Somatic dysfunction during carisoprodol cessation: Evidence for a carisoprodol withdrawal syndrome

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Carisoprodol is a commonly used skeletal muscle relaxant with potential for abuse because of its active metabolite, meprobamate, and several reports have suggested that patients abruptly stopping intake of carisoprodol may have a withdrawal syndrome. The authors studied changes in the occurrence of somatic dysfunctions in five patients during an 8-day period following discontinuation from large doses of carisoprodol. Results showed that the number of somatic dysfunctions changed significantly during the withdrawal period. Each patient had an increase in the number of somatic dysfunctions during the first 3 days after cessation of carisoprodol with return to at or near baseline by the eighth day. This was reflected statistically in a significant-within-subjects effect for time. Results of supplemental analyses revealed a significant component of the effect and a trend for the quadratic component to be significant. Increases in the number of somatic dysfunctions during carisoprodol discontinuation support the existence of a carisoprodol withdrawal syndrome.

(Key words: carisoprodol, meprobamate, somatic dysfunction, withdrawal, addiction)

Carisoprodol (Soma) is a centrally acting skeletal muscle relaxant commonly used in the treatment of musculoskeletal conditions with muscle spasms. The exact mechanism of action is unknown, but the drug is thought to act by causing sedation rather than by direct skeletal relaxation. Carisoprodol is metabolized in the liver to hydroxycarisoprodol, hydroxymeprobamate, and meprobamate, which are excreted by the kidneys. The pharmacologically active metabolite is meprobamate, which has a half-life of 11.3 hours, or up to 48 hours with chronic usage.

Meprobamate is a controlled substance with known abuse potential. Although carisoprodol is metabolized to meprobamate, it is not a controlled substance at the federal level. However, a number of reports suggest that it has potential for abuse and probably should also be a controlled substance. Reports of carisoprodol abuse have included a patient trying to obtain multiple prescriptions from multiple physicians; a patient against whom legal action was taken for forging carisoprodol prescriptions; a group of four patients regularly obtaining carisoprodol and then using it in excessive amounts to achieve mind-altering effects; a group of patients attempting to use the drug as a substitute for opiates; a patient who abused carisoprodol after obtaining it through a veterinary mail order service; a patient who became dependent on carisoprodol as a sleep aid; a patient who used carisoprodol as a substitute for more potent illicit drugs; a patient who used the drug to calm himself after using cocaine; and a woman who took 30 to 50 tablets daily for 2 years.

Carisoprodol may also be used to augment the effect of sedatives such as benzodiazepines or alcohol. A retrospective study of cases examined at the Jefferson County (Alabama) Coroner’s Office from January 1, 1986, to October 31, 1997, revealed that carisoprodol was present in 24 cases, and the reviewers concluded that the drug was probably partly responsible for those deaths. In part because of reports such as these, some states have begun to restrict the availability of carisoprodol. Effective January 1, 1998, carisoprodol became a schedule IV drug in Alabama.

A number of investigators have described withdrawal symptoms such as restlessness, insomnia, anxiety, muscle twitching, incoordination, loss of appetite, nausea, and vomiting after abrupt cessation of meprobamate treatment. Severe withdrawal from large doses can produce agitation, hallucinations, and seizures. However, other controlled studies suggest that if meprobamate treatment is kept within the recommended dosage range, few patients have withdrawal discomfort. Evidence of a carisoprodol withdrawal syndrome has not been firmly established.

