Notice of Retraction: Ramipril Markedly Improves Walking Ability in Patients With Peripheral Arterial Disease

TO THE EDITOR: Following admission of data fabrication by the first author, Anna Ahimastos, in a similar study of ramipril for patients with peripheral arterial disease (1), Baker IDI Heart and Diabetes Institute conducted an independent investigation of the trial, published in Annals in 2006 (2). Based on that investigation and our own analysis, we, the undersigned authors, wish to retract this article due to an inability to adequately validate primary data sources. Dr. Ahimastos maintains the integrity of the data and validity of reported results and has declined to answer additional questions. The investigation did not find culpability on our part, and we apologize unreservedly to the editors, reviewers, and readers of Annals of Internal Medicine. Given the clinical indications for ramipril and other angiotensin-converting enzyme inhibitors, we believe there is no risk that these possibly invalid trial data harmed trial participants or patients with peripheral arterial disease taking ramipril.

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Editor’s Note: The above-named authors agreed to this retraction. Attempts on the part of the journal office to obtain input regarding this retraction from Dr. Ahimastos, first author of the retracted article, were unsuccessful.

References

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[Summary for Patients]
This summary for patients (1) was based on an article that has been retracted (2, 3); as a result, the summary is also being retracted.

References


Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

TO THE EDITOR: Smith and colleagues (1) conclude that “trials of . . . counseling therapies and graded exercise therapy [GET] suggest benefit for some . . . whereas evidence for . . . harms is insufficient.” As a physician bedridden with myalgic encephalomyelitis (ME) for more than a decade who is totally dependent on others, all thanks to a major relapse caused by GET, I am in a unique position to answer how harmful GET and cognitive behavioral therapy (CBT) really are. The basis of these therapies is false illness beliefs, meaning that it is all in the mind. These beliefs ignore all of the evidence that ME is a physical disease, such as intracellular immune dysfunctions, which not only restrict exercise capacity but also worsen with exercise (2).

The main characteristic of ME is an abnormally delayed muscle recovery after doing trivial things, not chronic fatigue, and GET and CBT force you to ignore your symptoms to exercise your way back to full fitness. If you do that, you exceed your limit and cause a relapse, and the more you exceed your limit, the bigger the relapse and the less likely you are to recover from it. Many patents with this condition have become homebound and bedridden because of a major relapse caused by GET, and we will get our health and independence back only if we receive proper medication.

The Norwegian rituximab studies suggest that ME is an autoimmune disease and that two thirds of respondents are still in remission at 36-month follow-up (3). The ME Association recently published a big study that concludes that CBT, which increases the risk for worsening symptoms, has no role and that GET is harmful and should be discontinued immediately (4). Falk Hvidberg and associates recently found that patients with ME/chronic fatigue syndrome (CFS) have the lowest health-related quality of life of those with 21 conditions that were evaluated, including chronic renal failure, stroke, and lung cancer (5). In reality, only 2 sorts of patients with ME can participate in GET: a few in whom the disease is in remission and those who are misdiagnosed. In all other patients, GET causes severe relapses and breaches the do-no-harm principle of medicine.

Falk Hvidberg and associates’ alarming findings show that CBT and GET, tried by most patients with ME, are not effective. They also show that effective medication for this debilitating disease is urgently needed so that we can get our health and independence back, stop receiving benefits, and return to work.

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TO THE EDITOR: Smith and colleagues (1) conclude that “trials of...counseling therapies and graded exercise therapy [GET] suggest benefit for some patients meeting case definitions for CFS, whereas evidence for...harms is insufficient.” Although we support the general conclusion of benefit with these treatments, we suggest that some aspects of this review may be misinterpreted. First, the most frequently tested behavioral intervention has been CBT, which aims to reduce symptoms and improve functioning. Considering this as “counseling,” which has different objectives and content, would be unusual. One would not combine different types of medicines in a review; why do so with therapies? A review that combines counseling and CBT simply dilutes the efficacy of CBT, which has been amply shown in several previous meta-analyses (2).

