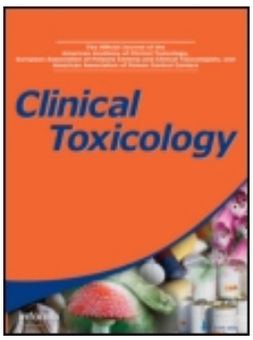

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CRITICAL CARE

Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely

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Context. Tramadol is a commonly used centrally acting analgesic associated with seizures and suspected to cause serotonin toxicity in overdose. *Objective*. This study sought to investigate the effects of tramadol overdose, and included evaluation for serotonin toxicity based on the Hunter Serotonin Toxicity Criteria where the seven clinical features of spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor and hyperreflexia are examined for in all patients taking serotonergic medications; seizures and central nervous system depression. *Materials and methods*. This was an observational cases series based on a retrospective review of tramadol overdoses (>400 mg) admitted to a tertiary toxicology unit from November 2000 to June 2013. Demographic details, information on ingestion (dose and co-ingestants), clinical effects, complications (seizures, serotonin toxicity and cardiovascular effects) and intensive care unit (ICU) admission were extracted from a clinical database. *Results*. There were 71 cases of tramadol overdose (median age: 41 years, range: 17–69 years; and median ingested dose: 1000 mg, interquartile range [IQR]: 800–2000 mg). Seizures were dose related and occurred in 8 patients, one of them co-ingested a benzodiazepine compared with 16 patients without seizures. There were no cases of serotonin toxicity meeting the Hunter Serotonin Toxicity Criteria. Tachycardia occurred in 27 and mild hypertension occurred in 32. The Glasgow Coma Score was < 15 in 29 and < 9 in 5 patients; three co-ingested tricyclic antidepressants and two tramadol alone (3000 mg and 900 mg). Respiratory depression occurred in 13, median dose: 2500 (IQR: 1600–3000) mg which was significantly different ($p = 0.003$) to patients without respiratory depression, median dose: 1000 (IQR: 750–1475) mg. Eight patients were admitted to ICU, five due to co-ingestant toxicity and three for respiratory depression. *Discussion*. Tramadol overdose was associated with a significant risk of seizures and respiratory depression in more severe cases, both which appear to be related to the ingested dose. There were no cases of serotonin toxicity, while opioid-like effects and adrenergic effects were prominent. *Conclusion*. Tramadol overdose is associated with seizures and respiratory depression, but is unlikely to cause serotonin toxicity.

Keywords Overdose; Poisoning; Respiratory depression; Seizure; Tramadol

Introduction

Tramadol is a centrally acting analgesic that is structurally related to codeine and morphine. Tramadol is a racemic mixture of two enantiomers, the (1R,2R)-(+)- and (1 S,2 S)-(–)-stereoisomers, which have differing affinities for μ-receptors and monoamine reuptake. (+)-Tramadol enantiomer inhibits serotonin reuptake and (–)-tramadol inhibits noradrenaline reuptake.[1] The action of these two enantiomers is both complementary and synergistic and results in the analgesic effect of (±)-tramadol. Side effects predominate in one or other of the enantiomers and partly antagonize each other, reducing the severity of side effects seen in the racemic mixture.[2] Much of the toxicity in tramadol overdose is thought to be due to the monoamine uptake inhibition rather than its opioid effects.[3] Tramadol is metabolised by CYP2D6 to O-desmethyl tramadol which is a more potent μ-receptor agonist, and has a longer half-life (9 h) compared with the parent (6 h), which contributes to the duration and analgesic potency.[1]

Since tramadol was marketed in Australia in late 1998 its use has increased dramatically,[4] similar to its introduction into the United States in 1995 and the United Kingdom in 1997.[5] While there is a large amount of information supporting the effectiveness of tramadol for pain, there is an increasingly large body of evidence from post-marketing surveillance showing that there are significant adverse effects, including seizures. In 1999 the Australian Adverse Drug Reactions Advisory Committee[4] received 19 reports of adverse events, and this had increased to 726 reports of adverse events by March 2004. In 453 of the reports, tramadol was the sole suspected drug. These reactions suggest that the decision to prescribe tramadol should be carefully considered.[6] In addition to adverse effects associated with

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tramadol prescription, the increasing availability of tramadol is also associated with deliberate self-poisoning.

