

DPP-IV INHIBITOR-ASSOCIATED ARTHRALGIAS

To the Editor:

One of the relatively newer classes of medication used to treat diabetes are the dipeptidyl peptidase-IV inhibitors, which are increasing in use due to their efficacy, tolerability, and the option to use them in renally impaired patients. Here, we report a patient, a practicing physician, who developed severe arthralgias on the DPP-IV inhibitors sitagliptin and saxagliptin.

A 48-year-old Indian physician with a history of type 2 diabetes mellitus who was previously well-controlled on metformin (hemoglobin A1C [HgbA1c] <6.5%), noticed his HgbA1c trending upward. Sitagliptin was added, and 2 weeks later he developed morning stiffness and progressively worsening pain and erythema of his metacarpal joints. A rheumatologic work-up was negative for connective tissue disease. The severe pain in his joints was debilitating; he had difficulty writing or typing, driving, and walking up stairs, to the point that he contemplated filing for disability. Six weeks after starting sitagliptin, he developed a diffuse rash that resolved 48 hours after discontinuing the medication, and 6 weeks later there was marked arthralgia improvement. He then began taking saxagliptin, which similarly precipitated arthralgias after a few weeks. Again, all symptoms resolved after discontinuing the medication.

Arthralgia is a nonspecific symptom that may be chemically induced or related to an underlying autoimmune disorder. Sitagliptin is well tolerated with a low side effect risk profile (1), but there is a paucity of reports of arthralgias associated with sitagliptin. In our patient, serologic evaluation did not reveal any signs of autoimmune disease. Medication-induced arthralgias comprise 2 types of adverse drug reactions: typical and predictable and uncommon and unpredictable (2). The unpredictable reaction is autoimmune-mediated by IgE, IgG, or T cells (2). There are two reported cases in the Japanese population with demonstrated causal associations between the use of DPP-IV inhibitors and the development of remitting seronegative symmetrical synovitis (3). Although the cause and effect relationship was not definitive in this case, the temporal relationship to medication initiation was highly suggestive. One should be aware of the possible association of DPP-IV inhibitors and severe arthralgias and discontinue the medication before pursuing potentially costly evaluations.

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DISCLOSURE

The author has no multiplicity of interest to disclose.

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LEVODOPA-CARBIDOPA TREATMENT AND FALSELY HIGH URINARY DOPAMINE LEVELS

To the Editor:

A 69-year-old African-American man was seen in the Endocrine Clinic at the Baltimore Veterans Administration Hospital for evaluation of an adrenal nodule. He had a history of neurofibromatosis type 1. An abdominal computed tomography (CT) scan had been performed for evaluation of abdominal pain and showed a 3-cm right adrenal mass. Laboratory studies showed plasma free metanephrines of 539 pg/mL (normal, 0 to 205 pg/mL), and normetanephrines of 449 pg/mL (normal, 0 to 148 pg/mL). The 24-hour urine showed a creatinine level of 0.6 g/24 hours (normal, 0.6 to 2.5 g/24 hours), epinephrine of 6 µg/24 hours (normal, 0 to 20 µg/24 hours), and norepinephrine of 18 µg/24 hours (normal, 15 to 100 µg/24 hours). An abdominal magnetic resonance imaging (MRI) scan showed a 2.6 × 1.8 cm right adrenal nodule that was bright on T2, suspicious for pheochromocytoma, which did not show any drop in signal on the opposed phase images. A laparoscopic right adrenalectomy was performed and pathology confirmed a benign pheochromocytoma.

Six months after discharge, the patient was readmitted with nausea, vomiting, and dehydration. Abdominal CT and MRI scans showed multiple small-bowel masses. Plasma and urine metanephrines were 205 pg/mL (normal, 0 to 205 pg/mL) and 61 µg/24 hours (normal, 90 to 315 µg/24 hours), respectively, but his 24-hour urine dopamine was elevated twice, 1,994 and 1,361 pg/mL (normal, 0 to 30 pg/mL). Because of concern for a malignant dopamine-secreting pheochromocytoma, an octreotide scan was performed, which was negative. Endoscopic ultrasound and small-bowel biopsy were negative for malignancy. Prior to this admission, the patient had been diagnosed with Parkinson's disease after complaining of tremor and bradykinesia, and had been started on L-dopa 25/100 mg three times a day. His L-dopa was stopped for a week and a repeat 24-hour urine dopamine was undetectable.

