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Safety of elobixibat and lubiprostone in Japanese patients with chronic constipation: a retrospective cohort study

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ABSTRACT

Background: We aimed to discuss and compare reported adverse reactions and drug add-ons associated with elobixibat and lubiprostone use in chronic constipation treatment, as the safety of these drugs has not been well examined in post-marketing clinical settings.

Research Design and Methods: In this retrospective cohort study, using records of community pharmacies in Japan, we identified new users of elobixibat and lubiprostone. The Japan Pharmaceutical Association sent questionnaires regarding baseline and event data to community pharmacists. The incidence of events and hazard ratio (HR) associated with the study drugs were evaluated.

Results: New users of elobixibat (n = 979) and lubiprostone (n = 829) were identified (mean age: 74 and 77 years; females: 59% and 53%, respectively). Although the crude risk ratio of adverse events for elobixibat was 0.79 (95% confidence interval: 0.63–0.99), there was no significant difference in the HR for any of the common events, including drug add-ons (n ≥ 5), compared with those for lubiprostone.

Conclusion: No new safety concerns have been raised in relation to elobixibat and lubiprostone use for treating chronic constipation, although the HR of different events varied. Further larger-scale study is needed as the estimates for events of small numbers were unstable

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1. Introduction

Chronic constipation is a common gastrointestinal condition [1], the prevalence of which ranges from 1.9% to 27.2% in North America [2] and is reportedly higher in females and individuals older than 65 years [3]. The Comprehensive Survey of Living Conditions in Japan reported that the prevalence of constipation symptoms has increased by approximately 1.4 times from 24.5 per 1,000 person-years in 2016 to 34.8 per 1,000 person-years in 2019, and so has the prevalence in the elderly population (65.0 per 1,000 person-years in 2016 to 68.6 per 1,000 person-years in 2019) [4]. As the disease is associated with patients' quality of life [1], mortality, and cardiovascular disease prevalence [5,6], its management with appropriate treatment is important.

Among the laxatives used to treat constipation [7–11], magnesium and stimulant laxatives are widely used in Japan [12]. Recently, novel drugs for chronic constipation have been introduced. Lubiprostone was approved in 2012, and it stimulates chloride secretion via the activation of type-2 chloride channels in the gastrointestinal tract [13]. Elobixibat, which inhibits the uptake of bile acids, was approved in 2018 [14]. Lubiprostone has been marketed in some countries, including the United States, whereas elobixibat is authorized only in Japan as of March 2020. In a retrospective cohort study comparing users of elobixibat and lubiprostone [15], the incidence of nausea in users of lubiprostone 48 μg was 3.4 times higher than that in users of elobixibat 10 mg. The incidence of adverse events caused by elobixibat (9%) was significantly lower than that caused by lubiprostone (15%) with a daily dose of 24 μg. However, as this was a single-center study with an observation period of 2 weeks, the generalizability of the findings may be limited.

Nausea is the most common adverse event associated with lubiprostone use [16], but serious adverse events have been rarely reported in association with elobixibat or lubiprostone use [17,18]. However, monitoring and evaluation of drug safety should be continued in actual clinical settings to identify the differences in the incidence proportion of common adverse events such as diarrhea, abdominal pain, and abdominal discomfort to benefit patients suffering from constipation and ensure adherence to treatment. The aim of this retrospective cohort study involving community pharmacists was to examine the safety of the new drugs elobixibat and lubiprostone post marketing.

