

A Review of Adverse Reactions in Infants From Medications in Breastmilk

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Abstract

The types and rate of adverse drug reactions experienced by breastfed infants whose mothers are taking medications has not been well defined. This article reviews the literature on adverse drug reactions in infants since a previous review in 2002. Case reports and studies of adverse drug reactions in breastfed infants whose mothers were taking a prescribed or over-the-counter medication were selected. Fifty-three case reports and 16 studies were located. Serious acute adverse drug reactions from drugs in breastmilk appear to be uncommon. Infants under 2 months of age, and especially those under 1 month, appear to be most susceptible. Similar to previous reviews, free iodine, opioids, and the use of multiple central nervous system drugs simultaneously were identified as drugs of concern. A few narrowly focused studies are now available on long-term effects of maternal drug therapy on breastfed infants and they are mostly reassuring.

Keywords

breastfeeding, milk, human, drug-related side effects, adverse reactions

Introduction

In 2002, we attempted to locate and evaluate all case reports of adverse reactions to maternally administered drugs in breastfed infants that had been published at that time.¹ In this article, we used the same methodology to collect and assess case reports since 2002. We also reviewed studies designed to determine the frequency of adverse effects from specific drugs or drug classes. Using these 2 methods, we identified likely risk factors that predispose breastfed infants to adverse effects from medications taken by their mothers.

Methods

Publications were identified by searching several databases. PubMed was searched from 2002 through December 2014 using the following Medical Subject Headings (MeSH) terms: milk, human or colostrum or lactation or breast feeding with the additional application of the MeSH subheadings, drug effects, drug therapy, and pharmacokinetics applied to locate drug-related articles. Embase was searched 2002 to December 2014 using the following terms: chemicals and drugs and (milk level or breast milk or lactation). Searches were limited to articles in humans. The textbooks *Drugs in Pregnancy*

and *Lactation*² and *Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment*³ were hand-searched for additional cases and studies. Finally, the reference lists of all adverse reaction articles found in this manner were scanned for additional publications, and 2 authors were contacted to obtain additional information. The time period of the searches overlapped with the end of the time period covered in our previous article, and cases reported in the previous article were excluded.

Only reports of medications taken as therapeutic or diagnostic agents were included. Social and recreational drugs (alcohol, caffeine, nicotine, marijuana, etc), foods, nutraceuticals, and environmental contaminants were excluded. Articles on opioids were included only when used therapeutically; articles on opioid abuse were excluded. Reports of breastfed infants who experienced neonatal abstinence reactions from drugs the mother took during pregnancy near term were excluded. If a mother

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took a drug during pregnancy and breastfeeding, trans-placental passage was considered a possible alternative cause for the reaction when assessing causality. Cases of mild, asymptomatic laboratory test abnormalities were also excluded unless they were sufficiently well documented to plausibly infer causality. Case reports described in pharmacokinetic studies were treated as case reports. Studies that specifically aimed to study adverse effects in breastfed infants were summarized separately. Foreign language articles were translated by an author fluent or conversant in the language.

Each case report was reviewed independently by the primary author (POA) and 1 of the 2 other authors who classified it as to the likelihood the reaction was caused by the medication(s) using the Naranjo algorithm.⁴ The algorithm consists of 10 questions relating to different elements of the case report. The answers to the questions can be scored from -1 to +2 and are then totaled. The total score determines whether the case will be scored "definite," "probable," "possible," or "doubtful." When the first 2 authors disagreed on the final classification, the third author rated the article and it was assigned the classification agreed upon by 2 authors. Case reports that were rated "doubtful" (score of 0 or less) were excluded from the final analysis of case reports.

Results

After removal of duplicate records, 3297 records were initially located that met the search criteria. Of these, we located 70 case reports of adverse reactions in 63 publications that met inclusion criteria and 16 studies on adverse drug reactions in breastfed infants. Seventeen of these case reports were eliminated during the evaluation process because the authors judged that they met one of the exclusion criteria. A summary of the remaining 53 case reports is shown in Table 1.

