe use of medications and provide risk information on labels so that users are fully aware of the potential for harm.

Since the proposal was first introduced in 2006, some manufacturers have already voluntarily made recommended labeling changes. However, the FDA says the policy contains new label requirements that must be addressed by drugmakers because the new regulations apply to generics and other OTC drugs, like cold medicines, that contain pain relievers. Drugmakers will have one year to make labeling revisions.

➤ **Synvisc-One™ Injection – FDA Approval for Osteoarthritis**

Genzyme Corporation announced a February 2009 approval of Synvisc-One — a single intra-articular injection of a sodium hyaluronate mixture called hylan G-F 20 — for the treatment of knee pain in patients with osteoarthritis. The product is intended as an alternative treatment to the company's Synvisc® three-injection regimen. Hylan G-F 20, a natural substance found in the body, is injected into the knee joint to replace synovial fluid that has lost its cushioning ability, potentially offering significant pain relief for up to six months. The single injection therapy can offer convenience and cost savings without the potential systemic adverse effects that can be caused by steroids or anti-inflammatory drugs.

➤ **Morphine Sulfate Extended-Release Capsules (Avinza®)
– Two New Strengths Approved**

King Pharmaceuticals made a February 2009 announcement regarding the FDA approval of 45 mg and 75 mg dosing strengths of Avinza, a long-acting opioid. Avinza was developed for patients with moderate to severe chronic pain who require continuous, extended pain relief. The once-daily dosing can purportedly benefit patients with malignant and nonmalignant pain conditions, including osteoarthritis and low back pain. It is currently available in 30 mg, 60 mg, 90 mg, and 120 mg strengths; the new capsule strengths will provide additional options for more individualized pain therapy in opioid-tolerant patients with chronic pain.

➤ **Generic Oxycodone Hydrochloride – FDA Approval**

Sun Pharmaceutical Industries Ltd. announced an April 2009 FDA approval of their generic oxycodone hydrochloride tablets, a therapeutic equivalent to Roxicodone® which is produced by Xanodyne Pharmaceuticals. Immediate-release oxycodone tablets are used in the management of moderate to severe pain in patients who are opioid-tolerant. The generic tablets are available in three strengths: 5 mg, 15 mg, and 30 mg.

➤ **Tramadol Hydrochloride Extended-Release Tablets (Ryzolt™)
– FDA Approval**

In January 2009, Labopharm announced the FDA approval of Ryzolt, a once-daily formulation of the oral analgesic tramadol, a centrally-acting analgesic. The drug — designed to provide around-the-clock relief for adult patients with moderate to severe pain — uses Contramid® controlled-release technology (a dual-matrix delivery system with immediate- and extended-release characteristics). The Canadian drugmaker stated that its U.S. marketing partner, Purdue Pharma, plans a launch of Ryzolt tablets in the second quarter of 2009 in 3 dosage strengths: 100 mg, 200 mg, and 300 mg.



Download Ryzolt prescribing information PDF at:

<http://www.purduepharma.com/pi/prescription/Ryzolt.pdf>

➤ **Generic Topiramate – FDA Approval For Treatment of Seizures**

Seventeen makers of topiramate received a March 2009 approval for generic versions of the antiseizure drug. While the generic topiramate is equivalent to Topamax® — also approved as migraine prophylactic therapy — the generic labeling information will differ because some of the indications for Topamax continue to be protected by patents and exclusivity. Healthcare providers are reminded that both generic and branded topiramate come with important safety warnings about the potential for metabolic acidosis (requiring a blood test to monitor patient levels of serum bicarbonate) and serious eye problems that can lead to blindness.

➤ **Antiepileptic Drug Class – Safety Labeling Change Required**

Following 2 safety alerts issued by the FDA in 2008, healthcare professionals were notified in May 2009 of an approved labeling requirement to alert patients and practitioners that the FDA analysis showed an increased risk of suicidal thoughts or behavior with antiepileptic agents. Eleven drugs were included in the analysis, but the FDA expects that the increased risk of suicidality is shared by all antiepileptic drugs. Two of the antiepileptic agents analyzed — Gabapentin (Neurontin®), and Pregabalin (Lyrica®) — are commonly used adjunctively in the management of neuropathic pain and as prophylactic migraine therapy. All manufacturers of drugs in this class will be required to include a safety warning on their label and develop a medication guide for patients alerting them to the increased risk of suicidal thoughts or behavior. Healthcare professionals should evaluate the relative risk of suicidality against the therapeutic need for the drug, as well as provide education to patients and family members on the potential increased risk of suicide and the need to be alert for unusual behavior.

➤ **Botulinum Toxin Types A and B – FDA Follow-up to February 2008 Early Communication**

Manufacturers of licensed botulinum toxin products (including Botox Cosmetic Type A and Myobloc Type B) were notified by the FDA in April 2009 of the need to strengthen warnings on product labeling. They were instructed to add a boxed warning on the potential for adverse events in cases when the effects of the toxin spread beyond the injection site. The memo states that the development and implementation of a Risk Evaluation and Mitigation Strategy (REMS) is needed as well as an increased requirement for safety data reporting. The full communication (available at the link below) reviews the uses for which botulinum toxin products have been approved and summarizes the reported adverse events. Most adverse events reported for children involved the use of botulinum toxin products used to treat muscle spasticity in cerebral palsy (an unapproved use), and the majority of the distant spread of toxin effects in adults were in patients who were being treated for spasticity (an unapproved use) or cervical dystonia (an approved indication). In recent years, studies have reported the use of botulinum toxin A for chronic pain relief in low back pain, focal painful spasticity, myofascial pain syndrome of cervical or shoulder muscle origin, and other uses. The FDA memo reminds healthcare professionals to be aware of the variations in potency among botulinum products and to educate patients in the potential signs of distant toxic effects and systemic adverse effects following an injection.

➤ **Efalizumab (Raptiva®) – Voluntary Market Withdrawal by Genentech**

Following a February 2009 FDA public health advisory regarding the increased risk of progressive multifocal leukoencephalopathy (a rare brain infection), Genentech, Inc. has notified prescribers of a phased voluntary withdrawal of the drug Raptiva. Three adults treated with Raptiva for more than 3 years have been confirmed to have died from the brain infection. The product — a once-weekly injection — was used to treat severe plaque psoriasis and psoriatic arthritis. The advisory instructs prescribers not to initiate Raptiva therapy for

any new patients and current patients should be counseled on the termination of the drug in an appropriate manner not later than June 8, 2009.

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