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2. Patients and methods

2.1. Study design

This was a retrospective cohort study performed using the new-user design [19]. Drug event monitoring (DEM) by the Japan Pharmaceutical Association (JPA) [20] includes both event monitoring and reported event evaluation. For DEM, the JPA sent paper-based questionnaires (Supplemental) to 48,382 community pharmacies affiliated to the JPA (as of February 2020); pharmacists in 5,562 pharmacies completed the questionnaire. Study patients were then identified from 2,343 pharmacies (Figure 1). The data from the questionnaires were entered into a web-based online report form prepared in advance. When pharmacists entered the data in the online form, the information of individual patients was anonymized using study identification data (ID) for each pharmacy. First, the pharmacists identified new users of elobixibat and lubiprostone using pharmacy records; study patients were those who had newly started taking the study drug in September 2019 after 6 months of non-study drug use; patients who did not visit the pharmacy before February 2019 were excluded. To prevent comparison between patients with chronic constipation of different severities, we restricted our study to patients who did not take either elobixibat or lubiprostone. Although pharmacists in community pharmacies do not have the right to access the medical records of patients in clinics or hospitals, pharmacy records contain data on health insurance; prescription; follow-up during treatment by pharmacists; and demographic characteristics obtained from patients, including allergy, current smoking, alcohol consumption, over-the-counter drug use, comedications, and comorbidities. According to Article 25–2 of the Pharmacists Act in Japan, pharmacists as professional service providers offer a patient or a person caring for the patient the necessary guidance based on pharmaceutical knowledge and monitor the effects of drugs and changes in the patient's physical condition during drug use.

Next, the pharmacists collected the baseline data (demographic data, co-medication [use of anti-hypertensives, anti-diabetics, lipid-lowering drugs, steroids without external use, anti-ulceratives, anti-depressants/hypnotic drugs, anti-Parkinson's drug, dabigatran, and digoxin], comorbidity [hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, and cancer], and a history of admission) for 6 months before the initiation of the study drugs (elobixibat and lubiprostone), along with events data during the follow-up period between September 2019 and December 2019. Whether or not there was a corresponding co-medication or comorbidity in pharmacy records was described in the questionnaire.

2.2. Definition of events

An event in the follow-up period included any suspected drug reaction, unexpected deterioration (or improvement) in a concurrent illness, reasons for stopping the study drug use (if stopped), or adding a new drug (if added). Information on add-on drugs may be used to characterize an event and an improvement in concurrent illness may complement the event regarding drug discontinuation. The adverse events were partially defined using the methodology of Modified Prescription-Event Monitoring (M-PEM) [21]. The pharmacists involved in patient care at the pharmacies determined a suspected event due to a drug and deterioration of or improvement in concurrent illness. We used the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 22.1 to encode reported events [22]. After selecting the lowest level terms in the MedDRA, we converted them to the preferred term level.

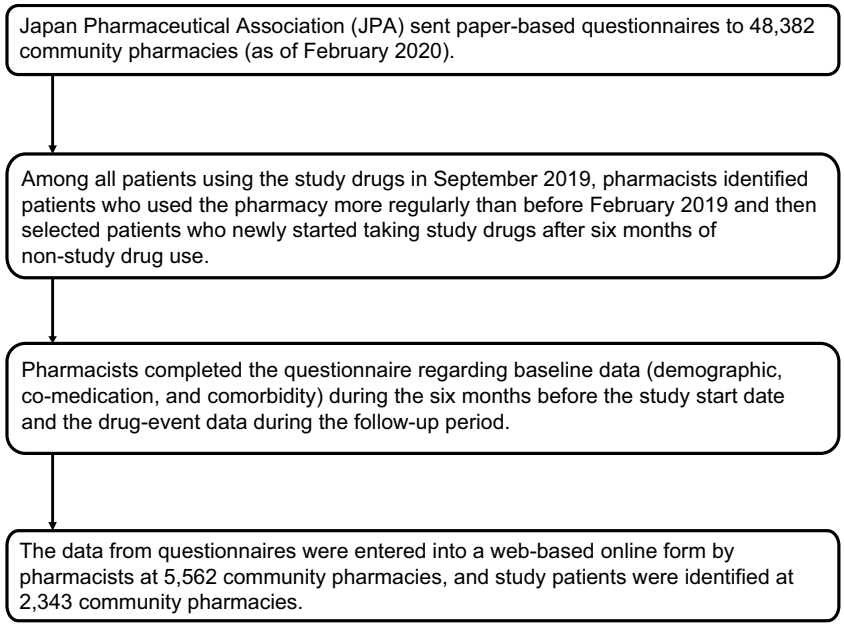

Figure 1. Drug-event monitoring study design and process

2.3. Statistical analysis

Summary statistics describe demographic characteristics, comorbidities, and co-medications of study patients. We present the number and proportion of patients with these covariates at baseline. The standardized difference [23] was used to evaluate the difference in baseline characteristics between the drug groups. The absolute standardized difference greater than 0.1 suggested imbalances between the groups.

