ORIGINAL ARTICLE

An assessment of the centrally acting muscle relaxant tolperisone on driving ability and cognitive effects compared to placebo and cyclobenzaprine

Judy Caron PhD | Randall Kaye MD | Thomas Wessel MD, PhD
Amy Halseth PhD | Gary Kay PhD

1Neurana Pharmaceuticals, Inc., San Diego, CA, USA
2Drug Development, Cognitive Research Corporation, St. Petersburg, FL, USA

Correspondence
Randall Kaye, Neurana Pharmaceuticals, Inc., 4370 La Jolla Village Drive, Suite 860, San Diego CA 92122, USA.
Email: rkaye@neuranaapharma.com

Funding information
Funding for this study was provided by Neurana Pharmaceuticals, Inc.

Abstract

What is known and objective: Tolperisone is a centrally acting muscle relaxant under development in the United States as a treatment for acute and painful symptoms of muscle spasms. The objective of this three-way, randomized, blinded, three-period crossover study was to assess the safety and cognitive effects of tolperisone compared to placebo and the widely used muscle relaxant cyclobenzaprine in healthy volunteers.

Methods: Subjects were randomized to 1 of 3 treatment arms to receive tolperisone (150 mg), cyclobenzaprine (10 mg) or placebo 3 times per day (TID) in 3 separate study periods. Subjects completed a driving test on the Cognitive Research Corporation’s Driving Simulator (CRCDS Mini-Sim), a validated driving simulator, on day 1 at time to maximum plasma concentration, on day 2 before the morning dose of study drug and on day 3 at steady state following the morning dose. Subjects were assessed on various driving parameters and on a computer-administered digit-symbol substitution test (CogScreen symbol digit coding test). The driving scenario is a monotonous 100 km highway route on which subjects are instructed to maintain speed and lane position.

Results and discussion: The performance of subjects who had received tolperisone was not significantly different from those who had received placebo in terms of the primary end point: standard deviation of lateral position, a measure of weaving. Subjects who had received tolperisone also performed comparably to those who had received placebo on a range of secondary measures assessing driving ability, cognition and psychomotor performance. In contrast, subjects who had received cyclobenzaprine showed significant impairment compared to placebo ($P < .01$) on the primary end point of standard deviation of lateral position and on the majority of the secondary end points of driving ability. Despite their markedly poorer driving performance after receiving cyclobenzaprine, few subjects reported feeling unsafe to drive.
Although low back pain (LBP) is ranked among the top 5 reasons for visits to a physician in the United States, its management remains challenging. According to 2007 guideline recommendations, the first-line treatment of LBP typically involves acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). While NSAIDs have become the cornerstone of pain management for LBP, they are associated with serious gastrointestinal, cardiovascular and renal adverse events (AEs) and have been reported to be responsible for 11% of preventable drug-related hospital admissions. A public health advisory was issued in 2015 by the US Food and Drug Administration (FDA) stating that NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Approximately 35% of patients receive skeletal muscle relaxants (SMRs) for treatment of acute LBP; though effective for short-term relief, they are responsible for up to 50% of AEs in this patient population. Cyclobenzaprine, the most prescribed SMR for the treatment of LBP, can augment the effects of other central nervous system (CNS) depressants and is often misused and abused, according to the US Drug Enforcement Administration. Somnolence is also a common problem, making it unsafe to drive or operate machinery while on this medication. Indeed, the FDA recommends that for drugs with the potential to impair driving a dedicated driving study be conducted with either over-the-road testing or with a driving simulator.

Tolperisone is a centrally acting muscle relaxant that has been available in Europe and Asia for more than 30 years and is currently under investigation in the United States. At doses up to 450 mg/day (150 mg 3 times per day [TID]), tolperisone has been shown to treat acute and painful muscle spasm and spasticity in adults and elderly patients. In contrast with other centrally acting muscle relaxants, tolperisone has not been associated with hepatotoxicity, drowsiness or impairment of cognitive function. In this study in healthy volunteers, we have assessed the impact of tolperisone on driving ability and cognitive functioning compared to placebo and the widely used muscle relaxant cyclobenzaprine.

