Opioid Doses and Increased Risk for Overdose

TO THE EDITOR: Dunn and colleagues (1) present sobering data on opioid overdose, showing a direct correlation between daily morphine equivalents and overdose rates. As echoed in the accompanying editorial by McLellan and Turner (2), these data remind every clinician prescribing opioids to thoroughly review the indication, effectiveness, and safety with patients.

One safe medication-taking practice that is often overlooked is asking patients receiving long-term opioid treatment to contact the office when they are feeling unwell. Providers and patients, especially elderly patients and those with multiple comorbid conditions, should understand that the effective opioid dose when feeling relatively well may be harmful when feeling ill. Volume depletion can increase plasma concentrations of opioids (3), decreased glomerular filtration rate can promote accumulation of active opioid metabolites (4), and any co-occurring alteration in sensorium due to a variety of medical illnesses can be dramatically exacerbated by a patient’s typical opioid dose. Most worrisome is that patients who feel unwell may attempt to treat symptoms by increasing their doses of opioids or other psychoactive medications.

Although adding another box to the checklist of safety reminders might make opioid prescribing even more onerous to clinicians, we strongly believe that common-sense safety measures must be part of every prescriber’s protocol to minimize adverse outcomes.

William C. Becker, MD
David A. Fiellin, MD
Yale University School of Medicine
New Haven, CT 06510

Robert D. Kerns, PhD
Veterans Affairs Connecticut Healthcare System
West Haven, CT 06516

Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: We commend Dunn and colleagues (1) on their findings of a dose–response relationship between opioid dose and overdose risk. Although some participants misused opioids, most had not received opioids for at least 6 months. The authors found that opioid doses of 20 mg/d were associated with lower potential for overdose than higher doses. The daily doses reported were the cumulative dose dispensed over 90 days, divided by 90, with no indication of the prescribed duration. All participants filled at least 3 opioid prescriptions, but the daily supply was not reported. This may lead to misinterpretation of their findings. Consider the scenarios of patients A and B, who had been opioid-naïve for at least 6 months and whose calculated average daily opioid dose was 20 mg over the 90-day period. Patient A received morphine, 150 mg/d, for 12 days, and patient B received morphine, 20 mg/d, for 90 days. Both patients filled 3 morphine prescriptions and ingested a cumulative dose of 1800 mg over 90 days, with an average of 20 mg/d. However, patient A may be at a substantially higher risk for opioid-related overdose.

Additional information, including the daily supply of opioid prescriptions filled, could have been useful, but their absence does not negate the value of the authors’ findings, which offer guidance on safe initial doses of opioids for chronic noncancer pain in opioid-naïve patients.

Milap C. Nahata, PharmD, MS
Katy E. Trinkley, PharmD
Ohio State University
Columbus, OH 43210

Potential Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: Dr. Becker and colleagues and Drs. Nahata and Trinkley raise valuable points. Dr. Becker and colleagues note that the risk for adverse effects from opioids may differ depending on changes in intercurrent illness, particularly in older patients with many comorbid conditions. About 6% to 7% of all adults aged 65 years or older receive long-term opioid therapy for chronic noncancer pain (1). Remarkably little research has been done to evaluate risks and risk factors for adverse medical and behavioral effects of long-term opioid use, particularly in elderly patients. Possible adverse effects of opioids include serious fractures due to falls (2); acetonophenox toxicity (3); hyperalgesia; aspiration pneumonia; complications of chronic constipation; apathy, deactivation, and depression; and cognitive impairment. Careful evaluation of patient suitability for long-term opioid use, cautious prescribing, clear explanation of how to use opioids safely and of the potential risks, close medical monitoring of patients receiving opioids on a long-term basis, safety reminders, and other universal precautions could reduce risks for adverse effects. However, research evaluating harm-reducing interventions in patients receiving opioids for chronic noncancer pain is sparse, as is research weighing the long-term benefits against the full range of medical and behavioral risks.

Drs. Nahata and Trinkley correctly identify a limitation of our research: We assessed overdose risk relative to estimated average daily dose. Risks could differ substantially depending on the actual pattern of opioid consumption. In fact, we know little about how physicians prescribe and patients use opioids for chronic pain in community practice. Because millions of U.S. adults receive long-term opioid therapy, research is needed on how opioids are actually used by patients with chronic pain, the risks and benefits of alternative opioid treatment regimens, and the effectiveness of universal precautions for...
Letters

preventing adverse effects. Without an adequate evidence base for current prescribing practices, a cautious and vigilant stance toward long-term opioid prescribing for patients with chronic noncancer pain seems prudent.