The use of L-dopa for Parkinson's disease in our case resulted in markedly elevated urine DA levels, which in combination with small-bowel masses, raised concern for metastatic pheochromocytoma. Recent reports in the Parkinson's disease literature have shown significant increases in urinary DA levels of up to 100 times normal in patients treated with L-dopa, with severity related to drug dose (1-3). In our case, the urinary DA level was 40 to 60 times higher than normal, enough to raise suspicion of pheochromocytoma recurrence. Clinicians should be aware of the potentially dramatic effect of L-dopa on urinary catecholamines as a confounder in the evaluation of pheochromocytoma.

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THE ETHICS AND VALUE OF PROFESSIONAL MEDICAL WRITING ASSISTANCE

To the Editor:

We, the Global Alliance of Publication Professionals (www.gappteam.org), were mostly pleased to read the recommendations by Weber et al on how physicians should collaborate with industry (1). We felt that their article was sensible and measured in recognizing both the value of such collaborations and the risks inherent in mixing science and commercial interests, and their recommendations for minimizing such risks were welcome.

However, we are disappointed with some of the recommendations in their section on publications concerning the use of professional medical writers. Weber et al describe professional medical writing assistance as "ghostwriting," which is an unfortunate confusion of two separate things.

Ghostwriting is widely agreed to be unethical, and Weber et al are quite correct in their recommendation that physicians should play no part in it. As professional medical writers, we condemn ghostwriting; so, too, do associations representing professional medical writers (e.g., the American Medical Writers Association, the European Medical Writers Association, and the International Society for Medical Publication Professionals). Ghostwriting is defined as a contribution to a manuscript by someone whose role is not disclosed to the reader. A ghostwriter may be a junior researcher, a colleague, or someone from an unethical writing company. The prevalence of ghostwriting appears to be decreasing (2), and those who know about guidelines for ethical medical writing practices are significantly less likely to ghostwrite (2).

While ghostwriting is unquestionably unethical, this does not mean that physicians should decline support from external writing agencies, merely that they should be satisfied that the writers from those agencies work in accordance with guidelines for ethical publication, such as those from the European Medical Writers Association (3), so that, unlike ghostwriters, their role is transparently disclosed. Professional medical writing is an ethical, legitimate, and much needed service. The need for and value from professional medical writers has been recognized by medical journal editors and regulators. As we highlight in our recent editorial, evidence—not just opinion—supports the use of professional medical writers (4). The Association of Clinical Researchers and Educators (ACRE) Statement failed to mention that manuscripts prepared with medical writing support are less likely to be retracted for misconduct, more likely to comply with best-practice reporting

guidelines, and are accepted more quickly for publication (4). What evidence does ACRE have to actively discourage academics from using professional medical writing assistance?

We believe it would be highly counterproductive for physicians to decline support from professional medical writers at external writing agencies. It is hard enough to ensure that all research is published even without help, and, as we have argued (4), seeking help with writing publications is likely to be an important weapon in the fight against the pervasive and persistent unethical practice of non-publication.

DISCLOSURE

I am a former president of the European Medical Writers Association, and I run a company that provides ethical professional medical writing services. My fellow GAPP members are also active medical writing professionals.

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IN RESPONSE:

We are pleased that the Global Alliance of Publication Professionals (GAPP) found overall value in the recommendations of the ACRE Writing Committee regarding relationships between physicians and industry. We understand the concern that publication professional have with the term “ghost writing,” and agree that this term is often misused. In fact, the heading of the relevant section of

our recommendations is “Editorial Assistance,” and we preferentially use this description, although noting that the pejorative term “ghost writing” is sometimes used. The explanation by Dr Jacobs of why this expression can be inappropriate and misleading is most helpful, and we appreciate the clarification.