**What is new and conclusion:** Subjects who received tolperisone (150 mg TID) experienced no impact on various measures of driving, self-reported sleepiness and cognition measures compared to placebo, in contrast to those who received the widely used muscle relaxant cyclobenzaprine (10 mg TID).

**KEYWORDS**
cognition, low back pain, pain

---

### 2 | METHODS

#### 2.1 | Study design

This study (ClinicalTrials.gov number NCT03353922) was a three-way, randomized, blinded, three-period crossover study that was conducted at 2 independent research sites in the United States. The protocol and informed consent form were approved by a centralized institutional review board (Chesapeake Institutional Review Board, Columbia, MD) prior to study initiation. All subjects were healthy volunteers who provided written informed consent.

#### 2.2 | Subjects

Eligible subjects were aged 21-55 years and required to be in general good health. The age range ensured that experienced drivers were enrolled who did not have the known issues and variability of younger or older drivers. In addition, their clinical laboratory assessments and physical examinations demonstrated no relevant clinical abnormalities. Subjects were required to be active drivers (>10,000 miles per year for the previous 3 years) and to be reasonably capable of driving tasks, as demonstrated by performing no worse than 1 standard deviation (SD) above the mean based on normative data for drivers completing the 20-minute Country Vigilance Divided Attention (CVDA) driving scenario. Excluding the variability added by less experienced novice drivers is typical for driving studies of this size. Drivers who cannot maintain stable and controlled steering and consistent speed were also excluded as their performance would be judged as impaired and not generalizable to the overwhelming majority of drivers. No psychoactive or sleep-promoting concomitant medications were permitted. Alcohol use and smoking were not allowed 24 hours prior to admission and throughout the study until discharge from the clinic.

#### 2.3 | Study drugs and dosing

Subjects were randomized to 1 of 3 treatment arms and received blinded tablets of tolperisone 150 mg TID, cyclobenzaprine 10 mg TID (acting as a positive control) and placebo TID in 3 separate study
periods. Subjects received a total of 7 doses of each study drug. Study drug was administered in each study period in the morning, at midday and at bedtime on days 1 and 2, and in the morning only on day 3. The washout periods exceeded 5 half-lives for each drug (tolperisone half-life = 2–3 hours; cyclobenzaprine half-life = 18 hours).

2.4 | CVDA driving scenario

The CVDA driving scenario is a 100 km, monotonous, 2-lane highway driving task that includes a secondary visual vigilance task. This scenario has been demonstrated to be sensitive to the effects of low-dose alcohol, sleepiness, over-the-counter antihistamines, muscle relaxants, anxiolytics and benzodiazepine and to the residual effects of a night-time medication for insomnia (ie zopiclone).18-21 The primary end point of the CVDA scenario is the standard deviation of lateral position (SDLP). This is a measure of an individual's ability to maintain lane position. Secondary driving end points derived from the CVDA include parameters related to lane exceedance, speed deviation, excessive speed in corners, divided attention and collisions.

Subjects were screened for simulator sickness and were familiarized with the driving simulation. On day –1, following admission to the clinic, subjects performed a 20-minute practice drive. At 1 hour after the midday dose of study drug on day 1 (at time to maximum plasma concentration \(T_{\text{max}}\)), subjects began the 1-hour CVDA driving scenario. On day 2, to assess next-day residual effects of the drug, subjects completed the CVDA driving test prior to receiving the morning dose of study drug. On day 3, subjects began the CVDA driving test after the morning dose of study drug to evaluate the effects of repeated dosing.