Michael Von Korff, ScD
Group Health Research Institute
Seattle, WA 98101

Kate Dunn, PhD
Keel University
Keel ST5 5BG, United Kingdom

Potential Conflicts of Interest: None disclosed.

References

Menopausal Hormone Therapy and Risk for Cardiovascular Disease in the WHI Trial

TO THE EDITOR: We applaud Toh and colleagues (1) for delving deeper into the still-controversial issue of inconsistencies in the outcomes of cardiovascular disease (CVD) between the Women’s Health Initiative (WHI) estrogen plus progestin hormone trial and previous large observational studies. Current evidence suggests that both the timing of initiation and the duration of menopausal hormone therapy (2, 3) are important determinants of the risk–benefit ratio. The data presented by Toh and colleagues suggest that the slightly higher CVD risk in the first 2 years of treatment leads to a lower risk after 6 or more years of use only in WHI participants who adhere to treatment and initiate treatment sooner than 10 years after menopause, which is relevant to both timing of initiation and treatment duration issues.

We regret that the authors focused on the statistically nonsignificant early increase in risk and discounted possible long-term benefits by saying that, “because the typical duration of use of hormone therapy is short, most women contemplating estrogen plus progestin therapy for the relief of menopausal symptoms should not expect protection against CHD [coronary heart disease].” On the contrary, before publication of the original WHI report in 2002 (4), long-term menopausal hormone therapy was frequently prescribed to reduce risks for both osteoporotic fractures and CVD. Ironically, the WHI conclusion that menopausal hormone therapy produced net harm was the primary basis for the change in the U.S. Food and Drug Administration official guidance and for subsequent clinical practice discouraging long-term menopausal hormone therapy. The initial report did not differentiate between the risks and benefits in recently versus remotely menopausal women, which WHI investigators and others (5) have tried to address in follow-up analyses. Thus, it seems that an alternative interpretation of the new analysis by Toh and colleagues would be that recently menopausal women have little to fear in the early period of hormone treatment, when incident CVD rates are low, and may benefit from long-term continuation of menopausal hormone therapy into the later postmenopausal years, when CVD risk is much higher. This may be a matter of perspective (glass half-empty vs. glass half-full), but the health and lives of millions of women will depend on how the results of this and future research are interpreted by the medical community and the public.

S. Mitchell Harman, MD, PhD
Kronos Longevity Research Institute
Phoenix, AZ 85016

Eliot A. Brinton, MD
University of Utah School of Medicine
Salt Lake City, UT 84108

Frederick Naftolin, MD, PhD
New York University School of Medicine
New York, NY 10016

George R. Merriam, MD
University of Washington School of Medicine
Seattle, WA 98195

Marcelle I. Cedars, MD
University of California at San Francisco
San Francisco, CA 94115

Ruth G. Freeman, MD
Albert Einstein College of Medicine and Montefiore Medical Center
Bronx, NY 10461

Nanette Santoro, MD
University of Colorado at Denver
Aurora, CO 80045

Potential Conflicts of Interest: All authors are co-principal investigators of KEEP5 (Kronos Early Estrogen Prevention Study), an investigation of cardiovascular effects of oral versus transdermal hormone treatment in recently menopausal women.

References
TO THE EDITOR: Since the first article from the WHI in 2002, the validity of the methods of data analysis has been debated. First, debate focused on the use of adjusted or unadjusted hazard ratios, then on the issue of combining the data from the group that received conjugated equine estrogen with medroxyprogesterone acetate and the group that received conjugated equine estrogen alone, or the data from the WHI clinical study and the WHI observational study. Recently, when age became an important variable in the risk–benefit balance of hormone therapy, another debate involved the “timing hypothesis.” Although these arguments are the domain of epidemiologists and statisticians, the lay physicians who practice menopause medicine and prescribe hormones should receive clear messages from the WHI investigators, and patients should be informed and educated to a similar extent. It is therefore of the utmost importance not to send conflicting messages, but the article by Toh and colleagues (1) unfortunately does exactly that. The key conclusions in the article’s abstract are different from those of the patient summary in the same issue (2). The conclusion of the abstract says “[n]o suggestion of a decreased risk for CHD was found within the first 2 years of estrogen plus progestin use, including in women who initiated therapy within 10 years after menopause. A possible cardioprotective effect in these women who initiated therapy closer to menopause became apparent only after 6 years of use.” This message on risk for CHD seems neutral and perhaps even a bit positive.