The age at first onset of the adverse reaction could be determined in 49 of the cases. Figure 1 shows the age distribution of these infants. Of note is that 31 (63%) of the reactions occurred in the first month of life and 8 (16%) occurred in the second month of life, for a total of 79% of reactions occurring in the first 2 months of life. Eleven cases in which drug exposure occurred during both pregnancy and breastfeeding are noted with an asterisk in Table 1. Other cases might have had pregnancy exposure also, but were not clearly documented in the case report.

Table 2 shows the distribution of case reports by drug class. Thirty-seven (70%) of adverse reactions involved central nervous system (CNS) active drugs, which encompassed opioids, antidepressants, anticonvulsants, antipsychotics, lithium, sedatives, and some of the multiple drug class exposures.

Twenty-eight (53%) of the cases were rated "possible," and 25 (47%) were rated "probable" using the Naranjo algorithm.

Studies performed since our previous review and their principle outcomes are listed in Table 3. These studies have, in general, found no serious adverse effects in breastfed infants. Two studies did find an excess of adverse reactions in breastfed infants.^{51,52} However, in each case another study was published on the same drug class that did not find an increased risk.^{53,54}

Discussion

The age distribution of case reports in the current study is similar to results in our previous article, which found that 63% of adverse reactions occurred in the first month and 15% in the second month of life. The combined data from both studies are composed of 140 cases in which infant age could be identified. Sixty-three percent of cases occurred in the first month of life and 16% occurred in the second month of life, for a total of 79% occurring in the first 2 months of life. Figure 2 shows the combined results of the 2 reviews. These values are similar to those found in a recently published article that reviewed 174 cases of adverse reactions in breastfed infants reported to pharmacovigilance centers in France over a 25.5-year period. The French authors found that 67% of cases occurred in the first month and 11% in the second month, for a total of 78% of the adverse reactions occurring in the first 2 months of life.⁶⁸ Our review contained 4 cases from France that might have been included in the French database.

Several factors might explain the predominance of early adverse reactions. First, newborns have a low capacity for drug metabolism and excretion.⁶⁹ Second, infants receive the highest drug dosage relative to their body weight in the first month of life because their milk intake is greatest relative to their body weight during that time.^{69,70} Finally, mothers are more likely to be nursing or exclusively nursing their infants during the first 2 months postpartum than in later months, so the youngest infants might have greater exposure to drugs in milk than older infants.⁷¹

In our previous article, 51% of cases involved CNS depressants, and in this study, they account for 69%.¹ Overall, of the 153 cases from our 2 reviews, 88 (58%) cases involved drugs with CNS activity. All deaths reported in this article and in our previous article involved one or more CNS depressants. The recent French pharmacovigilance publication classified drugs somewhat differently, but at least 37% of the reactions were caused by drugs acting on the nervous system. The authors reported that the most frequently reported types of adverse reactions were CNS reactions, which also

Table 1. Case Reports of Adverse Drug Effects.