2.5 | Cognitive function test

On days 1-3 of each study period, the CogScreen (CogScreen LLC; St. Petersburg, FL) symbol digit coding (SDC) test, a computer-administered digit-symbol substitution test, was completed prior to the driving simulation. The SDC test provides measures of attention, visual scanning, working memory and speed of information processing.19,22

2.6 | Self-reported measures

On days 1-3 of each study period, the Karolinska Sleepiness Scale and self-perceived safety to drive tests were completed to assess subjects’ drowsiness and awareness of driving capability. Subjects provided a yes or no answer to whether they felt safe to drive prior to the driving simulation. In addition, after each driving simulation test, subjects answered 2 questions: 1) How well you think you drove for the last 60 minutes? and 2) How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects recorded their response to each question by drawing a vertical line on a 100 mm horizontal visual analog scale with anchors for the scale of ‘not satisfactory’ and ‘satisfactory’ and ‘not motivated’ and ‘motivated’ for the 2 questions.

2.7 | Pharmacokinetic sample collection and processing

Blood samples for pharmacokinetic analysis were collected before the morning dose of study drug on days 1-3 and at 15 to 30 minutes after completion of the CVDA driving scenario on days 1 and 3 (approximately 2 hours after the second dose and morning dose of study drug, respectively).

2.8 | Sample size and statistical methods

This study was designed to test the non-inferiority of tolperisone relative to placebo, with a cyclobenzaprine test versus placebo to confirm the sensitivity of the driving simulator to detect treatment effects. Formal statistical tests were two-sided and were tested at the alpha = 0.05 level of significance. Control for multiple comparisons was only included in the analysis of the primary end point. This was accomplished using a hierarchical testing approach with the following sequence of testing: day 1 (single dose), day 2 (residual effect) and day 3 (steady state). Non-inferiority assessments for tolperisone versus placebo at each time point were to occur if prior comparisons also indicated non-inferiority. No adjustments to alpha levels were made for either the comparison of cyclobenzaprine to placebo or tolperisone (cyclobenzaprine was included to test for assay sensitivity) or for secondary end points or analyses. For this reason, \(P\)-values for cyclobenzaprine comparisons and for secondary end points should be interpreted with caution. For non-parametric secondary end points (eg lane exceedance), \(P\)-values were derived from log-transformed data. No imputation of missing data was performed.

The primary end point, SDLP, was analysed using a normal theory mixed effects model with fixed effects for sequence, period, and treatment, and a random effect for a subject within the sequence. An unstructured covariance structure and Kenward-Roger degrees of freedom were used. Pairwise comparisons (hypothesis tests) of differences in the least squares means and 95% confidence intervals on differences were provided for initial dose effect: cyclobenzaprine versus placebo, tolperisone versus placebo and tolperisone versus cyclobenzaprine all following day 1 afternoon dose. Hypothesis tests were also shown for next-day residual dose effect: cyclobenzaprine versus placebo, tolperisone versus placebo and tolperisone versus cyclobenzaprine all prior to day 2 morning dose. Hypothesis tests were shown for steady state dose effect: cyclobenzaprine versus placebo, tolperisone versus placebo and tolperisone versus cyclobenzaprine all following day 3 morning dose. Pairwise within-subject differences in SDLP between placebo and historical levels linked to crash risk23,24 were compared using McNemar’s test. These pairwise within-subject
differences in SDLP were also tested for symmetry about zero using the maximally selected McNemar test. Summary statistics were provided for SDLP for each time point and treatment period.

The relationship between tolperisone and cyclobenzaprine plasma drug levels and driving performance was assessed by correlational analyses.

### 3 | RESULTS AND DISCUSSION

#### 3.1 | Subject disposition and demographics

Of the 35 subjects enrolled in this study’s intent-to-treat population, 31 (88.6%) subjects completed the study and received all planned doses of all 3 study drugs. After day 1 of tolperisone administration, 1 subject prematurely withdrew from the study due to a moderate AE of a Crohn’s disease flare-up that was considered by investigators to be unrelated to study drug. Three other subjects withdrew from the study before receiving all 3 study drugs. Two additional subjects were removed from the efficacy analysis population due to a confirmed mistake in dosing in which subjects received cyclobenzaprine instead of tolperisone during period 2. Subject demographics are presented in Table 1.