In contrast, the patient summary is phrased in a more alarming way. It describes the problem by saying that “[w]omen who receive hormone therapy after menopause have an increased risk for heart attacks and other problems related to the arteries in their heart.” It says that the results of the study were that “[a] possible increased risk was present in the first 2 years in women who started hormone therapy within 10 years after menopause, and increased risk persisted until about 6 years after use.” Finally, it says that the implications are that “[m]ost women use combined hormone therapy to treat the symptoms of menopause, which means they start hormone therapy soon after menopause and generally use it for less than 6 years . . . [these women] may need to worry about a possible slightly increased risk for heart attacks.” Such discrepancies between the investigators’ own conclusions and the patient summary are unethical and will probably increase confusion and anxiety in women who need this therapy. We urge Annals to address this misleading conclusion and provide an explanation from the authors.

Amos Pines, MD
David Stardee, MBBS, MD, DA
The International Menopause Society
Lancaster LA2 8WY, United Kingdom

Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: The WHI was based on an expectation of no less than a 30% reduction in CVD mortality in women receiving hormone replacement therapy (HRT) (1). With the “timing hypothesis” effectively eliminated by Toh and colleagues (2), the meaning of the results of the trial should be revisited. Failure to show any reduction in mortality, let alone a 30% reduction, has far-reaching implications beyond the recommendation that HRT not be used for prevention of CVD. The large expected decrease in disease was related to the much lower CVD rates of menstruating women. The fact that the WHI found no mortality decrease with HRT, even in newly postmenopausal women, raises questions about the belief that menstruating women are protected from CVD by the direct effects of female hormones. The working conclusion seems to be that young women are protected by their hormones but that, at whatever age menopause occurs, this protection is lost. An alternative, simpler view consistent with WHI findings is that female hormones confer a small cardiovascular risk at any age. In other words, risk is lower in young, menstruating women despite the disease-promoting effects of female hormones. Premenopausal women may be protected by some other factor that, when lost after menopause, makes this increased risk apparent in those receiving HRT. An alternative protective factor in menstruating women has been proposed (3–6).

Jerome L. Sullivan, MD, PhD
University of Central Florida College of Medicine
Orlando, FL 32816

Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: We agree with Dr. Harman and colleagues about the importance of both the timing of initiation of postmenopausal hormone therapy and the duration of treatment in relation to CHD, a point we made in our article. Unlike several analyses of observational studies, the WHI estrogen plus progestin trial found no benefit of postmenopausal hormone therapy on either CHD risk or mortality. In contrast, the WHI findings were consistent with observational analyses for stroke, venous thromboembolism, breast cancer (increased risk), hip fractures, and colorectal cancer (decreased risk) (1).
Subsequent reanalyses of the observational data (2, 3) suggest that an early harmful effect of estrogen plus progesterin therapy on CHD may explain the randomized-observational discrepancy: The WHI trial fully captured the early events, whereas several previous analyses of observational data did not. Our analyses of data from WHI and the Nurses’ Health Study indicate that women who started estrogen plus progesterin therapy long after menopause had a greater CHD risk during at least the first 8 years of treatment and that women who started therapy within 10 years after menopause did not have a lower CHD risk during the first 3 to 6 years of treatment (3). In fact, as Drs. Pines and Sturdee point out, our findings are also consistent with a small increase in the short-term CHD risk in these younger women. Regardless of whether one chooses to emphasize the lack of early benefit (as we did in our article) or the possibility of early harm, the insufficient evidence for long-term CHD benefit, plus the adverse effects on stroke, venous thromboembolism, and breast cancer, argue against returning to estrogen plus progesterin therapy (at least not the regimen studied in the WHI) as a viable option for the prevention of chronic diseases.

In response to Dr. Sullivan, it is unclear whether natural menopause is associated with a sharp increase in CHD incidence beyond the log-linear relationship with age (4). In addition, findings from the WHI trial regimens (orally administered conjugated equine estrogen with or without medroxyprogesterone acetate) may not be directly relevant to a possible role of endogenous sex hormones in explaining the sex difference in CHD rates.

Potential Conflicts of Interest: None disclosed.