Drugs	Age First Affected	Adverse Effects	Naranjo Classifications	References
Amoxicillin/clavulanate, gentamicin	2 months	Urticaria	Probable	Cherif et al ⁵
Antituberculars	4.6 years	Mild speech delay*	Possible	Drobac et al ⁶
Antituberculars	5.1 years	Hyperactivity*	Possible	Drobac et al ⁶
Azathioprine	Not stated	Decreased blood count	Possible	Khare et al ⁷
Benzodiazepines, quetiapine	<10 weeks	Drowsiness	Possible	Seppälä ⁸
Bupropion	6 months	Seizure	Possible	Chaudron et al ⁹
Bupropion, escitalopram	6.5 months	Sleep disturbances, emesis, tonic-clonic seizure-like symptoms	Probable	Neuman et al ¹⁰
Carbamazepine, clonazepam	Not stated	"Lazy at the breast" and tired	Possible	Schaefer et al ¹¹
Carisoprodol	1 month	Slight sedation*	Possible	Briggs et al ¹²
Citalopram	2 months	Irritability, restlessness	Possible	Lee et al ¹³
Clonidine	2 days	Drowsiness, hypotonia, suspected generalized seizures*	Possible	Sevrez et al ¹⁴
Clozapine	1 year	Speech disturbance*	Possible	Mendhekar et al ¹⁵
Codeine	7 days	Apnea, lethargy, death	Probable	Koren et al ¹⁶
Codeine	8 days	Lethargy, sedation, respiratory arrest	Probable	Lam et al ¹⁷
Codeine	7 days	Lethargy, pinpoint pupils	Probable	Lam et al ¹⁷
Codeine	3 days	Difficult to arouse, limpness	Probable	Lam et al ¹⁷
Codeine	2 days	Respiratory arrest	Probable	Lam et al ¹⁷
Codeine	4 days	Drowsy, difficult to arouse	Possible	Lam et al ¹⁷
Codeine	7 days	Lethargy, difficult to arouse	Possible	Lam et al ¹⁷
Desogestrel	4 months	Scrotal hair growth*	Possible	Janus et al ¹⁸
Diclofenac	15 days	Urticaria	Possible	de Cerqueira et al ¹⁹
Dihydrocodeine	2 days	Respiratory depression	Possible	Eleftheriou et al ²⁰
Escitalopram	<11 days	High-pitched crying	Possible	Schaefer et al ²¹
Escitalopram	1 month	Irritability, vomiting, fever, poor weight gain, abnormal liver enzymes	Possible	Merlob ²²
Escitalopram	5 days	Necrotizing enterocolitis*	Possible	Potts et al ²³
Iodine, topical	2 weeks	Abnormal thyroid function tests	Probable	Smith et al ²⁴
Iodine, topical	15 days	Elevated TSH, low fT4	Probable	Kurtoğlu et al ²⁵
Iodoform, topical	17 days	Hypothyroidism	Probable	L'Italien et al ²⁶
Labetalol	2 weeks	Bradycardia	Probable	Mirpuri et al ²⁷
Lamotrigine	17 days	Apnea, cyanosis*	Probable	Nordmo et al ²⁸
Lamotrigine, levetiracetam	3 days	Bradycardia, decreased oxygen saturation*	Probable	Wüller et al ²⁹
Levetiracetam, phenytoin, valproate	7 days	Hypotonia, poor feeding	Probable	Kramer et al ³⁰
Levetiracetam, topiramate, clobazam	25 days	Sedation, vomiting, weight loss	Possible	Paret et al ^{31,32}
Levetiracetam, clobazam	15 days	Poor weight gain	Possible	Paret et al ³¹
Lithium	4 weeks	Mild, transient TSH elevation	Probable	Marin et al ³³
Mesalamine	4.5 months	Hypotonia, thrombosis, thrombocytosis	Possible	Barriuso ³⁴
Methadone	13 months	Cyanosis, miosis, bradypnea	Probable	West et al ³⁵
Methadone, hydrocodone, acetaminophen	5 weeks	Sedation, apnea	Probable	Meyer et al ³⁶
Nefazodone	Not stated	Increased bowel movements	Possible	Lee et al ³⁷
Olanzapine	>3 weeks	Sedation	Possible	Gardiner et al ³⁸
Olanzapine, clonazepam, sertraline, valproate, thioridazine, droperidol	Not stated	Developmental delay	Possible	Gardiner et al ³⁸

(continued)

Table 1. (continued)

Drugs	Age First Affected	Adverse Effects	Naranjo Classifications	References
Oxycodone	4 days	Sedation, weak suck reflex, pinpoint pupils, hypothermia	Probable	Timm ³⁹
Oxycodone	45 days	Constipation, decreased feeding, shallow and labored breathing, low oxygen saturation, small pupils, urine positive for hydromorphone	Probable	Sulton-Villavasso et al ⁴⁰
Oxycodone, butalbital carisoprodol, codeine	10 months	Drowsy, sleeping, snoring, difficulty breathing, death	Possible	Levine et al ⁴¹
Paroxetine	18 months	Vomiting, dehydration	Possible	Abdul-Aziz et al ⁴²
Phenobarbital	1 to 3 days	Lethargy, absence of suck*	Probable	Pote et al ⁴³
Probenecid, cephalexin	9 days	Green liquid stools, diarrhea, crying		Ilett ⁴⁴
Propoxyphene	10 days	Difficulty nursing, poor weight gain	Probable	Rigourd et al ⁴⁵
Sertraline, clonazepam	1 day	Tremor*	Possible	Morales ⁴⁶
Topiramate	40 days	Diarrhea	Probable	Westergren et al ⁴⁷
Yellow fever vaccine	23 days	Fever, irritability, refusal of the breast, meningoencephalitis and convulsions	Probable	CDC ⁴⁸
Yellow fever vaccine	5 weeks	Focal seizures	Probable	Kuhn ⁴⁹
Yellow fever vaccine	38 days	Convulsions, meningoencephalitis	Probable	Traiber ⁵⁰

*Drug exposure also occurred during pregnancy.