#### 3.2 | Primary driving scenario end point

For the primary end point of SDLP on days 1-3, there was no significant difference between tolperisone and placebo (all $P > .7$). Results for tolperisone did not exceed the a priori non-inferiority criteria of 4.4 cm (ie the magnitude of increase in SDLP seen at 0.05% blood alcohol content). Paired differences between tolperisone and placebo were found to be symmetrical about zero. In contrast, the positive control, cyclobenzaprine, showed significant impairment compared to placebo on day 1 ($P < .001$), day 2 ($P < .001$) and day 3 ($P = .0081$) (Figure 1). Again, in contrast to tolperisone, analysis of paired differences between cyclobenzaprine and placebo was found to be asymmetric, with significantly more subjects showing an increase in SDLP under the cyclobenzaprine condition (Figure 2). On days 1 and 2, 58.6% (17/29) and 44.8% (13/29) of subjects receiving cyclobenzaprine had increases in SDLP that exceeded the crash-risk threshold (ie, an increase of 4.4 cm or more in SDLP).

#### 3.3 | Secondary Driving scenario end points

Secondary driving end points related to lane position control, speed control, total collisions and excessive speed in corners all showed no significant differences between tolperisone and placebo (Table 2). In contrast, at most time points for the secondary end points, there was a significant difference between cyclobenzaprine and placebo, indicating increased driving impairment. Measures related to divided attention assessed during the driving simulation are shown in Table 3. Generally, there were no differences between groups in the number of correct responses, omission errors or commission errors.

#### 3.4 | Cognitive function test

The key assessment on the SDC test, the number of correct responses, showed no significant effect for tolperisone compared to placebo on days 1, 2 or 3. In contrast, there were significantly fewer ($P < .05$) correct responses for cyclobenzaprine compared to placebo on day 2 (Table 4). In addition, there was no evidence of decline in accuracy with tolperisone compared to placebo. In contrast, there was a significant decline in accuracy with cyclobenzaprine compared to placebo on day 2 ($P < .05$). Reaction time variability (ie SD of reaction time) on the SDC test was not significantly impacted for tolperisone compared to placebo, but for cyclobenzaprine, it approached significance on day 1 and was significantly higher on day 2; this finding indicated more inconsistency in response speed ($P < .05$).

#### 3.5 | Self-reported measures

Self-reported sleepiness, self-reported motivation and self-appraised driving performance showed no significant effects for tolperisone compared to placebo, while subjects reported increased sleepiness (day 1), decreased motivation (days 1 and 2) and worse performance on the driving task (days 1 and 2) with cyclobenzaprine (Table 5). In addition to their actual performance on the driving test, the data demonstrate a lack of awareness of driving impairment following dosing with cyclobenzaprine (Table 6). When asked prior to the

### TABLE 1  Demographic characteristics

| Characteristic                  | Overall N = 35 |
|---------------------------------|----------------|
| Age, y                          | 35.4           |
| Mean                            | 35.4           |
| Standard deviation              | 9.5            |
| Median                          | 32             |
| Range                           | 22-54          |
| Gender, n (%)                   |                |
| Male                            | 24 (68.6)      |
| Female                          | 11 (31.4)      |
| Ethnicity, n (%)                |                |
| Not Hispanic or Latino          | 25 (71.4)      |
| Hispanic or Latino              | 10 (28.6)      |
| Race, n (%)                     |                |
| Black or African American       | 17 (48.6)      |
| White                           | 17 (48.6)      |
| Asian                           | 1 (2.9)        |
| Body mass index, kg/m²          |                |
| Mean                            | 25.1           |
| Standard deviation              | 2.9            |
| Median                          | 25.2           |
| Range                           | 18.6-31.5      |
driving test whether they felt safe to drive during cyclobenzaprine treatment, only 10.3% and 3.4% of subjects reported on days 1 and 2, respectively, that they felt unsafe.