The incidence proportion of reported events including discontinuation in patients during treatment with the study drugs was calculated, and the crude risk ratio (RR) was estimated for adverse reactions. The hazard ratio (HR) and its 95% confidence interval (CI) were estimated for common events using the Cox proportional hazards model, with the incidence rate of an event for lubiprostone as the reference. Adjustments for age, sex, anti-diabetic usage, and laxative usage were made using the Cox proportional hazards model. Confounding factors with absolute standardized differences greater than 0.1 were incorporated in the Cox regression model. The observation period for the assessment of an event was defined as the period from the start date of elobixibat or lubiprostone to the incidence date, date of switching or stopping the study drug, last visit date, or 31 December 2019, whichever came first. Results with $p < 0.05$ were considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

2.4. Ethical consideration

This retrospective cohort study adhered to the tenets of the Declaration of Helsinki and the study protocol was approved by the ethics review committee of the JPA (no. 2019–002). The ethics committee waived the need for individual informed consent as the study data were fully anonymized.

3. Results

There were 2,866 prevalent elobixibat users and 4,056 lubiprostone users during the study period. Of these, 979 patients using elobixibat (34%) and 829 using lubiprostone (20%) were identified as new users of the drugs.

3.1. Patient characteristics

Table 1 shows the baseline characteristics of the study participants. The average observation period was approximately 80 days for both drugs. The mean age was 74 years for elobixibat users and 77 years for lubiprostone users; the proportion of females was 58.5% among elobixibat users and 53.1% among lubiprostone users. Age, sex, and anti-diabetic and laxative usage had absolute standardized differences greater than 0.1 between the groups.

3.2. Proportion of discontinuation and improvement

The treatment was discontinued by 26.3% (n = 257) of the elobixibat users and 21.0% (n = 174) of the lubiprostone users, and the crude RR was 1.25 (95% CI: 1.06–1.48) compared with that for lubiprostone. Treatment discontinuation due to improvements was observed in 8.7% (n = 85) of 257 patients in the elobixibat group and 5.9% (n = 49) of 174 patients in the lubiprostone group, and the crude RR was 1.47 (1.05–2.06). Discontinuation due to any suspected adverse drug reaction was reported in 7.3% (n = 71) of patients in the elobixibat group and 8.6% (n = 71) of patients in the lubiprostone group, and the crude RR was 0.85 (0.62–1.16). Among the remaining patients in the elobixibat group, 68 discontinued treatment due to a lack of response (7.0%) and 33 discontinued treatment for unknown reasons (3.4%), whereas in the lubiprostone group, 49 discontinued treatment due to a lack of response (5.9%) and 25 discontinued treatment for unknown reasons (3.0%).

Table 1. Baseline characteristics of new users of elobixibat or lubiprostone.

	Elobixibat (n = 979)	Lubiprostone (n = 829)	Standardized difference
Mean age, years (SD)	74 (15.2)	77 (13.1)	−0.182
Female (%)	573 (58.5)	440 (53.1)	0.110
Mean daily dose	8.7 mg	34.1 μg	-
Mean observation period (days)	81.1	83.6	0.039
Current smoking (%)	78 (8.0)	49 (5.9)	0.081
Alcohol drinking (%)	188 (19.2)	132 (15.9)	0.081
Comorbidity (%)			
Hypertension	536 (54.7)	474 (57.2)	−0.049
Diabetes mellitus	183 (18.7)	188 (22.7)	−0.099
Dyslipidemia	315 (32.2)	268 (32.3)	−0.003
Myocardial infarction	23 (2.3)	34 (4.1)	−0.099
Cancer	75 (7.7)	60 (7.2)	0.016
Co-medication (%)			
Anti-hypertensives	534 (54.5)	491 (59.2)	−0.095
Anti-diabetics	183 (18.7)	193 (23.3)	−0.113
Lipid-lowering drugs	337 (34.4)	278 (33.5)	0.019
Laxatives without elobixibat/lubiprostone	416 (42.5)	411 (49.6)	−0.143
Anti-ulceratives	363 (37.1)	347 (41.9)	−0.098
Steroids, except for external use	31 (3.2)	28 (3.4)	−0.012
Anti-depressants/ hypnotic drugs	303 (30.9)	270 (32.6)	−0.035
Anti-Parkinson's drug	41 (4.2)	36 (4.3)	−0.008
Dabigatran etexilate	3 (0.3)	1 (0.1)	0.040
Digoxin	7 (0.7)	6 (0.7)	−0.001
History of admission (%)	44 (4.5)	45 (5.4)	−0.043