The usual therapeutic dose is 50 mg orally and the maximum daily dose should not exceed 400 mg per day.[7,8] Immediate-release formulations normally require oral administration 4–6 times daily (50-mg capsules or soluble tablets) while slow-release formulations provide the opportunity for administration only twice daily (100-, 150- and 200-mg tablets).[1,9,10]

In overdose it is reported to cause seizures,[6,11] agitation, tachycardia and hypertension (attributed to its monoamine oxidase inhibitor effect), and opioid-like effects (coma and respiratory depression).[3] Seizures appear to be the most commonly reported serious effect but there is limited information on the frequency and timing of seizures with tramadol overdose and whether this is related to ingested dose. Tramadol has been associated with serotonin toxicity in case reports of therapeutic combinations of tramadol and another serotonergic drug.[12–18] If tramadol alone causes serotonin toxicity then this will be seen with tramadol overdoses similar to selective serotonin reuptake inhibitor overdoses.[19]

The aim of this study was to investigate the frequency and severity of clinical effects of tramadol overdose in patients admitted to a tertiary toxicology unit. We hypothesised that serotonin toxicity would occur with tramadol overdose and that seizures and coma would be the most important major effects.

Methods

This was an observational case series based on a retrospective review of tramadol overdoses admitted to a tertiary toxicology unit. The toxicology service provides an inpatient service to a population of over 300,000.

All overdose presentations to the toxicology service are recruited prospectively and patient demographic and admission data are collected using a preformatted admission sheet,[20] including demographics, clinical effects, complications, investigations and treatments. Serial data are recorded for clinical effects (including heart rate, blood pressure, oxygen saturation, respiratory rate, Glasgow Coma Score [GCS]), investigations (as clinically indicated including electrocardiograms) and treatments. Data are entered into a relational database within a week of each patient admission by trained research staff blinded to the outcomes of this study. Each week all admissions are reviewed and any additional information is obtained directly from the attending clinical toxicologist or the medical record. All patients admitted to the service are seen by the toxicology team daily and treatment is determined by the attending medical toxicologist. The Institutional Ethics Committee has previously granted an exemption in regard to the use of the database and patient information for research.

All overdose presentations to the toxicology service from November 2000 to June 2013 where greater than 400 mg of tramadol was ingested (that is, above the maximum recommended daily dose) were included. Ingestion was confirmed from patient history and collateral history recorded by ambulance, emergency staff and mental health staff. All overdoses were included irrespective of co-ingestants and even if the co-ingestants were a major part of the overdose (e.g., tramadol 500 mg and amitriptyline 2500 mg). However, complications and outcomes clearly attributable to co-ingestants are acknowledged in the results.

Demographic details, information on ingestion (dose and co-ingestants), clinical effects, specific complications (seizure and time of seizure, serotonin toxicity, coma, respiratory depression and cardiovascular effects), length of stay,[21] intensive care unit (ICU) admission and mechanical ventilation were extracted from the clinical database. Additional information on specific data elements was obtained from the medical record retrospectively, including response to naloxone and time to respiratory depression.

The seven major outcomes were (1) seizures; (2) serotonin toxicity based on the Hunter Serotonin Toxicity Criteria where the seven clinical features of spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor and hyperreflexia are examined for in all patients taking serotonergic medications and was used as the diagnostic criteria;[22,23] (3) coma (GCS <9); (4) respiratory depression (oxygen saturation $<94\%$ and/or respiratory rate <12 breaths per minute, including time to onset of respiratory depression); (5) ICU admission (for ongoing airway support, continuous invasive hemodynamic monitoring or inotropic support, ongoing abnormal GCS (<9), or multi-organ impairment); (6) mechanical ventilation; (7) administration of naloxone (and response) and (8) death. All of these outcomes are pre-defined outcomes entered in the database within a week of patient admission, except for coma and respiratory depression which are based on recorded data (GCS, RR and oxygen saturations).

Continuous variables are reported as median values with interquartile ranges (IQRs) and ranges. All analyses and graphics were done in GraphPad Prism version 6 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com.