Second, evidence of harm caused by GET is minimal; a Cochrane systematic review of 8 trials of exercise therapy for CFS published this year concluded that “no evidence suggests that exercise therapy may worsen outcomes” (3). Suggesting evidence of harm by stating that “1 trial reported...significantly more serious adverse events...and more nonserious adverse events...in the GET versus comparison groups” (1) without mentioning that serious adverse events were independently judged to be unrelated to the intervention and that the differences between nonserious adverse events was not statistically significant is potentially misleading. Adding that “in a trial of GET, 20% of patients declined to repeat exercise testing because of perceived harm of testing” (1) encourages further misunderstanding by failing to state that the exercise testing was not part of the therapy and that similar proportions of patients in the control group also declined or did not finish exercise testing (4). There is a world of difference between the effects of maximum exercise testing and GET. It is important not to overemphasize the harms associated with an effective treatment when so few others are available.

Finally, the authors conclude that we need trials that analyze patients who meet different case definitions; we agree, and these have already happened. My coauthors and I (5) found no statistically significant differences in the efficacy of CBT and GET in subgroups of patients meeting Oxford criteria for CFS as well as the Centers for Disease Control and Prevention (CDC) criteria for CFS or ME.

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References

TO THE EDITOR: I read Smith and colleagues’ review (1) with interest and would like to make 2 points in response to White and associates’ comment. First, counseling, with its more modest, noncurative goal of helping patients adapt to limitations imposed by chronic disease and disability, does not posit a primary causative role for cognitive behavioral factors.
However, the cognitive behavioral model for CFS does posit such a role and hence claims curative potential by modifying those factors through CBT (2).

No clinical trials are available that directly compare counseling and CBT for CFS, but 2 trials do so for chronic fatigue, a defining symptom of this condition. In 2001, Ridsdale and coworkers (3) reported "equivalent" therapeutic outcomes for counseling and CBT and suggested that the choice between these approaches depends on nontherapeutic factors, such as cost and accessibility. In 2012, Ridsdale and coworkers (4) found no difference among counseling, GET, and usual care plus a CBT booklet. Smith and colleagues (1) were also unable to distinguish between counseling and CBT for efficacy. These results, the low-moderate effect sizes of CBT and GET for CFS, the predominantly subjective self-report basis of those effects and their general discordance with the more objective outcome measures (particularly for CBT), and the principle of parsimony all question the value of assuming a primary causative role for cognitive behavioral factors in CFS (1, 2).

Second, if patients with CFS are already operating at or near maximum physical capacity, then they may not find a "world of difference between the effects of maximum exercise testing and GET." In clinical trials, patients may be, by necessity, substituting formal exercise therapy for other activities without increasing their overall fitness or physical activity. Alternatively, patients may not be adhering to the therapy protocol or accurately reporting that fact. Both possibilities could also affect harms reporting.

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2. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al; PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377:823-36. [PMID: 21334061]

TO THE EDITOR: In their comment on Smith and colleagues' review (1), White and associates state that "My coauthors and I found no statistically significant differences in the efficacy of CBT and GET in subgroups of patients meeting Oxford criteria for CFS as well as the CDC criteria for CFS or ME." However, the ad hoc application of these case definitions in the PACE (Pacing, Graded Activity and Cognitive Behaviour Therapy: A Randomized Evaluation) trial may undermine the reliability of those subgroup analyses. All trial participants were first screened using the Oxford CFS criteria and then further stratified into subgroups meeting modified versions of the CDC CFS criteria and London ME criteria. The Oxford criteria are not entirely compatible with other case definitions because they uniquely require that fatigue be the dominant symptom (2, 3), and the medical assessments in the trial may have excluded clinical characteristics of ME that other case definitions allow.

The PACE trial only counted additional CFS symptoms (including postexertional malaise) over the previous week instead of 6 months as required by the CDC criteria (3). Evans and Jason (4) studied different recall time frames for each of the 8 additional CDC symptoms and reported that the optimal time frame for reliable reporting was 6 months for postexertional malaise, unrefreshing sleep, memory/concentration difficulties, muscle pain, headaches, lymph node pain, and sore throat and 1 month for joint pain. They conclude that investigators interested in assessing CFS symptoms should account for recall time frame.