3.6 | Pharmacokinetics

Tolperisone has a $T_{\text{max}}$ of 1 hour and a half-life of 2-3 hours. In contrast, cyclobenzaprine has a $T_{\text{max}}$ of 7 hours and a long half-life (>18 hours); thus, it continued to accumulate over the 3 dosing days. Mean $\pm$ SD plasma tolperisone concentrations approximately 2 hours after dosing on day 1, prior to dosing on day 2 and approximately 2 hours after dosing on day 3 were 28.9 $\pm$ 26.0, 3.5 $\pm$ 3.6 and 20.2 $\pm$ 15.7 ng/mL. There were no relationships between tolperisone plasma concentrations on any of the days and measures of driving performance (including the primary end point of SDLP), cognitive functioning or self-report measures.

3.7 | Safety

Safety was assessed in all subjects who received at least 1 dose of study drug. The incidence of AEs was 36.4% (12/33) in subjects receiving tolperisone, 45.5% (15/33) in subjects receiving...
cyclobenzaprine and 29.0% (9/31) in subjects receiving placebo. The most common AEs for subjects receiving tolperisone, cyclobenzaprine and placebo, respectively, were somnolence (15.2%, 30.3% and 6.5%), headache (6.1%, 0% and 0%) and dizziness (3.0%, 9.1% and 6.5%). Most AEs were mild or moderate in intensity, and there were no serious AEs. There was 1 severe AE of dizziness reported by a subject receiving cyclobenzaprine.

### WHAT IS NEW AND CONCLUSIONS

Psychotropic medicines and those that impact the CNS, including SMRs, have been shown to result in impairment and have an effect on various measures of driving performance. Le Roy and Morse utilized an administrative pharmaceutical claims database in a project for the National Highway Traffic Safety Administration to determine...
how often various combinations of medications were observed among drivers who experienced a motor vehicle crash compared to those who did not. Their study evaluated the medication use of 33,519 drivers who had motor vehicle crashes (5378 were aged >50 years) and the medication use of >100,000 matched controls (3 for each case, matched for age and gender; 16,134 were aged >50 years). Focusing on driving impairments in drivers aged >50 years, drivers were 1.2 to 7.5 times more likely to have been involved in a motor vehicle crash if they had taken medications in 35 of 90 medication classes identified as potentially driver-impairing. They determined that SMRs are associated with a twofold increase in the risk for motor vehicle crashes (odds ratio, 2.09; \( P < .01 \)). SMRs create greater susceptibility to adverse CNS

### Table 3
Measures of divided attention during the driving test (per protocol population)

|                  | Placebo | Tolperisone | Cyclobenzaprine | P-value |
|------------------|---------|-------------|-----------------|---------|
| **Correct response** |         |             |                 |         |
| Day 1            | 19.6 (0.73) | 19.4 (0.96) | 19.1 (2.02)     | .2135   |
| Day 2            | 19.7 (0.72) | 19.7 (0.70) | 19.5 (1.18)     | .9753   |
| Day 3            | 19.6 (0.57) | 19.7 (0.71) | 19.2 (2.72)     | .9245   |
| **Omission errors** |         |             |                 |         |
| Day 1            | 0.4 (0.73)  | 0.5 (0.96)  | 0.9 (2.02)      | .2719   |
| Day 2            | 0.3 (0.72)  | 0.3 (0.69)  | 0.5 (1.18)      | .9806   |
| Day 3            | 0.3 (0.55)  | 0.3 (0.71)  | 0.4 (1.10)      | .0671   |
| **Comission errors** |         |             |                 |         |
| Day 1            | 0.1 (0.26)  | 2.4 (13.29) | 0.2 (0.40)      | .9297   |
| Day 2            | 0.1 (0.26)  | 2.7 (14.04) | 0.1 (0.34)      | .6941   |
| Day 3            | 0.1 (0.41)  | 2.6 (13.74) | 0.1 (0.35)      | .5728   |
| **Reaction time (RT)** |       |             |                 |         |
| Day 1            | 1.33 (0.38) | 1.20 (0.30) | 1.40 (0.47)     | .0155   |
| Day 2            | 1.28 (0.38) | 1.25 (0.34) | 1.32 (0.36)     | .4567   |
| Day 3            | 1.26 (0.35) | 1.23 (0.33) | 1.29 (0.37)     | .4408   |
| **Standard deviation of RT** |   |             |                 |         |
| Day 1            | 0.52 (0.24) | 0.44 (0.22) | 0.51 (0.31)     | .0342   |
| Day 2            | 0.47 (0.26) | 0.38 (0.23) | 0.51 (0.27)     | .1389   |
| Day 3            | 0.40 (0.24) | 0.40 (0.25) | 0.52 (0.31)     | .7368   |