SD, standard deviation

3.3. Proportion of events

The incidence proportion of highly reported events among elobixibat and lubiprostone users is shown in Table 2. Some events, including diarrhea, abdominal pain, and laxative and anti-hypertensive use, were common in both groups. For elobixibat, the proportion of any adverse reaction was 12.4%, with diarrhea (2.9%), abdominal pain (1.4%), and constipation (0.8%) being the most frequent adverse events. Other drugs were added for 19.7% of elobixibat users; of these, the most reported were laxatives without lubiprostone (11.3%), antihypertensives (1.8%), and lubiprostone (1.4%), in that order. The occurrence of any adverse reaction was 15.7% for lubiprostone, with diarrhea (4.0%), constipation (1.5%), and abdominal pain (1.1%) being the most reported adverse events. Other drugs were added to 21.2% of lubiprostone

Table 2. Events* reported frequently for elobixibat and lubiprostone usage.

Event	Number (%) Elobixibat (n = 979)	Lubiprostone (n = 829)
Any adverse reaction	121 (12.4)	130 (15.7)
Diarrhea	28 (2.9)	33 (4.0)
Abdominal pain	14 (1.4)	9 (1.1)
Constipation	8 (0.8)	12 (1.5)
Blood pressure increased	7 (0.7)	3 (0.4)
Soft feces	5 (0.5)	6 (0.7)
Hospitalization	4 (0.4)	7 (0.8)
Nausea	1 (0.1)	6 (0.7)
Any drug add-on	193 (19.7)	176 (21.2)
Laxative except lubiprostone†/ elobixibat‡	111 (11.3) †	97 (11.7) ‡
Anti-hypertensive	18 (1.8)	14 (1.7)
Lubiprostone	14 (1.4)	0 (-)
Elobixibata	0 (-)	11 (1.3)
Anti-ulcerative	11 (1.1)	7 (0.8)
Antacid	6 (0.6)	7 (0.8)
Non-steroidal anti-inflammatory drug	5 (0.5)	7 (0.8)
Antibiotic	5 (0.5)	6 (0.7)
Anti-allergic	5 (0.5)	3 (0.4)
Diuretic	0 (-)	10 (1.2)
Hypnotic	0 (-)	7 (0.8)
Anti-flatulent	4 (0.4)	5 (0.6)
Analgesic	3 (0.3)	5 (0.6)

*n ≥ 5 reported or serious events

users, and the most reported were laxatives without elobixibat (11.7%), anti-hypertensives (1.7%), and elobixibat (1.3%) in that order. The top three adverse events (diarrhea, abdominal pain, and constipation) and added drugs (laxatives, anti-hypertensives, and study drugs) after the initiation of the study drugs were similar. The pre-identified risk of nausea was 0.72% (n = 6) for lubiprostone and 0.1% (n = 1) for elobixibat. Details of events related to hospitalization in both drug groups were unknown.

3.4. Comparison of common events between the drugs

The crude RR of any adverse reaction for elobixibat was 0.79 (95% CI: 0.63–0.99) compared with that of lubiprostone. Table 3 shows unadjusted and adjusted HRs for the common events including the event of drug add-on after the initiation of elobixibat, using those of lubiprostone as the reference. No significant difference was found for each of the common events, including drug add-on (n ≥ 5), between the study drug groups. The adjusted HR of nausea for lubiprostone was 7.09 (0.85–58.8) compared with that for elobixibat, although the CIs were wide.