Although the modified version of the rarely used London ME criteria requires postexertional fatigue orfatigability, it does not require postexertional malaise or the fluctuation of other important symptoms usually worsened or precipitated by physical or mental exercise, which the original version stipulated was “absolutely characteristic” (www.meassociation.org.uk). Goudsmit, 1 of the authors of the original London ME criteria, has publicly rejected the version used in the PACE trial as flawed, incomplete, and nonrepresentative (5).

In conclusion, none of the diagnostic criteria as applied in the PACE trial adequately measured or required postexertional symptomatology. The Institute of Medicine recently released new diagnostic criteria for CFS that require postexertional malaise, unrefreshing sleep, and cognitive impairment or orthostatic intolerance; it noted that participants in therapy trials have not met these requirements. The full report on the Pathways to Prevention Workshop called for the obsolete Oxford criteria to be retired because, as Smith and colleagues note, they can result in the "selection of participants with other fatiguing illnesses or illnesses that resolve spontaneously" (1).

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References

TO THE EDITOR: In their comment on Smith and colleagues' review (1), White and associates state that "My coauthors and I found no statistically significant differences in the efficacy of CBT and GET in subgroups of patients meeting Oxford criteria for CFS as well as the CDC criteria for CFS or ME." However, the ad hoc application of these case definitions in the PACE (Pacing, Graded Activity and Cognitive Behaviour Therapy: A Randomized Evaluation) trial may undermine the reliability of those subgroup analyses. All trial participants were first screened using the Oxford CFS criteria and then further stratified into subgroups meeting modified versions of the CDC CFS criteria and London ME criteria. The Oxford criteria are not entirely compatible with other case definitions because they uniquely require that fatigue be the dominant symptom (2, 3), and the medical assessments in the trial may have excluded clinical characteristics of ME that other case definitions allow.

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In conclusion, none of the diagnostic criteria as applied in the PACE trial adequately measured or required postexertional symptomatology. The Institute of Medicine recently released new diagnostic criteria for CFS that require postexertional malaise, unrefreshing sleep, and cognitive impairment or orthostatic intolerance; it noted that participants in therapy trials have not met these requirements. The full report on the Pathways to Prevention Workshop called for the obsolete Oxford criteria to be retired because, as Smith and colleagues note, they can result in the "selection of participants with other fatiguing illnesses or illnesses that resolve spontaneously" (1).

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References
TO THE EDITOR: We concur with Smith and colleagues (1) that GET can harm some patients with ME/CFS. However, we believe that the benefits of this therapy would have been reduced and the assessment of harms even greater if the following points had been considered.

First, the authors recognized that the nonspecific nature of the Oxford criteria might recruit participants “with other fatiguing illnesses or illnesses that resolve spontaneously” (1), yet they analyzed studies using these criteria together with those using the Fukuda criteria. This is similar to lumping persons who have congestive heart failure, chronic obstructive pulmonary disease, and pneumonia together because all 3 diagnoses share shortness of breath as a symptom. Assessing trials using the Fukuda and Oxford criteria separately and then comparing those findings with the combined results would have been more informative. Darbishire and associates (2) found that fitting the Fukuda criteria was the factor most predictive of a poor outcome when a GET or CBT regimen was applied to a group of participants with chronic fatigue.

Second, Núñez and coworkers are classified in Appendix Table 1 as not reporting any harms (1). However, their study found not only that the combined GET/CBT intervention had no benefit but that these treatments caused a statistically significant decline in physical function and increase in bodily pain scores as measured by the 36-item Short-Form Survey at 12 months.

Third, Smith and colleagues appropriately suggest that future research should strive to include the input of patients and advocates. Because their review was based on clinical trials, however, it did not include clinician and patient experiences outside of trials. On average, 50% of thousands of patients internationally have reported worsened health due to treatments involving exercise (3). Clinicians specializing in ME/CFS do not recommend GET and instead advise patients to balance their active periods with rest breaks (4). This cautious attitude is supported by studies (5) showing that patients with ME/CFS do not respond to or recover from physical activity in the same way as healthy persons or those with other medical conditions.