References

Risk for Venous Thromboembolism in Patients With Superficial Venous Thrombosis

TO THE EDITOR: Congratulations to Decousus and colleagues (1) on their excellent article. After reading it, I had a few questions. Were the 844 patients part of a consecutive series among the practices that agreed to participate in the study? Why did the authors encounter problems with slow enrollment? Was the disease frequency lower than expected, or were the authors missing patients who were not being enrolled because of local practice issues or because they declined to participate?

Michael S. Lauer, MD
National Heart, Lung, and Blood Institute
Bethesda, MD 20824

Potential Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: I read with great interest the article by Decousus and colleagues (1), which describes the risk factors for venous thromboembolism in patients with superficial venous thrombosis (SVT), including male sex, history of deep venous thrombosis (DVT), previous cancer, and absence of varicose veins. However, tobacco consumption was not investigated. Thromboangiitis obliterans is a vasculitis that develops in young patients with superficial thrombophlebitis, arterial upper-limb involvement, and the Raynaud phenomenon in the absence of atherosclerotic risk factors other than smoking (2, 3). Its cause is unknown, but the relationship with tobacco has been demonstrated, and its frequency is perhaps underestimated. The most effective treatment is smoking cessation. Superficial thrombophlebitis is observed in 9.5% to 65% of patients with thromboangiitis obliterans, depending on the study and its geographic origin (2–4). In a retrospective Iranian study involving 86 patients (4), 65.4% had a history of superficial thrombophlebitis. In 25%, it was the initial presentation, and in 4.7%, it was the primary symptom. It occurred an average of 9 years (with a maximum of 22 years and a minimum of 4 months) before the patient presented with any other sign of thromboangiitis obliterans. Because deep venous thrombophlebitis is unusual in thromboangiitis obliterans, Decousus and colleagues should have evaluated tobacco consumption in their study patients.

Claude Bachmeyer, MD
Centre Hospitalier Universitaire Tenon (AP-HP)
75020 Paris, France

Potential Conflicts of Interest: None disclosed.

References


TO THE EDITOR: I found the article by Decousus and colleagues (1) very interesting in relation to the apparently not-so-benign course of symptomatic SVT. This study adds more evidence for the need to screen for DVT in patients with SVT and raises valid questions about the potential benefit of systemic anticoagulation. However, this is known to be a heterogeneous population, and patients who will definitely benefit from full anticoagulation are those with thrombophilic disorders. It is striking that even though Decousus and colleagues describe only 5% of known biological thrombophilia, in patients who had only isolated SVT at diagnosis, more than 50% (348 of 634) had a history of SVT, DVT, or pulmonary embolism. That proportion increases to 87% (554 of 634) if we also include positive family history. These numbers, together with the fact that some previous studies (2, 3) showed a higher-than-expected prevalence of thrombophilic states in patients with SVT, raise the question of whether some of these patients might have had a basal hypercoagulable state. It would be particularly interesting to know if those patients who had only SVT but developed thrombotic complications over the following 3 months were tested for known hypercoagulable disorders. It is unclear whether screening for those disorders is cost-effective in patients with SVT. Information retrieved from a prospective clinical trial, such as this one, could have significant value.

Matias E. Valecchi, MD
Albert Einstein Medical Center
Philadelphia, PA 19141

Potential Conflicts of Interest: None disclosed.

References


TO THE EDITOR: In response to Dr. Lauer’s questions, we cannot confirm that all centers enrolled consecutive patients into the study. However, this approach was strongly recommended when the study design was explained to them. We believe that the slowness of recruitment reflected practical considerations of the physicians and patients’ willingness to participate in the study rather than a lower-than-expected disease frequency.

We agree with Dr. Bachmeyer that SVT is common in patients with Buerger disease (1). However, in western European patients, Buerger disease is relatively rare (1). In the POST (Prospective Observational Superficial Thrombophlebitis) study, very few patients had Buerger disease: Only 2.3% of patients presented with an autoimmune disease, including not only Buerger disease but also other autoimmune diseases, such as Behçet disease and lupus-like syndromes. Therefore, although exposure to tobacco smoke is indeed a key factor in the progression of Buerger disease, its prognostic value was not analyzed.