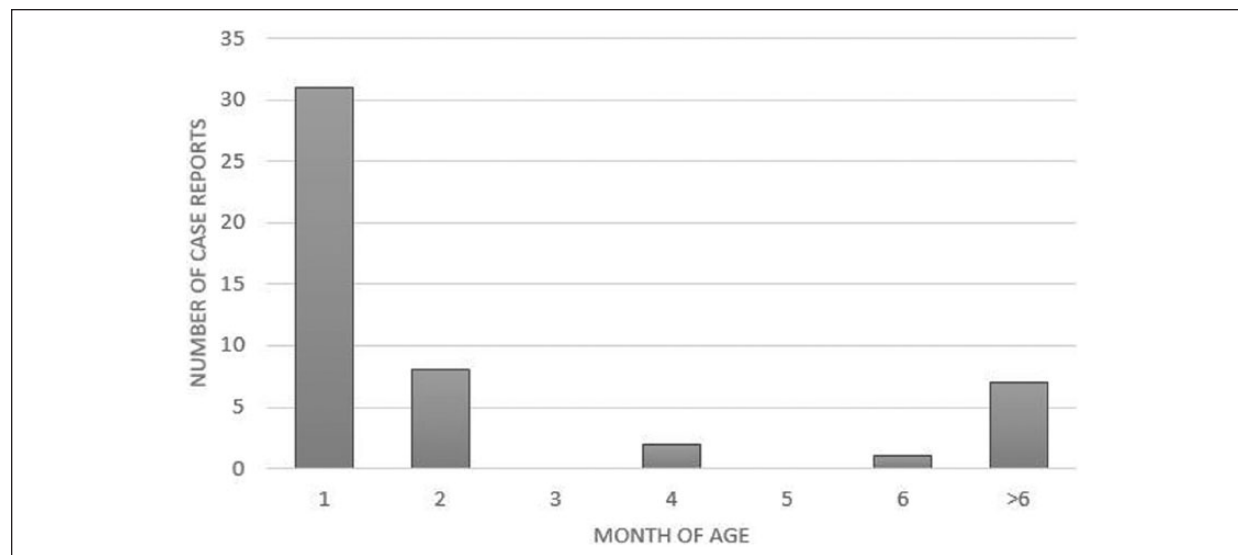


Figure 1. Number of adverse reaction reports by age, 2002-2014.

accounted for more than a third of reactions classified as “serious.”⁶⁸ A review of cases reported to a Swedish pharmacovigilance center also found adverse CNS effects to be one of the most common adverse effects in breastfed infants exposed to drugs in breastmilk.⁷²

The use of multiple CNS depressants simultaneously seems to add to the risk. Eleven of the case reports of adverse reactions occurred in infants exposed to more than one CNS depressant. A study on benzodiazepine use in nursing mothers found the use of multiple CNS

Table 2. Case Reports by Drug Class.

Opioids	25%
Antidepressants	15%
Multiple drug classes	11%
Anticonvulsants	11%
Iodine	6%
Antimicrobials	6%
Yellow fever vaccine	6%
Antipsychotics	4%
Cardiovascular drugs	4%
Sedatives	4% ^a
Nonsteroidal anti-inflammatory drugs	2%
Hormonal drugs	2%
Gastrointestinal drugs	2%
Immunosuppressants	2%
Lithium	2%

^aIncludes carisoprodol and phenobarbital given as single agents.

Table 3. Studies on Adverse Effects.