We also accept the argument by Dr Jacobs that articles prepared with professional writing support are more likely to comply with journal submission requirements and be accepted more quickly for publication than those prepared without such support. We do not deny these claims. The ACRE Guidelines acknowledge that this type of assistance, if managed rigorously, can be valuable in writing derivative or review articles, and we also note that external writers with appropriate expertise can make valuable contributions to relevant sections of original reports that require specialized technical input.

The main issue lies with the primary writing of original research reports. ACRE believes that this should remain the responsibility of the investigators who conducted the research; after all, these are the individuals who developed the study’s underlying hypothesis and participated actively in its design and in analyzing its data, interpreting its findings, and providing context for the conclusions. By and large, academic physicians who wish to be regarded as responsible investigators should be able to contribute to these tasks and describe them accurately and effectively in writing. At the same time, we consider authorship to be a complex and nuanced activity, particularly in the context of reporting the results of major scientific research projects, and therefore rigid definitions of authorship should be avoided.

There are many critical roles for professional medical writers who provide editorial input, and those of us who have worked with them can attest to their skill and integrity. At the same time, physicians must not sidestep their own responsibilities in reporting their work.

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The authors have no multiplicity of interest to disclose.

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CLARIFICATIONS REGARDING ACCME STANDARDS

To the Editor:

We appreciate that Dr. Weber and colleagues (1) recognize that the Accreditation Council for Continuing Medical Education (ACCME) requirements concerning commercial support of CME activities are “stringent.” They are correct when they say that many CME activities accredited in the ACCME system (referred to as accredited CME) do not receive commercial support; 79% of activities offered by ACCME-accredited providers do not receive commercial support (2).

However, we need to correct some misrepresentation of our accreditation system. The article says that commercially supported activities are “often” jointly planned by medical education companies and accredited providers. Our data show that 35% of commercially supported activities are offered by nonaccredited organizations in joint sponsorship with accredited providers (7% of all ACCME-accredited CME).

Accredited CME providers must ensure that all decisions regarding CME activities are made free of industry control, including the choice of faculty and content selection and presentation. Faculty members are required, not “strongly encouraged,” to ensure that content is accurate and based on scientific evidence. The accredited provider controls the content. The presence of commercial support does not affect the content of accredited CME.

The article states that programs that do not receive commercial support “do not encompass physician/industry relationships.” This perception is mistaken. Even when there is no commercial support, faculty, authors, and CME committee members may have relationships with industry. The ACCME Standards for Commercial Support: Standards to Ensure Independence in CME Activities (3) mandate that *all* who are in a position to control the CME activity content must disclose all relevant financial relationships with industry to the accredited provider.

The authors’ recommendation that “standard acknowledgment of support procedures should be applied” even for non-commercially supported CME activities is not a high enough standard. Since 2004, accredited CME providers have been required to go beyond disclosure. They must implement strategies for identifying and resolving conflicts of interest.

The authors’ statement that ACCME rules require that presentations avoid specific products is inaccurate. Rather, presentations must give a balanced view of therapeutic options, and while the use of generic names contributes to this impartiality, the use of trade names is allowable (3).

The ACCME Standards for Commercial Support: Standards to Ensure Independence in CME Activities are

designed to support the free flow of scientific exchange while safeguarding accredited CME from commercial influence and product promotion. CME must serve health professionals’ learning and practice needs, as well as the public interest.

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IN RESPONSE:

We thank Dr Kopelow for his comments on the Association of Clinical Researchers and Educators (ACRE) Guidelines regarding continuing medical education (CME).

It should be emphasized that the primary focus of our guidelines has been both to draw attention to the multiple ways in which physicians may interact directly with industry, and to provide recommendations on how best to manage these relationships. CME is an important example of our interest. As would be expected, our guidelines are influenced by the perspectives and experience of academic physicians who have engaged in these activities. Our guidelines recognize that relationships between physicians and industry can be relevant to CME programs even in the absence of commercial support, but we are grateful for Dr Kopelow’s further elaboration of the ACCME standards.

I should add that in a climate of increased scrutiny of physician-industry relationships, CME events will be of growing importance in conveying vital clinical information to practitioners, regardless of how these events are supported. It is critical that ACRE and the physician community, together with the ACCME, remain committed to maintaining the integrity and independence of CME.

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The authors have no multiplicity of interest to disclose.

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