As indicated in Table 1 of our article, the percentage of patients with a personal and family history of thrombosis is actually lower than that calculated by Dr. Valsecchi by adding together the number of patients with a history of SVT, the number of patients with a history of DVT or pulmonary embolism, and the number of patients with a family history of thrombosis. Although this table presents data relating to each of these 3 variables separately, the same patient could be positive for more than 1; therefore, the number of patients with a personal and a family history of thrombosis cannot be obtained by simply combining the 3 sets of data. In fact, the percentage of patients with a history of SVT, DVT, or pulmonary embolism was 46.5% (289 of 621), and the percentage of patients with both a personal and a family history of thrombosis was 61.2% (383 of 625).

At baseline, 5.4% of patients with isolated SVT had known biological thrombophilia, but biological thrombophilia was not systematically tested in patients with thrombotic complications at 3 months. However, in univariate analysis, this variable did not seem to be a risk factor for thromboembolism at 3 months (hazard ratio, 0.39 [95% CI, 0.05 to 2.81]; P = 0.35). Therefore, as for DVT and pulmonary embolism, we believe that the value of screening for biological thrombophilia in patients with SVT is questionable (2–4).

Hervé Decousus, MD
INSERM CIE3, Université de Saint-Etienne
42055 Saint-Etienne, France

Isabelle Quére, MD
Saint Eloi University Hospital
34295 Montpellier, France

Alain Leizorovicz, MD
Faculté Laennec
69376 Lyon, France

Potential Conflicts of Interest: None disclosed.

References


6 July 2010 Annals of Internal Medicine Volume 153 • Number 1 63
TO THE EDITOR: The recent articles by Baggish and colleagues (1) and Wheeler and colleagues (2) indicating the additional value of electrocardiography (ECG) in detecting serious cardiovascular abnormalities and the cost-effectiveness of this addition are important to primary care physicians and parents of young athletes. The addition of ECG to the history and physical examination by nonspecialized clinicians increased the overall sensitivity and negative predictive value to 99.8% and, compared with cardiovascular screening by history and physical alone, saved 2.1 life-years per 1000 athletes at an incremental cost of $88 per athlete. Although the American Heart Association consensus panel (3, 4) does not endorse ECG, what mandatory screening is currently performed in the United States, and at what cost? In Michigan, student athletes in public schools are required to have yearly “sports physical” forms completed and on file in the school’s athletic office to participate in activities. Some of these examinations are performed in mass screening centers, such as auditoriums, and others at individual physician offices. The fees range from $5 to several hundred dollars for routine “physicals.” Most insurance copayments are approximately $20, making the average 4-year high school out-of-pocket fees approximately $80, with much higher insurance costs. There is no requirement for what is examined, and many examinations are brief and done in noisy auditoriums.

Chelsea Community Hospital, in conjunction with physician and staff volunteers, has been performing athletic screening of appropriately 1500 adolescents since 2003. The screening sessions are free and are done once or twice per year. Approximately one quarter of the athletes screened receive limited echocardiography. We also offer ECG and limited echocardiography on all weekdays for $55. This was initiated to help prevent sudden death in adolescents involved in high school sports, which was a direct result of one of the author’s children being involved in high school sports.

As a parent, wouldn’t you rather pay $88 once for your high school student to receive effective screening for potential cardiovascular sudden death rather than yearly ineffective and unproven “sports physicals”? This cost is less than that of a pair of athletic shoes. We hope that the American Heart Association will consider the articles by Baggish and colleagues and Wheeler and associates to determine their recommendations. We believe that, at a minimum, all adolescent athletes should have a standard screening questionnaire for conditions related to sudden death in addition to blood pressure recording; cardiac auscultation in the supine and seated position; and because of this new evidence, ECG. If there is a concern about potential for sudden cardiovascular death, limited echocardiography could be considered.

Steven A. Yarows, MD
IHA
Chelsea, MI 48118

Frank A. Smith, MD
St. Joseph Mercy Hospital
Ypsilanti, MI 48197

Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: The description by Drs. Yarows and Smith of an ambitious community-based athlete preparticipation screening service is welcome. Similar programs run by competent, dedicated, and well-intending clinicians exist in many regions of the United States. The sharing of outcomes data from such efforts, particularly those describing diagnostic yield, financial cost, and local incidence of sudden death, is also welcome and will continue to inform scientific opinion.

Our study confirmed the hypothesis that inclusion of 12-lead ECG improves the sensitivity of screening for cardiovascular disease in athletes. However, it does so at a high cost that extends far beyond dollar figures. An ECG-based screening program that falsely identifies 16% (our experience) or 25% (limited echocardiography rate quoted by Drs. Yarows and Smith) of athletes as having a cardiovascular issue is problematic. Until this shortcoming is addressed, widespread implementation of ECG-based screening may do more harm than good.