Drug or Class	Findings	Reference
Amoxicillin-clavulanate and cefuroxime	No serious adverse effects	Benyamini et al ⁵⁵
Antidepressants	Normal weight gain	Hendrick ⁵⁶
Antiepileptic drugs (carbamazepine, lamotrigine, phenytoin, valproate)	No adverse developmental effects at 6 years	Meador et al ⁵⁷
Antiepileptic drugs (carbamazepine, lamotrigine, valproate)	Breastfeeding protected against neurologic disturbances	Veiby et al ⁵⁸
Antiretrovirals	No increased risk of neutropenia	Bae et al ⁵⁹
Azathioprine	No serious adverse effects; one case of mild neutropenia among 30 infants	Bernard et al ⁶⁰
Benzodiazepines	No adverse effects used alone; ADR risk increased with more CNS depressants	Kelly et al ⁶¹
Codeine toxicity	No increased risk of adverse effects	Juurink et al ⁵³
Codeine toxicity	Genetic differences in toxic infants	Madadi et al ⁵¹
Lithium	No serious ADRs; mild elevations in laboratory tests in 3 of 10 infants	Viguera et al ⁶²
Loratadine	No increased risk of adverse effects	Merlob et al ^{2,63}
Macrolide antibiotics	Increased risk of hypertrophic pyloric stenosis	Sørensen et al ⁵²
Macrolide antibiotics	No increased risk of hypertrophic pyloric stenosis	Goldstein et al ⁵⁴
Oxycodone	Increased risk of CNS depression	Lam et al ⁶⁴
Olanzapine	No increased risk of adverse effects	Gilad et al ⁶⁵
Paroxetine	No adverse effect on weight gain	Merlob et al ⁶⁶
Tranexamic acid	No long-term adverse effects	Gilad et al ⁶⁷

Abbreviations: ADR, adverse drug reaction; CNS, central nervous system.

^aMerlob P. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal loratadine treatment (1999-2002). Unpublished manuscript.

depressants, but not benzodiazepines alone, was a risk factor for adverse infant reactions. The greater the number of CNS depressants the mother took, the greater was the likelihood of an adverse effect.⁶¹

Opioid drugs accounted for a greater percentage of cases in the current study than in the previous study. Many

of these case reports might have been generated because of increased vigilance following the death of a neonate whose mother was taking codeine and was a supermetabolizer of CYP2D6.¹⁶ Indeed, 9 of the opioid case reports cited the case of this codeine death and many case reports were from the same institution as the initial report.

