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.

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Potential Conflicts of Interest: None disclosed.

References
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.

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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.

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Potential Conflicts of Interest: All authors are co-principal investigators of KEEPS (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.

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Potential Conflicts of Interest: None disclosed.

References
Subsequent reanalyses of the observational data (2,3) suggest that an early harmful effect of estrogen plus progestin 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 progestin 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 progestin 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.

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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?

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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 thromboembolitis, 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 thromboembolitis 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 thromboembolitis. 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.

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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 heterogenic 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.

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Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: 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 Behc¸et 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).

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Potential Conflicts of Interest: None disclosed.

References
Should Electrocardiography Be Used in Cardiovascular Screening of High School Athletes?

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 inefficient 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 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.

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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, multilocation 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 screen-

References

Potential Conflicts of Interest: None disclosed.
ing promotes resource concentration and will enable the best care, for the most people, at the lowest cost.

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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.

Figure. Self-reported vs. observed percentage of encounters in which the trainee or attending provider asked about nutraceutical and OTC use.
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.

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.

References
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 Ensembl 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.

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References

CORRECTION

Correction: Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

In the corresponding author address for the article by Weng and colleagues (1), Dr. Zhao’s affiliation is Beijing Chaoyang Hospital. In the online Appendix, the second line of the first paragraph should have read: “We therefore used a Bayesian hierarchical (random-effects) meta-analytic model to analyze these 31 studies.” This has been corrected online.

Reference