More study is needed before U.S. public health recommendations can be effectively revised. Two important areas hold promise. First, ECG criteria for distinguishing athletic cardiac remodeling from true underlying disease must be established. A relevant European consensus document (1) has become available, but we still need criteria based on data rather than opinion. In addition, screening must be studied in a large, multicenter, multination, prospective trial that is powered to determine how different screening options affect the incidence of sudden death.

While we await the necessary work, immediate action can be taken. First, there is important heterogeneity with respect to who performs screening, what constitutes adequate screening, and how the results of screening are managed. Those responsible for overseeing the health of student athletes may wish to start not by rushing to perform 12-lead ECG, but by making every effort to ensure that the current American College of Cardiology/American Heart Association recommendations are adhered to by competent providers. This is best accomplished with more extensive education for clinicians, athletes, and families. In addition, group efforts can and should replace the traditional practice of office-based individualized sport clearance examinations. Group screening...
ing promotes resource concentration and will enable the best care, for the most people, at the lowest cost.

Aaron L. Baggish, MD
Massachusetts General Hospital
Boston, MA 02114

Potential Conflicts of Interest: None disclosed.

Reference

Clinical Observations

Clinicians and Nutraceutical Use in Cardiology Patients: Ignorance and Neglect

Background: Half of all patients worldwide, and especially those with chronic illnesses, use nutraceuticals and nonprescription over-the-counter (OTC) drugs (1, 2). Persons with cardiovascular disease rank foremost in this respect (3). Many patients do not discuss their use of these agents with clinicians (1, 2).

Objective: To evaluate the accuracy of cardiovascular clinicians’ efforts in determining patient use of these agents and to measure clinicians’ attitudes about assessing use of these agents.

Methods: We conducted an institutional review board–approved, prospective, single-blind, observational study of attending cardiology specialists and cardiologists-in-training. A clinical pharmacist observed clinical encounters without interacting with the patient or provider and recorded how the provider asked about nutraceutical and OTC drug use. After the provider left the room, the pharmacist asked the patient about nutraceutical and OTC drug use. At the end of the day, the pharmacist asked providers, “What percentage of time do you ask patients about nutraceutical use and OTC use?” by using a structured 6-item questionnaire that included distracter questions. We classified OTC drugs as agents that were designated and regulated by authorities as a general-sale medication, were available off the shelf, and required no pharmacy handling. We classified nutraceuticals as other agents that were neither food nor drugs, including herbal and nutritional supplements.

Results: We observed 21 providers during 78 patient encounters (3.7 visits per provider; range, 1 to 6). Ten were attending physicians (40 patient encounters; 1 to 26 years in academic practice at a rank of assistant professor or higher), and 11 were trainees who saw patients in collaboration with an attending physician (38 patient encounters). Of the 78 patients, 40 were men and 38 were women (mean age, 58 years [SD, 14]), 41 were white, 35 were African American, and 2 were Asian. The pharmacist identified 54 patients who together were using 86 nutraceuticals and 45 OTC drugs (mean, 2.4 per patient [SD, 2.1]). Providers detected nutraceutical or OTC use during 7 encounters. The pharmacist observed providers asking patients about nutraceutical and OTC drug use during 2% of encounters (range, 0% to 20%) for attending physicians and 16.3% for trainees (range, 0% to 50%). Providers estimated that they asked patients about nutraceutical and OTC drug use during 47.1% of encounters (median, 50%; range, 10% to 90%): 57.0% for attending physicians and 38.2% for trainees. Overall, 5 providers (1 attending and 4 trainees) asked at least 1 patient about nutraceutical or OTC use (Figure).

Discussion: Use of nutraceuticals and OTC drugs in our ambulatory cardiology clinic is high and is largely ignored by clinical providers. It is possible that providers neglect evaluation of these agents because they consider them innocuous; lump them with dietary measures and lifestyle interventions; or consider them to be “natural” and, therefore, safe and effective.

Conclusion: Clinicians should use a structured approach for identifying patient use of nutraceuticals and OTC drugs.