Results

There were 112 admissions for tramadol overdoses during the study period. The dose was unknown in 16 admissions and less than 400 mg was ingested in a further 25 admissions, leaving 71 admissions meeting the inclusion criteria. The 71 admissions were in 70 patients with one patient presenting with two tramadol overdoses. The median age in the 71 admissions was 41 (IQR: 28–47, range: 17–69) years with 43 (61%) being female. The median dose of tramadol ingested was 1000 (IQR: 800–2000; range: 450–6000) mg. In 22 of the 71(31%) admissions the patient took the slow-release formulation of tramadol. Tramadol patients also co-ingested a number of different medications, in particular serotonergic medications and benzodiazepines (Table 1). A comparison between patients who took tramadol only ($n = 20$) and patients who took tramadol in combination with co-ingestant/s ($n = 51$) is included in Table 2.

Clinical effects

Seizures occurred in 8 patients (11%) with one of these patients who ingested 4000 mg having a total of six seizures.

Table 1. Type and number of co-ingestants taken by tramadol overdose patients.

Co-ingestant	No. Patients*
Proconvulsant	
Tricyclic Antidepressant	3
Benzodiazepine	16
Serotonergic	
Serotonin selective reuptake inhibitor (SSRI)	13
Serotonin–norepinephrine reuptake inhibitor (SNRI)	10
Anti-serotonergic	2
Other Sedative	3
Other	23

*Some patients took more than one co-ingestant.

For patients having a seizure the median dose was 2100 (IQR: 1600–3250; range: 750–4000) mg which was significantly different to patients not having a seizure with a median dose of 1000 mg (IQR: 775–1550 mg; range: 450–6000 mg; $p = 0.018$ Mann–Whitney test) (Fig. 1). The patient who had a seizure after taking 750 mg of tramadol also had benzodiazepine withdrawal. Another patient who ingested 1200 mg and had a seizure had a history of a previous seizure not associated with a drug overdose. The other 6 patients having seizures ingested 2000 mg or higher dose (Fig. 1). One of the eight seizure patients co-ingested a benzodiazepine (12.5%) compared with 16 of 63 (25%) patients without seizures. The median time from ingestion to the first seizure was 8.5 (1.5–22.7) h which differed for patients ingesting the immediate-release preparation (1.5–11 h) compared with those ingesting the slow-release preparation (6.5–22.7 h) (Fig. 2). Seizures occurred in three of the 16 admissions where the dose was unknown.

Table 2. A comparison of tramadol only ingestion to tramadol with other medication co-ingestant/s.

	Tramadol only	Tramadol + Co-ingestant/s
No. Patients	20	51
Gender (M/F)	10/10	18/33
Age, y		
Median (IQR)	34 (28–46)	41 (30–49)
Range	18–53	17–69
Dose, mg		
Median (IQR)	1200 (800–2025)	1000 (800–2000)
Seizures, *n* (%)	2 (10)	6 (12)
Seizure Tramadol Dose, mg	2100	2100
No Seizure Tramadol Dose, mg	1150	1000
Serotonin Toxicity, *n*	0	0
Gastrointestinal Symptoms, *n*	10	26
ICU, *n*	0	8
Intubated/Ventilated, *n*	0	4
LOS, h		
Median (IQR)	13.5 (8.8–17.0)	19.9 (13.6–35.7)
Range	3.1–30.7	1.8–227.8
Max HR, bpm		
Median (IQR)	96 (84 120)	95 (88–106)
Max Sys BP		
Median (IQR)	137 (130–142)	138 (128–150)

M/F, Male/Female; IQR, Interquartile range; ICU, Intensive care unit; LOS, length of stay; HR, Heart rate; BP, Blood pressure.

There were no cases of serotonin toxicity that met the Hunter Serotonin Toxicity Criteria.[22] One patient who ingested 1000 mg of tramadol and 800 mg of escitalopram developed ocular clonus but did not meet the criteria for serotonin toxicity.