4. Discussion

Using data from the Japan system of DEM, which plays the dual role of collecting and evaluating reported events, the safety of elobixibat and lubiprostone usage in chronic constipation treatment was examined by community pharmacists. Although the proportion of any adverse reaction associated with elobixibat was 21% lower than that with lubiprostone, the proportion of common events including new drug add-ons and discontinuation owing to any suspected adverse drug reaction in both groups was similar and not significantly different. Events with symptoms of constipation or laxative-associated diarrhea are most commonly reported with the use of laxatives. Furthermore, diarrhea caused by other newly commercialized drugs (e.g. linaclotide) is common [24]; it is also associated with lubiprostone use, although multiple electrolyte abnormalities, hypovolemia, and diarrhea have been reported to be associated with magnesium in conventional drugs [25]. In addition to paying attention to the co-medication and comorbidity related to constipation, better patient care for chronic constipation is recommended, taking into account the expected events.

In randomized placebo-controlled phase II and III trials for elobixibat, the frequently reported adverse events were abdominal pain (12%–26%) and diarrhea (5%–15%), although no severe adverse drug reactions occurred [14,26]. Diarrhea (6%) and abdominal pain (5%) were reported as common events in a retrospective cohort study without a comparator group [27]; these results are consistent with our findings for

Table 3. HR of common events reported in both elobixibat and lubiprostone users.

Event	Unadjusted HR (95% CI) Lubiprostone	Elobixibat	Adjusted [a] HR (95% CI) Lubiprostone	Elobixibat
Any adverse reaction				
Diarrhea	1.0	0.72 (0.44–1.20)	1.0	0.71 (0.43–1.18)
Abdominal pain	1.0	1.34 (0.58–3.11)	1.0	1.28 (0.55–2.99)
Constipation	1.0	0.58(0.24–1.42)	1.0	0.60 (0.25–1.48)
Increased blood pressure	1.0	2.07 (0.54–8.00)	1.0	2.18 (0.56–8.45)
Soft feces	1.0	0.72 (0.22–2.36)	1.0	0.75 (0.23–2.46)
Hospitalization	1.0	0.50 (0.15–1.71)	1.0	0.49 (0.14–1.69)
Any drug add-on				
Laxative	1.0	1.00 (0.76–1.31)	1.0	1.02 (0.77–1.34)
Anti-hypertensive	1.0	1.14 (0.57–2.28)	1.0	1.21 (0.60–2.45)
Anti-ulcerative	1.0	1.38 (0.53–3.55)	1.0	1.35 (0.52–3.52)
Antacid	1.0	0.74 (0.25–2.21)	1.0	0.71 (0.23–2.13)
Antibiotic	1.0	0.74 (0.23–2.42)	1.0	0.73 (0.22–2.41)
Non-steroidal anti-inflammatory drug	1.0	0.63 (0.20–2.00)	1.0	0.67 (0.21–2.12)
Anti-allergic	1.0	1.46 (0.35–6.11)	1.0	1.48 (0.35–6.22)
Anti-flatulent	1.0	0.69 (0.19–2.58)	1.0	0.57 (0.15–2.19)
Analgesic	1.0	0.53 (0.13–2.21)	1.0	0.56 (0.13–2.36)

[a]Adjusted for age, sex, and antidiabetic and laxative usage
HR, hazard ratio, CI, confidence interval

the frequently reported events (diarrhea (3%) and abdominal pain (1%)).

Randomized trials on lubiprostone [13,28–30] have reported nausea, diarrhea, and abdominal pain as the frequent adverse events, whereas the proportion of events of headache, dizziness, and flatulence has been reported to be over 5% [28,29]. Nausea was reported as the most common adverse event during treatment with lubiprostone [16]. In our study, although the events of headache and dizziness were infrequent and the event of nausea was frequent, gastrointestinal events were similar to those reported in previous studies [13,28–30].

Although co-medication with digoxin and dabigatran was not frequent with elobixibat and lubiprostone use, less than 1% of patients used elobixibat in combination with these drugs. According to the package insert of elobixibat [31], the inhibitory effect on p-glycoprotein has been suggested to increase the blood concentration of these drugs. As our study included many elderly individuals, these drugs were not frequently used in combination; nevertheless, the attention of medical staff including pharmacists should be on the onset of symptoms due to increased drug blood levels.