In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from dosages as high as 1 g/kg/d. In a human study, abrupt cessation of 100 mg/kg/d (approx...
imately five times the recommended daily adult dosage) was followed in some subjects by only mild withdrawal symptoms such as abdominal cramps, insomnia, chills, headache, and nausea. Delirium and convulsions did not occur. However, several of the case studies reporting carisoprodol abuse demonstrated withdrawal phenomena. Luehr et al described a 46-year-old woman who abused carisoprodol at a dose of thirteen tablets at bedtime after receiving it from a veterinary mail order service. This woman had a daytime abstinence syndrome consisting of anxiety and tremors, which resolved with the ingestion of additional tablets. Features of withdrawal were reported by 69% of Indian carisoprodol abusers described by Sidkar et al and included body aches, anxiety, restlessness, and insomnia. Reeves et al described a patient who with cessation from six to eight carisoprodol tablets daily had severe paravertebral spasms and pain, headaches, nausea, and dysphoria as well as another patient taking four tablets at bedtime who with cessation of the medication had insomnia, irritability, back pain, and headache. Morse and Chua reported that a 44-year-old patient who took 30 to 50 tablets per day had anxiety, tremulousness, insomnia, and a desire to resume carisoprodol during attempts at abstinence. In a Norwegian study, carisoprodol was gradually withdrawn from nine prisoners who had been taking 700 to 2100 mg/d for at least 9 months. Most of the patients reported anxiety, insomnia, irritability, cranial and muscular pain, and vegetative symptoms.

Because carisoprodol is primarily prescribed for musculoskeletal conditions with muscle spasms and because withdrawal symptoms often include back pain or related symptoms, we decided to investigate the role of somatic dysfunction during carisoprodol withdrawal. The purpose of this study was to determine whether the changes in frequency of occurrence of somatic dysfunction support the concept of a carisoprodol withdrawal syndrome.

### Methods

Five patients who had taken carisoprodol in dosages of 2100 mg/d or more for at least 1 year were monitored closely on an outpatient basis following cessation of carisoprodol. (The usual dosage is one 350-mg tablet four times daily, 1400 mg/d.) The patients ranged in age from 26 years to 41 years old (average, 35.2 years), were in good physical health, and had been free of other drug or alcohol usage for at least 6 months. Further characteristics of each patient are shown in Table 1. All patients signed informed consent forms approved by Louisiana State University.

### Table 1: Characteristics of Patients Undergoing Carisoprodol Cessation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Carisoprodol dosage</th>
<th>Withdrawal symptoms</th>
<th>Time of onset of withdrawal symptoms</th>
<th>Time of maximum intensity of withdrawal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>F</td>
<td>2800 mg/d</td>
<td>Headache, back pain, insomnia, irritability, anxiety</td>
<td>Day 2</td>
<td>Day 5</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>2100 mg/d</td>
<td>Mild anxiety, irritability (minimal complaints)</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>M</td>
<td>≥4200 mg/d</td>
<td>Back pain, insomnia, irritability</td>
<td>Day 2</td>
<td>Day 4</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>F</td>
<td>2100 mg/d</td>
<td>Mild insomnia, anxiety (minimal complaints)</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>3500 mg/d</td>
<td>Headache, back pain, neck stiffness, anxiety, irritability</td>
<td>Day 2</td>
<td>Day 4</td>
</tr>
</tbody>
</table>
University (Shreveport) School of Medicine Institutional Review Board.

Patients were examined before discontinuing carisoprodol, and their somatic dysfunctions were identified (baseline). Each patient abruptly discontinued carisoprodol on a Sunday and underwent examination on the following Monday (day 1), Wednesday (day 3), Friday (day 5), and Monday (day 8). At each visit, patients were questioned for symptoms of withdrawal. The somatic dysfunctions present were determined, and the patients were examined for any other acute physical abnormalities (none were detected). Urine drugs screens were performed at baseline and on each subsequent visit to rule out the presence of alcohol or other drugs (all were negative). The patients were questioned to determine the time of onset of withdrawal symptoms as well as time of maximum intensity of the symptoms. Each of the patients was able to tolerate the withdrawal process without resuming carisoprodol intake, or treatment with another agent.

To determine somatic dysfunctions, musculoskeletal examination of the cervical, thoracic, and lumbar spine was performed as described by Greenman.21 The spine was examined for restrictions of sidebending, rotation, forward bending, and backward bending of individual vertebral segments by palpating cervical segments with the patient in a supine position21(pp127-134); by palpating thoracic segments with the patient in the sitting and prone positions21(pp151-153); and by palpating lumbar segments with the patient in the sitting and prone positions.21(pp205-206) While doing the palpatory maneuvers, any segmental asymmetry or abnormality of tissue texture was noted. Somatic dysfunction was defined as being present in any vertebral segment in which asymmetry, range of motion abnormality, or tissue abnormality was detected.