OTC = over-the-counter.
Successful Treatment of Generalized Pustular Psoriasis With the Interleukin-1-Receptor Antagonist Anakinra: Lack of Correlation With IL1RN Mutations

**Background:** Generalized pustular psoriasis (GPP) is a multisystemic inflammatory disease with disseminated pustular skin involvement that often responds poorly to currently available treatments, including tumor necrosis factor (TNF)-α inhibitors (1). The recent identification of mutations in the IL1RN gene coding for the interleukin (IL)-1 receptor antagonist in an autoinflammatory syndrome with pustular skin involvement provides a rationale to investigate the contribution of the IL-1β pathway to the pathogenesis of GPP (2).

**Objective:** To report the efficacy of the recombinant IL-1 receptor antagonist anakinra and to search for IL1RN gene mutations in 2 patients with GPP.

**Methods:** The IL1RN isoform-1 gene (GenBank accession number NM_173842) was sequenced. The 6 exons and flanking intronic sequences were amplified by polymerase chain reaction using specific primers. Both DNA strands were sequenced by using the Big Dye Terminator Cycle Sequencing Ready Reaction Kit (PE Applied Biosystems, Courtaboeuf, France). We measured serum IL-1β and IL-6 with enzyme-linked immunosorbent assay.

**Results:** The first patient was a 45-year-old woman who was admitted for high fever and generalized exanthema and was covered with pustules involving 50% of the body surface area. She had had psoriasis vulgaris since childhood and previously had 6 GPP flares that did not respond to such treatments as infliximab, adalimumab, or etanercept. The skin severity score (1) was 8, leukocyte count was $21.8 \times 10^9$ cells/L, and C-reactive protein level was 329 mg/L. Anakinra therapy was started at 100 mg/d for 7 days. Fever completely remitted on day 2, and the skin severity score decreased to 1 (Figure). At day 4, the C-reactive protein level was 15 mg/L. The patient was discharged on day 10, with the skin severity score stabilized at 2.

The second patient was a 31-year-old woman who was admitted in May 2009 for high fever, exanthema, and pustules involving 50% of body surface area. Psoriasis vulgaris and localized pustular psoriasis emerged in 2007; her first GPP flare remitted with difficulty in 2008, requiring isotretinoin, cyclosporine, and adalimumab. Treatment with anakinra was started at 100 mg/d. Apyrexia was observed on day 5, without the development of new pustular lesions. After initial improvement, 2 limited flares occurred, with pustules affecting less than 27% of body surface area that remitted within 3 days. Anakinra therapy was withdrawn because of bacteremia secondary to skin colonization with Staphylococcus aureus. The patient was discharged 1 week later and then readmitted for a new GPP flare. All symptoms remitted again after anakinra therapy was reintroduced.

**References**

**Figure.** Clinical evolution of the first patient.

A. Confluent inflammatory erythema covered with pustules involving the neck and the upper thoracic anterior area before the patient started anakinra therapy.

B. Substantial remission of erythema and pustules with peripheral desquamation 4 days after the patient started anakinra therapy.
No nucleotide change along the *IL1RN* gene coding sequence was found in patient 2. In patient 1, we identified several nucleotide variations, but did not consider them pathogenic because they were found in healthy control participants and most are reported as polymorphisms in the National Center for Biotechnology Information and Ensemble databases.

In patient 2, IL-6 and IL-1β serum levels were increased during the flare to 283 ng/L (normal, 0 to 8.6 ng/L), and 22.4 ng/L (normal, 0 to 15 ng/L), respectively, and decreased to 17.6 and 14 ng/L after anakinra therapy.

Discussion: Investigation of the role of IL-1 in GPP pathogenesis has thus far been limited (3, 4). In mice, transgenic overexpression of IL-1 agonists combined with invalidation of antagonists leads to cutaneous inflammation sharing common features with GPP, whereas expression of IL-1 agonists and IL-1–induced IL-6 and IL-8 have been found to be increased in human pustular psoriasis and psoriasis vulgaris (3, 5). The efficacy of anakinra therapy supports the role of IL-1 in the GPP inflammatory cascade. Because we did not detect any mutation in the *IL1RN* locus coding sequences, GPP pathogenesis probably involves inflammatory pathways other than the IL-1β to IL-1 receptor, which might be at least partly antagonized by anakinra. Likewise, GPP seems to differ from other IL-1–dependent autoinflammatory syndromes, such as the recently deciphered deficiency of the IL-1 receptor antagonist (2).

Conclusion: In patients with GPP, IL-1–targeted inhibition with anakinra may be an appealing alternative. However, the risk–benefit ratio remains to be investigated in further trials.

**References**