### Table 4
Cognitive function measures on days 1-3 of each treatment (per protocol population)

|                  | Placebo | Tolperisone | Cyclobenzaprine | P-value |
|------------------|---------|-------------|-----------------|---------|
| **Number of correct responses** |         |             |                 |         |
| Day 1            | 66.8 (11.38) | 66.4 (10.36) | 66.2 (10.35)    | .8201   |
| Day 2            | 68.8 (10.26) | 69.4 (10.12) | 66.3 (10.73)    | .1244   |
| Day 3            | 68.8 (10.59) | 70.1 (10.35) | 67.3 (11.42)    | .2106   |
| **Accuracy**     |         |             |                 |         |
| Day 1            | 99.41 (1.35) | 99.33 (1.33) | 99.18 (1.34)    | .8299   |
| Day 2            | 99.46 (1.08) | 99.30 (1.46) | 98.71 (2.33)    | .5387   |
| Day 3            | 99.46 (0.99) | 99.24 (2.51) | 99.63 (0.74)    | .4275   |
| **Standard deviation of reaction time** |       |             |                 |         |
| Day 1            | 0.51 (0.14)  | 0.53 (0.15)  | 0.56 (0.14)     | .3887   |
| Day 2            | 0.51 (0.13)  | 0.53 (0.16)  | 0.58 (0.18)     | .6483   |
| Day 3            | 0.54 (0.18)  | 0.48 (0.11)  | 0.57 (0.33)     | .5239   |
effects in elderly patients and pose a clear risk that is more broadly appreciated in the medical community, and SMRs continue to be included in the Beers criteria of potentially inappropriate medications in older adults.\textsuperscript{28} SMRs are poorly tolerated by elderly patients because they cause anticholinergic and other AEs related to their mixed pharmacological properties, frequently resulting in somnolence and weakness.\textsuperscript{29} Given the effects of SMRs on driving ability and their widespread use (in particularly cyclobenzaprine) in the treatment of LBP, the healthcare community has prioritized the need to develop an effective therapeutic option that is not associated with sleepiness, somnolence and driving impairment. This study demonstrated that tolperisone (150 mg TID) did not impair driving performance based on 3 criteria: (1) driving performance (ie SDLP, a validated driving performance measure) was not statistically different from placebo following dosing on day 1, the morning following the first day of dosing (day 2) or on day 3 at steady state; (2) under all 3 tolperisone dosing conditions, SDLP did not exceed the upper limit of the 95\% confidence interval for the effect of alcohol at 0.05\% BAC; and (3) symmetry analysis showed that the distribution of the paired differences between placebo and tolperisone was not asymmetrical around zero (for all 3 tolperisone dosing conditions). Results for secondary driving end points, measures of cognitive functioning and self-report measures also demonstrated no significant effects of tolperisone compared to placebo at $T_{\text{max}}$, on the morning following an evening dose and following repeated dosing. AEs with tolperisone were mild and were not related to driving outcomes. In contrast, patients who received cyclobenzaprine (10 mg TID) as a positive control demonstrated significantly impaired driving performance on most end points compared to placebo.