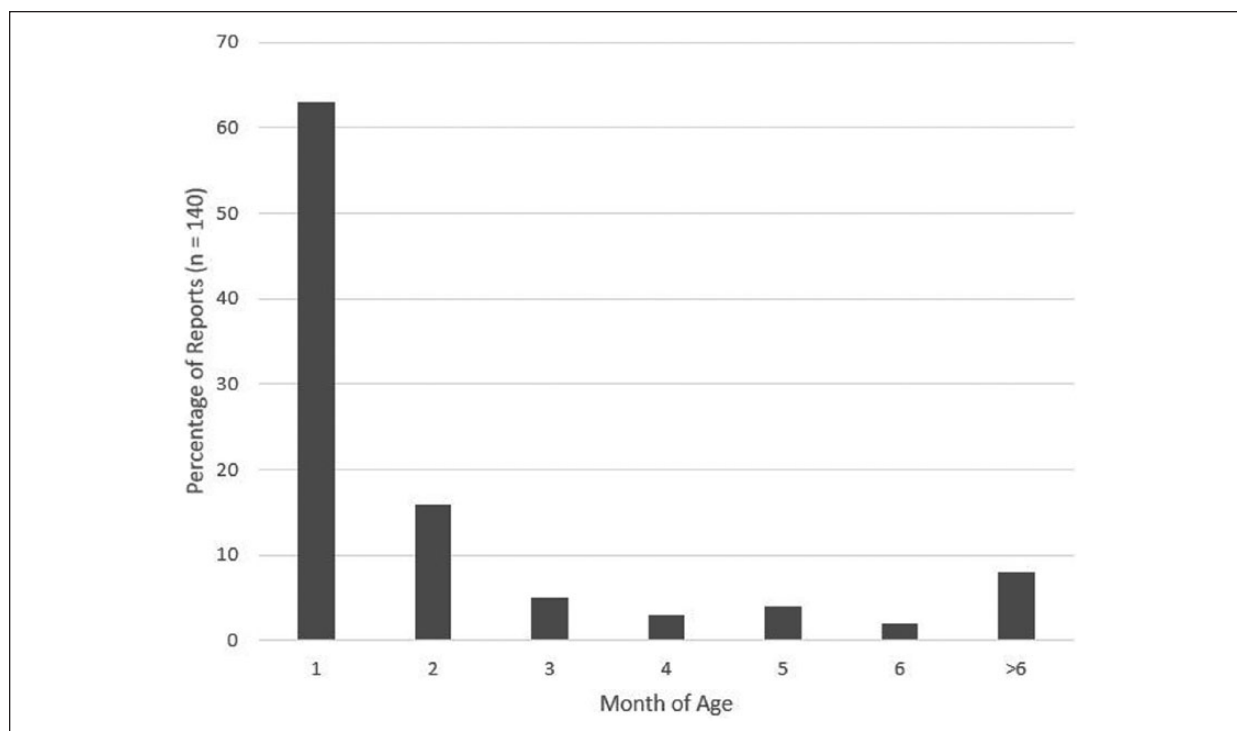


Figure 2. Combined number of adverse reaction reports by age, in this and the previous study.¹

Similar to this study, our previous article rated 52% of cases possible and 48% probable. The reason that a large percentage of cases are rated only possible seems partly related to the well-known incompleteness of case report descriptions.⁷³ Also, the Naranjo algorithm was not designed specifically for assessing adverse reaction in breastfed infants and might not be optimal for this purpose. The drug class with the highest numerical ratings and greatest interrater agreement on the Naranjo scale was iodine, with the cases assigned a numerical value of 8 by 2 raters, which is only 1 point below the threshold for a “definite” rating. Our previous article also reported 4 probable cases of thyroid dysfunction from iodine, and several cases of thyroid dysfunction have been reported in the newborns of Korean mothers who ingested large amounts of iodine from seaweed soup.⁷⁴⁻⁷⁷ Great caution should be taken to avoid exposure of nursing mothers to high amounts of free (ie, excluding contrast media) iodine, even topically.

Limitations

A review of case reports cannot provide a true frequency of adverse reactions because the number of women taking the drugs is not known and adverse reactions are notoriously underreported. Determination of causality is complicated by the poor quality of many case reports,

with some reported only in abstract form and not peer reviewed. Important variables such as the amount of breastfeeding, the dosage of drugs, timing of exposure, and the age of infants are often not included in case reports.

The frequency at which various classes of drugs caused adverse reactions is undoubtedly dependent partly on the frequency that they are prescribed to nursing mothers. Opioids are frequently used after cesarean section deliveries and antidepressants are commonly used to treat postpartum depression.

At least 11 (21%) of the reported adverse effects involve infants who were exposed to the drug(s) in utero as well as via breastfeeding, as noted in Table 1. This makes causality difficult to determine, particularly when long-term developmental effects are reported. We discarded 10 case reports that clearly resulted from in utero exposure, including neonatal abstinence symptoms.

Conclusions

This review of case reports and studies and previous reviews of adverse effects in breastfed infants from maternal medications indicate that serious adverse drug effects appear to be uncommon. These results are consistent with the only broadly based, prospective study on adverse effects in breastfed infants.⁷⁷ The occasional

reports of adverse reactions must be taken in the context of how frequently they are used and how many reports have been made of their use without adverse consequences. Studies that aimed to identify adverse reactions in breastfed infants confirm that adverse reactions in the specific drugs that were studied have a low frequency. A more complete frame of reference on adverse reactions can be obtained in the LactMed database, which reports not only adverse reactions but also reports of maternal drug use that had no adverse infant consequences.⁷⁸

From this and other reviews, it appears that infants under 2 months of age, and especially those under 1 month, are most susceptible to adverse effects from drugs in breastmilk. Almost 80% of adverse reactions occurred in the first 2 months postpartum in this and 2 other studies.

Certain drugs and drug classes also stand out as agents whose use should be minimized in nursing mothers. These include opioids, multiple CNS depressant drugs simultaneously, and topical and systemic free iodine. These drugs should be used in as low a dosage and for as short a time as possible or avoided altogether, especially while breastfeeding neonates. If these precautions are taken, adverse infant effects from drugs in breastmilk are unlikely to occur.

Author Contributions

POA designed the study, performed the literature searches and initial selection of articles, rated all case reports and drafted the manuscript. ASM and VV assisted in designing the study, rated case reports, and suggested changes to the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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