The generalizability of this study finding is high. Previous studies on elobixibat and lubiprostone [16,18] used a small number of patients (less than 500) and did not have an active comparator group. Patients diagnosed with cancer or Parkinson's disease were not included in the clinical trials [26,29]. In addition, although the main population in our study was an elderly population, populations in most previous studies [16,18,26,28,29] included only a few elderly individuals, except for some observational studies [15,27,32].

There are a few studies that have made a head-to-head comparison of elobixibat and lubiprostone. In a retrospective cohort study with 2-week follow-up using propensity score matching by Eguchi et al. [15], any adverse events due to elobixibat (9%) with a daily dose of 10 mg were significantly less than those due to lubiprostone (14.8%) with a daily dose of 24 μg ($p = 0.03$); the incidence of nausea caused by lubiprostone with a daily dose of 48 μg was approximately three times greater than that by elobixibat with a daily dose of 10 mg ($p = 0.01$). These findings are relatively consistent with our findings, although there were some differences in the observation period with the follow-up period of 3 months and methodology using the new-user design [19].

The cost of treatment with these drugs (200.4 yen/day for elobixibat and 232 yen/day for lubiprostone; the drug price of the standard daily dose) is considerably higher than that of conventional drugs for constipation (22.8 yen/day for magnesium and stimulant laxatives [11.4 yen/day for sennoside and 14.4 yen/day for sodium picosulfate]). Furthermore, the generic drugs can be selected as conventional drugs, but not as alternatives for elobixibat and lubiprostone, to reduce patient co-payments.

This study had some limitations. First, we did not have data regarding the time of drug administration. For elobixibat, predinner administration has been suggested to reduce abdominal pain and bloating [33]; the proportion of adverse reactions may be different based on the time of drug administration. Second, the follow-up period was approximately 3 months in our study; the events that might occur after a long-term will be missed. However, several studies on laxatives (including elobixibat and lubiprostone) have been conducted with a short period of observation (less than 3 months) [15,16,26,29,34]. Third, the proportion of reported events such as diarrhea and abdominal pain might be slightly underestimated in our study as they may differ depending on whether the study population included elderly individuals or not. The proportion of adverse events in the elderly population tend to be lower than that in the non-elderly population [16,32,35]. In addition, events that patients may have experienced but not reported or events that were treated at a hospital but not recognized as related to lubiprostone or elobixibat use may have been missed, although we selected the patients from the same pharmacy. Fourth, the estimate regarding the pre-identified risk of nausea in lubiprostone users may lack power. The adjusted HR of nausea for lubiprostone had a wide CI (HR = 7.09: 0.85–58.8) compared with that for elobixibat. However, the increasing trend of nausea risk was consistent with that for lubiprostone. Fifth, there may be residual confounding in this study, as the sample size and number of cases were relatively small. In further larger propensity score-matched cohort study, hypothesis-generating evidence of this study may have to be examined. Finally, details of constipation as an event are unknown. Rather than showing constipation as an adverse effect, the data may indicate that the drug lacked sufficient therapeutic effect because it was originally used in patients with constipation, although the event was reported for both drugs.

5. Conclusions

The study did not raise any new safety concerns related to the use of elobixibat and lubiprostone for treating chronic constipation in clinical settings; the relative risk of any adverse reaction was lower for elobixibat and the risk of nausea tended to be high in lubiprostone users. Nevertheless, the safety of these drugs needs to be monitored and evaluated continually over long periods. Taking into account the effects of underlying diseases, comorbidities, and concomitant medications and usual adverse reactions due to the use of laxatives, chronic constipation in elderly individuals should be treated with care. As there were some limitations to our study, including sample size, the findings as hypothesis-generating evidence should be tested in further larger propensity score-matched cohort studies.

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Author contributions

All authors were involved in the conception and design of the study. N. Ooba and M. Nagamura analyzed and interpreted the data. All authors critically reviewed the manuscript, revised the paper for intellectual content, provided detailed feedback, read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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