The GCS was less than 15 in 29 of the 71 patients (41%) (Fig. 3). The GCS was less than 9 in 5 patients, including three who co-ingested tricyclic antidepressants (GCS 3, 5 and 7) and 2 patients ingesting 3000 mg and 900 mg of tramadol who developed respiratory depression which responded to naloxone. Respiratory depression with oxygen saturation $< 94\%$ occurred in 13 patients (18%) with a median dose of 2500 (IQR: 1600–3000; range: 500–4000) mg which was significantly different to patients not developing respiratory depression with a median dose of 1000 mg (IQR: 750–1475 mg; range: 450–6000 mg; $p = 0.003$, Mann–Whitney test) (Fig. 4). The onset of respiratory depression could be ascertained in 9 of 13 patients, and was 2 h or less in 7 patients and 5 h and 8 h in the other 2 patients.

Gastrointestinal effects occurred in 36 (51%) patients, including vomiting in 31 and nausea alone in 5 patients. Cardiovascular effects including tachycardia in 27 (38%) patients, mild hypertension (systolic blood pressure > 140 mmHg) in 32 (45%) and 1 patient had a pre-existing left bundle branch block.

Outcomes and treatment

The median length of stay (LOS) for all patients was 16 (IQR: 11.3–24.4; range: 1.8–228) h with patients co-ingesting tramadol with another medication having a longer LOS in hospital, median LOS 19.9 (IQR: 13.6–35.7) h. Eight (11%) patients co-ingesting tramadol with another medication were also admitted to the ICU and in five of these the reason for admission to ICU was due to toxicity from the co-ingestants (tricyclic antidepressants [3], morphine [1] and atenolol [1]). The remaining three were admitted for respiratory depression, one was intubated, one was on a naloxone infusion and one developed pneumonia. There were no deaths. Naloxone was given to 9 patients with a median dose of 2.2 (range: 0.4–4.4) mg, seven of which had documented respiratory depression. Naloxone was reported to improve the patient's oxygen saturations or level of consciousness in 6 patients, provide partial improvement in 2 patients and had no effect in one. No seizures were reported after naloxone administration.

The frequency of seizures, gastrointestinal symptoms and seizure tramadol dose between the patients who ingested tramadol only compared with those who ingested tramadol with another medication were not different (Table 2).

Discussion

This study found that the most important effects following tramadol overdose were seizures, decreased level of consciousness and respiratory depression. In contrast to previous reports with tramadol, serotonin toxicity defined by the Hunter Serotonin Toxicity Criteria, which has been shown to be sensitive and specific, did not occur. Serotonergic effects only occurred in 1 patient who co-ingested an overdose of

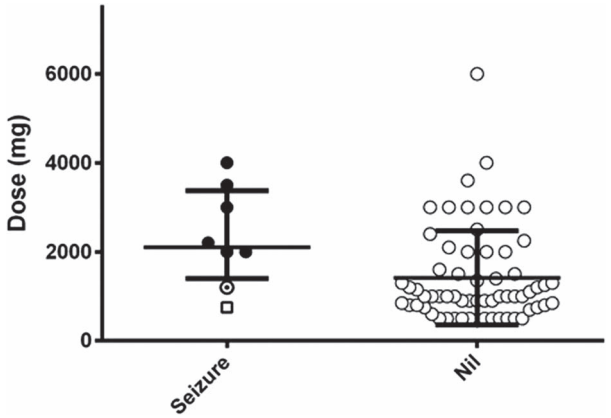

Fig. 1. Scatter plot of tramadol dose ingested for patients having a seizure compared with those not having a seizure which was statistically significant ($p = 0.021$). The bars are the median and IQR. The two lower-dose patients with seizures had predisposing reasons for seizures – benzodiazepine withdrawal (□) and previous primary seizure (Θ).

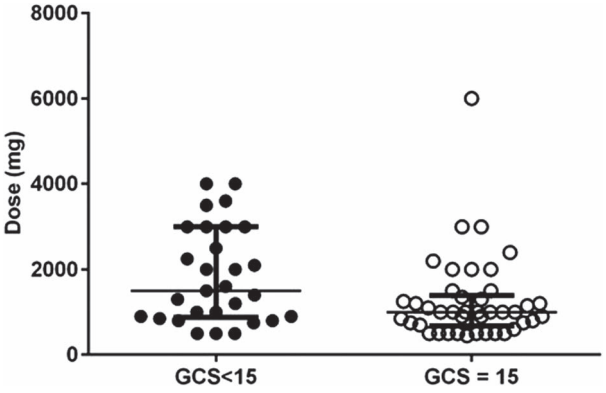

Fig. 3. Scatter plot of tramadol dose comparing patient with a GCS < 15 to patients with a GCS of 15. The bars are the median and IQR.