Once efficacy is established, and tolperisone would represent a novel SMR with the ability to treat patients without the drowsiness associated with other known SMRs and would be an important alternative for the treatment of acute muscle spasms. In patients aged $\geq 65$ years, the use of any type of SMR, including cyclobenzaprine, carisoprodol, orphenadrine, baclofen, methocarbamol, tizanidine and metaxalone, has been shown to have a 35\% higher likelihood of injury in the 60 days post-SMR initiation after controlling for confounding medications.\textsuperscript{29} Cyclobenzaprine and other SMRs are associated with driving impairment on various cognitive measures associated with driving.\textsuperscript{8} Although tolperisone needs to be tested directly, the lack of effect on driving performance and other measures of cognitive function demonstrated in the current study suggests that tolperisone could also be used in an elderly population to avoid the adverse CNS effects associated with other SMRs.

**ACKNOWLEDGEMENTS**

The authors would like to thank Johnna Hannah (Neurana Pharmaceuticals) and David McLaughlin (Cognitive Research) for critical review of the manuscript. The authors also thank Gary Withereill, PhD (WithMax Consulting, Inc), and David Gibson, PhD, CMPP (ApotheCom), for their writing and editorial support, which was funded by Neurana Pharmaceuticals, Inc.

**CONFLICTS OF INTEREST**

J. Caron, T. Wessel and A. Halseth own stock and/or stock options in Neurana Pharmaceuticals, Inc. R. Kaye is an employee of and owns stock in Neurana Pharmaceuticals, Inc. G. Kay is co-owner of Cognitive Research Corporation.
REFERENCES

1. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-491.

2. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiol Drug Saf. 2014;23:43-50.

3. Witenko C, Moorman-Li R, Motycka C, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. Pharm Ther. 2014;39:427-435.

4. US Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory. Published July 9, 2015. Accessed January 31, 2020.

5. Drug Enforcement Administration. Cyclobenzaprine (Brand Name: Flexeril®, Amrix®). Available at: https://www.deadversion.usdoj.gov/drug_chem_info/cyclobenzaprine.pdf. Published January 21, 2019. Accessed January 31, 2020.

6. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiol Drug Saf. 2014;23:43-50.

7. Vakulin A, Baulk SD, Catcheside PG, et al. The effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnoea. Ann Intern Med. 2009;151:447-455.

8. Hetland A, Carr DB. Medications and impaired driving: a review of the literature. Ann Pharmacother. 2014;48:494-506.

9. Kohnen R, Kruger HP, Dulin J. A human subject study of sedative effects of medications in combination with alcohol. Psycho. 1995;21:768-775.

10. Leung S, Croft RJ, Jackson ML, Howard ME, McKenzie RJ. A comparison of the effect of mobile phone use and alcohol consumption on driving simulation performance. Traffic Inj Prev. 2012;13:566-574.

11. Pratzel HG, Alken RG, Ramm S. Efficacy and tolerance of repeated oral doses of tolperisone hydrochloride in the treatment of painful reflex muscle spasm: results of a prospective placebo-controlled double-blind trial. Pain. 1996;67:417-425.

12. Stamenova PV, Koytchev R, Kuhn K, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of tolperisone and thiocolchicoside in acute low back pain and spinal muscle spasticity. Asian Spine J. 2012;6:115-122.

13. Agarwal S, Patel T, Shah N, Patel BM. Comparative study of therapeautic response to baclofen vs tolperisone in spasticity. Biomed Pharmacother. 2017;87:628-635.

14. European Medicines Agency. Assessment report for tolperisone-containing medicinal products. Procedure number: EMEA/H/A-31/1311. Available at: https://www.ema.europa.eu/en/documents/referral/assessment-report-tolperisone-containing-medicinal-products_en.pdf. Published January 21, 2013. Accessed January 31, 2020.