As they do with any illness, clinicians need to tailor treatments to the individual patient. If patients describe an exacerbation of symptoms and no improvement with exercise-related therapies, clinicians should consider that there is a problem and discontinue the treatment rather than attribute these reports to low motivation, distorted thinking, or exaggeration.

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References

TO THE EDITOR: We concur with Smith and colleagues that evidence on harms for such therapies as GET for ME/CFS is insufficient (1, 2). Trials of GET for these conditions have focused on efficacy measures, which do not provide good information on whether adverse events occurred (2). A systematic review by Marques and associates assessed the reporting of “treatment side effects” in 16 randomized, controlled trials (3). Eleven were allocated the lowest mark, with only 1, the PACE trial, awarded the top mark (3, 4).

One randomized, controlled trial is generally seen as insufficient to make firm recommendations. Moreover, questions remain about the level of GET adherence in the PACE trial: The only reported measure of treatment adequacy was the number of appointments attended, not the type, intensity, or duration of activity/exercise performed each week. If participants dutifully adhered to the exercise program, one would not expect no improvement in fitness in the GET group as has been reported (4). If participants do not take their medication in a trial, it will not yield reliable information on safety; similarly, if participants do not adhere to an exercise regimen,
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good information will not be obtained about the safety or harms of adhering to the intervention. A previous review of 3 trials of graded activity-oriented interventions for CFS found that, after treatment, intervention participants had not actually increased their activity levels (objectively measured using accelerometers) compared with control participants (5).

Data from outside of randomized, controlled trials can be useful to assess the safety or harms of interventions (2). A clinical trial can represent a somewhat artificial environment, so outcomes may not correspond directly to those in routine practice (2). One investigator (T.K.) previously reviewed the data from 8 surveys of patients with ME/CFS from 4 countries (2). Fifty-one percent of survey respondents (range, 28% to 82% [n = 4338]) reported that GET worsened their health. Such findings, along with the aforementioned poor reporting of harms in trials of GET for ME/CFS and the lack of evidence about adherence to the intervention in the trial with better harms reporting, mean that we should not rush to accept any claims that GET has been found to be safe for patients with ME/CFS.

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References

IN RESPONSE: We thank the authors for their comments and Dr. Speedy for sharing his personal experience. Regarding Dr. White and colleagues’ statements about the harms of exercise, we acknowledge that exercise testing differs from graded exercise programs. However, patients may consider both forms of exercise harmful. To clarify the results of Moss-Morris and associates’ trial, whereas 44% of participants in the intervention group declined repeated exercise testing, 20% did so because of their perception of harm (1). Also, although the Cochrane review did not identify harms of exercise, the authors drew similar conclusions to ours, stating that, “limited information makes it difficult to draw firm conclusions about the safety of exercise therapy” (2).

To address Dr. Chu and coworkers’ comment about safety data in Nuñez and colleagues’ trial, we agree that the intervention group reported a decline in physical function and increase in pain. However, the trial reported within-group differences and not between-group differences (3), which are necessary to support results of comparisons of interventions in the trial. Their statement about the importance of analyzing data on the basis of case definitions used for inclusion in trials is consistent with our approach. For example, in the CBT trials using the physical function item of the 36-item Short-Form Survey as an outcome measure, the 2 studies using the Oxford criteria indicated improvement, whereas the 2 using the CDC criteria reported no improvement.

We also agree with Dr. White and colleagues that combining counseling and CBT trials in a meta-analysis may dilute the individual effectiveness of each intervention, which is why our meta-analysis included only trials of CBT.

We excluded from our analysis the studies referenced by Dr. Chu and coworkers and Mr. Kirby about the comparative effectiveness of CBT and GET and predictors of outcomes because they included participants with chronic fatigue rather than ME/CFS (4, 5). One of the studies found that 31% of their fatigued participants met criteria for CFS (according to the CDC Fukuda criteria [5]). Although those with CFS had more fatigue and functional impairment than other participants, the authors did not compare case definitions or evaluate outcomes for those with CFS on the basis of intervention.

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