another serotonergic drug. Serotonin toxicity has previously been reported after therapeutic use/overdose of tramadol, but this has been with the co-administration of other medications, particularly serotonergic antidepressants.[12,13,15,17,24–30] Other common effects were nausea and vomiting in half of the patients, and tachycardia and hypertension in over a third, consistent with the noradrenergic reuptake effect of tramadol. The pattern of clinical effects reported in this study is similar to previous studies excepting the absence of serotonin toxicity.[3,10,31]

Seizures were relatively common for tramadol overdoses compared with most other overdoses including those with other proconvulsant drugs such as venlafaxine where the frequency of seizures is about 5% in overdose.[32] In the present study seizures occurred in 11% of cases which is similar to that reported by Spiller et al.[3] of 8% and by Marquardt et al.[31] of 14%. Two further studies from the poison centre in Tehran, Iran reported an unusually high frequency of seizures (35% and 46%).[10,33] This may have been due to the specific study population investigated, for example, the 132 patients recruited in the Talaie et al. study came from a cohort of 215 patients with seizure and a positive history of tramadol use. This was similar to the patient group in the Shadnia et al. study that also reported patients presenting to the Loghman Hakim Hospital Poison Centre in Tehran, Iran during a similar time period. Patients with an existing seizure disorder appear to be most at risk for adverse effects. In a study of tramadol abusers, Jovanovic-Cupic et al. found that 54.4% of the sample reported at least one tonic/clonic seizure during the three-year study period.[34] With regard to seizures in genuine overdoses, Thundiyil et al. examined all such cases logged by the California Poison Control System in 2003 and of the 386 identified cases of seizures with drug overdoses, tramadol accounted for 29 (7.5%).[35]

We found that seizures appeared to be dose dependent and only occurred with doses greater than 2000 mg in patients without a pre-existing risk of seizures (Fig. 1) and again this was consistent with previous studies where seizures were recorded to occur with higher doses of tramadol.[3,10] The Talaie et al. study found that seizures were not dose dependent and that most of the seizures occurred for doses

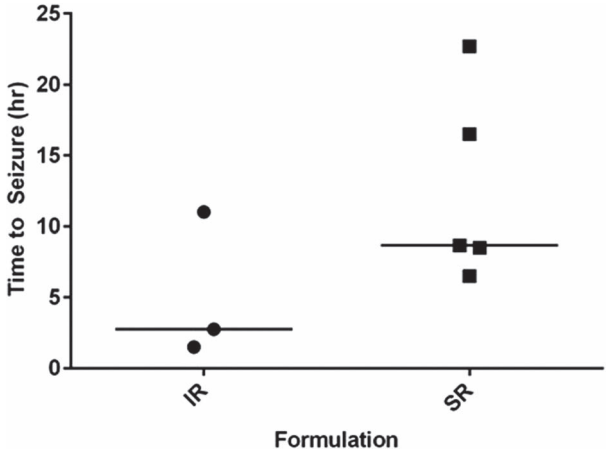

Fig. 2. Scatter plot of the time to seizure comparing patient ingesting the immediate-release (IR) formulation and those ingesting the slow-release (SR) formulation.

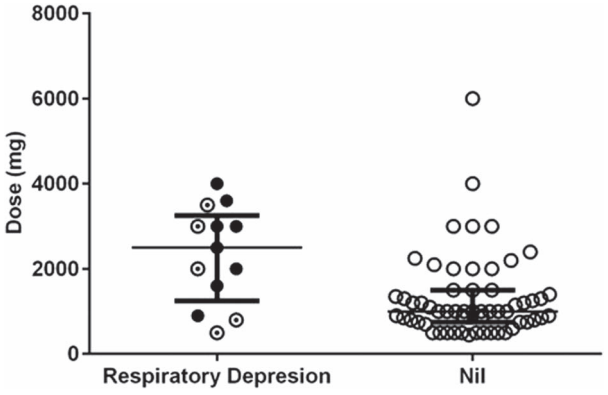

Fig. 4. Scatter plot of tramadol dose comparing patients with and without respiratory depression which was statistically significant ($p = 0.003$). The bars are the median and IQR. Five of the 13 patients with respiratory depression either co-ingested a tricyclic antidepressant (3) or promethazine (1) and had pneumonia (1) and are marked by a Θ.