Each patient was studied at baseline and at the specified times described previously. Data for the study consisted of the number of somatic dysfunctions detected for each patient at baseline and on days 1, 3, 5, and 8. Using the SPSS statistical package, the numbers of somatic dysfunctions were standardized of the three. This done, the effect of time was statistically significant, with an observed power of 0.57 and a moderate effect size (Eta squared) of 0.58. This analysis verified that there were statistically significant changes in the number of somatic dysfunctions detected during withdrawal from carisoprodol.

Within-subjects contrasts were then examined. The linear effect of time was statistically significant, with an observed power of 0.91 (F(1) = 20.00; P = .01). The linear trend is of clinical significance because it demonstrates a relationship between carisoprodol cessation and the increase in the number of somatic dysfunctions, though the demonstrated relationship is correlational rather than causal.

There is also a trend for the quadratic effect of time to be significant (F(1) = 6.30; P = .07). Observed power for this within-subjects contrast was an inadequate 0.48. Higher-order contrasts were not statistically significant. The quadratic contrast is of particular theoretical importance to the issue of whether the number of somatic dysfunctions tracks physiologic adjustment to the withdrawal of carisoprodol. The prediction that the number of somatic dysfunctions increases as withdrawal ensues and then decreases after withdrawal peaks and subsides would be supported by a significant quadratic
trend. The fact that there was a trend toward statistical significance despite low power suggests that given a modest increase in the number of subjects, statistical significance would be attained.

Discussion
This study shows that in individuals taking larger-than-recommended doses of carisoprodol, abrupt cessation of carisoprodol may result in an increase in the number of somatic dysfunctions for a period of time. This increase tends to be greater in patients taking larger doses of the drug and tends to occur concomitantly with changes in complaints of various physical symptoms, ie, the number of somatic dysfunctions tended to increase or decrease in concert with the patient’s complaints. However, as mentioned previously, changes in the number of somatic dysfunctions occurred with carisoprodol cessation even in those patients who had only minimal complaints.

It is not clear by what mechanism cessation from large doses of carisoprodol would cause changes in the number of somatic dysfunctions for a period of time. This increase tends to be greater in patients taking larger doses of the drug and tends to occur concomitantly with changes in complaints of various physical symptoms, ie, the number of somatic dysfunctions tended to increase or decrease in concert with the patient’s complaints. However, as mentioned previously, changes in the number of somatic dysfunctions occurred with carisoprodol cessation even in those patients who had only minimal complaints.

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Our findings support the argument that a carisoprodol withdrawal syndrome exists and that carisoprodol is a drug with potential for abuse. Our findings also suggest that the musculoskeletal system is affected in a quantifiable manner in some patients who have withdrawal from certain drugs. Potential exists for further research related to the role of somatic dysfunction during drug withdrawal and in related areas.

A limitation of this study is the small number of patients. This was unavoidable; in our institution, carisoprodol is viewed and managed as a controlled substance. Virtually all patients previously prescribed the drug for other than short periods in appropriate dosages have been taken off it, leaving few potential subjects for a study of this type. Recently, recommendations have been made that carisoprodol be classified as a controlled substance in our state.

In conclusion, patients may have a withdrawal syndrome if they abruptly stop taking large doses of carisoprodol. Carisoprodol is a drug with abuse potential because of its meprobamate metabolite and should be made a controlled substance at the federal level. However, despite a volume of evidence to support this conclusion, many physicians remain unaware of the abuse potential of carisoprodol.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>3</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>5</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Average, all patients 4.4 5.4 9.2 7.4 4.4

Average, patients with significant withdrawal symptoms* 4.7 6.0 10.7 9.0 4.3

Average, patients with minimal withdrawal symptoms† 4.0 4.5 7.0 5.0 4.5

*Patients 1, 3, and 5.
†Patients 2 and 4.
Figure. Changes in number of somatic dysfunctions during withdrawal of carisoprodol.
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References