15. Dulin J, Kovacs L, Ramm S, Horvath F, Ebeling L, Kohnen R. Evaluation of sedative effects of single and repeated doses of 50 mg and 150 mg tolperisone hydrochloride. Results of a prospective, randomized, double-blind, placebo-controlled trial. Pharmacopsychiatry. 1998;31:137-142.

16. Rao R, Panghate A, Chandranwale A, et al. Clinical comparative study: efficacy and tolerability of tolperisone and thiocholchicoside in acute low back pain and spinal muscle spasticity. Asian Spine J. 2012;6:115-122.

17. Prabhoo R, Keny S, Prabhoo T, Sinh A, Rana R. A phase IV observational multi-centre, open-label study on efficacy and safety of tolperisone 150 mg in patients with painful muscle spasm associated with degenerative or inflammatory diseases of the musculoskeletal system. J Assoc Physicians India. 2011;59:33-37.

18. Kay GG, Hochadel T, Sicard E, Natarajan KK, Kim NN. Next-day residual effects of flibanserin on simulated driving performance in premenopausal women. Hum Psychopharmacol Clin Exp. 2017;32:1-9.

19. Kay GG, Schwartz HI, Wingertzahn MA, Jayawardena S, Rosenbarg RP. Next-day residual effects of gabapentin, diphenhydramine, and triazolam on simulated driving performance in healthy volunteers: a phase 3, randomized, double-blind, placebo-controlled, crossover trial. Hum Psychopharmacol. 2016;31:217-226.

20. Simen AA, Gargano C, Cha JH, et al. A randomized, crossover, placebo-controlled clinical trial to assess the sensitivity of the CRCDS Mini-Sim to the next-day residual effects of zopiclone. Ther Adv Drug Saf. 2015;6:86-97.

21. Pearlman EM, Doty EG, Denney EB, et al. Effects of lamisilam in on driving performance: results of 2 randomized, blinded, crossover simulated driving studies with placebo and active controls [abstract IOR06]. Headache. 2019;59:22.

22. Statistics Solutions. Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV). Available at: https://www.statisticssolutions.com/wechsler-adult-intelligence-scale-fourth-edition-wais-iv. Accessed January 31, 2020.

23. Moskowitz H, Burns M, Fiorentino D, Smiley A, Zador P. Driver characteristics and impairment at various BACs (DOT HS 809 075). Washington, DC: Southern California Research Institute, National Highway Traffic Safety Administration; 2000.

24. Kay G, Ahmad O, Brown T, Veit A. Comparison of the MiniSim and STISIM driving simulators for the detection of impairment: an alcohol validation study. Proceedings of the Seventh International Driving Symposium on Human Factors in Driver Assessment, Training, and Vehicle Design. 2013. Available at: https://ir.uiowa.edu/cgi/viewcontent.cgi?article=1487&context=drivingassessment. Accessed January 31, 2020.

25. Laska E, Meisner M, Wenderling J. A maximally selected test of symmetry about zero. Stat Med. 2012;31:3178-3191.

26. Kay GG, Logan BK. Drugged driving expert panel report: a consensus protocol for assessing the potential of drugs to impair driving. 2011. Available at: https://www.nhtsa.gov/sites/nhtsa.dot.gov/files/811438.pdf. Accessed January 21, 2020.

27. LeRoy AA, Morse ML. Department of Transportation. HS 810 858. Multiple medications and vehicle crashes: analysis of databases. 2008. Available at: http://www.nhtsa.gov/DOT/NHTSA/Traffic%20Injury%20Control/Articles/Associated%20Files/810858.pdf. Accessed January 31, 2020.

28. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63:2227-2246.

29. Billups SJ, Delate T, Hoover B. Injury in an elderly population before and after initiating a skeletal muscle relaxant. Ann Pharmacother. 2011;45:485-491.