of 500–1000 mg. Further, they found that the mean tramadol dose was no different between patients with and without seizure which is also in contrast to the present study. The authors speculate that this may have been due to a predisposition of their study group to alcohol ingestion (a previously shown association[36]) although this could not be proven.[33] The LOS in our tramadol overdose patients was relatively short, which is similar to the median LOS for all overdose patients in the toxicology unit,[21] and is consistent with previous reports.[3,31] The time to the first seizure was shorter in patients taking the immediate-release preparation. Although there were only a small number of seizures in our study, they provide some insight into the observation period required for tramadol which is dependent on the formulation (Fig. 2).

Although tramadol is only a partial agonist at the μ-opioid receptor, a decreased level of consciousness was common in our series [41% (29/71)] and respiratory depression occurred in one-fifth of cases, both of which appear to respond to naloxone. Although respiratory depression was often associated with co-ingestants, it did occur in patients taking only tramadol. The majority of patients responded to naloxone. This is consistent with previous studies although lower rates of coma (5–23%) and respiratory depression/dyspnoea (2–11%) have been reported.[3,7] In one study naloxone reversed sedation and apnoea in half of the patients,[3] with one patient experiencing a seizure immediately following administration of naloxone, which has also been reported in animals.[37] Marquardt et al.[31] reported fewer patients with coma and respiratory depression, and a similar response to naloxone.

There have been reports about tramadol causing serotonin toxicity.[6,17,18] However, the majority of cases are reported with co-ingested serotonergic drugs and only one unusual severe case has been described.[16] In our study there were no cases of serotonin toxicity based on the Hunter Serotonin Toxicity Criteria suggesting that tramadol is not a potent serotonergic drug compared with even selective serotonin reuptake inhibitors where the frequency of serotonin toxicity in overdose is about 15%.[19] Other authors have suggested that serotonin toxicity occurs,[3,15] but acknowledge that noradrenergic effects are more common, including tachycardia and mild hypertension.

Tramadol may be expected to have additive effects when taken with other opioids or drugs that cause depression of the central nervous system.[38,39] The majority of patients in this current study co-ingested one or more other medications, in particular serotonergic medications and benzodiazepines with the tramadol, which is consistent with case reports describing tramadol toxicity.[12–15,40] An interesting association was that patients co-ingesting benzodiazepines were less likely to have seizures suggesting that benzodiazepines may decrease the risk of seizures.

There were a number of limitations in this study including the retrospective design, the possibility of inaccuracies in the dose ingested by the patient, reported drugs not routinely confirmed by laboratory analysis and no patient follow-up. Although the study was a retrospective review of data collected over 13 years, the data were entered prospectively into a database and was collected on a preformatted admission sheet. This meant that there was unlikely to be any bias in the extraction of the data. The majority of the data elements, including the diagnosis of serotonin toxicity, were made prospectively based on database definitions.

There have always been concerns about the accuracy of patient's history, including which drug they ingested and what the dose was. Numerous studies from this unit support the accuracy of the history for the drug taken and that the reported dose is a good estimate of the actual dose ingested.[41] In addition, we found that seizures were dose dependent similar to other studies of tramadol overdose, supporting the usefulness of reported dose.[3,10]

In conclusion, tramadol overdose was found to be associated with a significant risk of seizures and respiratory depression in more severe cases, both of which appear to be related to the ingested dose. There were no cases of serotonin toxicity suggesting that in therapeutic doses tramadol is unlikely to cause more than minor serotonergic effects, while opioid-like effects and adrenergic effects (tachycardia and hypertension) appear to be more prominent than serotonergic effects.

Author contributions

NMR: Performed the research, analysed the data and wrote the manuscript. GKI: Designed the study, performed the research, co-analysed the data and co-wrote the manuscript.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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