Published in final edited form as:

Drug Alcohol Depend. 2012 June 1; 123(1-3): 29–34. doi:10.1016/j.drugalcdep.2011.10.010.

Carisoprodol Tolerance and Precipitated Withdrawal

Michael B. Gatch, Jacques D. Nguyen, Theresa Carbonaro, and Michael J. Forster

Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX 76107-2699

Abstract

Aims—Carisoprodol is a muscle relaxant that acts at the GABA_A receptor. Concerns about the abuse liability of carisoprodol are increasing, but evidence that carisoprodol produces tolerance and a significant withdrawal syndrome has yet to be established. The purpose of the current study was to determine if repeated administration of carisoprodol produces tolerance and withdrawal signs in a mouse model.

Methods—Carisoprodol (0, 100, 200, 300, or 500 mg/kg bid, i.p.) was administered to Swiss-Webster mice for 4 days and loss-of-righting reflex was measured 20 to 30 minutes following each administration. On the fourth day, bemegride (20 mg/kg), flumazenil (20 mg/kg), or vehicle was administered following carisoprodol and withdrawal signs were measured. Separate groups of mice receiving the same treatment regimen and dose range were tested for spontaneous withdrawal at 6, 12 and 24 hr after the last dose of carisoprodol.

Results—The righting reflex was dose-dependently impaired following the first administration of carisoprodol. A 75 to 100% decrease in the magnitude of the impairment occurred over the four days of exposure, indicating the development of tolerance to the carisoprodol-elicited loss-of-righting reflex. Withdrawal signs were not observed within 24 hours following spontaneous withdrawal; however, bemegride and flumazenil each precipitated withdrawal within 15 to 30 min of administration.

Conclusions—Carisoprodol treatment resulted in tolerance and antagonist-precipitated withdrawal, suggesting it may have an addiction potential similar to that of other long-acting benzodiazepine or barbiturate compounds.

Keywords

tolerance; precipitated withdrawal; carisoprodol; GABA_A receptor; barbiturate site; benzodiazepine site; bemegride; flumazenil; mouse

© 2011 Elsevier Ireland Ltd. All rights reserved.

Address Correspondence to: Michael B. Gatch, Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX 76107-2699, USA, phone: 817-735-2062, fax: 817-735-0408, michael.gatch@unthsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

TC and JN conducted the experiments, searched the literature, and wrote initial drafts of portions of the manuscript. TC developed the rating scale. JN and MBG analyzed the data. MBG and MJF designed the experiments and wrote the final version of the manuscript. All authors approved the manuscript.

Conflict of Interest

None.

1. Introduction

Concerns about the abuse of carisoprodol (N-isopropylmeprobamate, Soma), a frequently prescribed muscle relaxant (Fass, 2010; Luo et al., 2004), have increased steadily within the past decade. In the year 2000, the Drug Abuse Warning Network (Substance Abuse and Mental Health Services Administration, 2001) ranked carisoprodol as the 20th most abused drug, and its nonmedical use more than doubled between 2004 and 2008 (Substance Abuse and Mental Health Services Administration, 2011). The abuse potential of carisoprodol in humans has been outlined in several reviews over the past decade (Bailey and Briggs, 2002; Hoiseth et al., 2009; Reeves and Burke, 2010).

These concerns are not surprising, given that the molecular and behavioral effects of carisoprodol are similar to those of barbiturate compounds (Gonzalez et al., 2009), which are well-known for their abuse potential. In that study, carisoprodol was found to allosterically activate and directly gate GABA_A receptor chloride channels in a manner similar to the barbiturates. These effects were blocked by bemegride, a barbiturate antagonist, but not flumazenil, a benzodiazepine antagonist. Although earlier consensus was that the effects of carisoprodol were mediated by its conversion to the anti-anxiety drug meprobamate (Bramness et al., 2004), these data indicate that carisoprodol acts directly at GABA_A receptors.

In addition, carisoprodol has been trained as a discriminative stimulus (Gonzalez et al., 2009). Pentobarbital (a barbiturate), chlordiazepoxide (a benzodiazepine) and meprobamate each fully substituted for the discriminative stimulus effects of carisoprodol. Further, bemegride fully blocked the discriminative stimulus effects of carisoprodol, whereas flumazenil produced partial and non-dose dependent reductions in carisoprodol-appropriate responding (Gonzalez et al., 2009). Taken together, these findings suggested that both electrophysiological and behavioral effects of carisoprodol are mediated by a barbiturate-like mechanism.

Unlike for the barbiturates and benzodiazepines, there has been little basic research on the ability of carisoprodol to produce tolerance and dependence. An early study reported that carisoprodol did not produce dependence or withdrawal signs in humans (Eddy, 1969; Fraser et al., 1961), whereas a number of more recent case reports have presented anecdotal evidence for tolerance and dependence (Eleid et al., 2010; Heacock and Bauer, 2004; Morse and Chua, 1978; Reeves et al., 2004; Rohatgi et al., 2005). However, these individuals were either taking doses many times larger than prescribed doses or were taking several other psychoactive compounds, so strong conclusions about the ability of carisoprodol to produce dependence in patients taking clinically appropriate doses cannot be made. In the first case, the adverse effects noted could have been toxicities induced by the high doses rather than withdrawal effects and, in the second case, the adverse effects noted could have been withdrawal signs from one or more of the other psychoactive compounds.

There is evidence that dependence and withdrawal from GABAergic compounds are difficult to observe in rodents. Meprobamate produces robust withdrawal signs in primates, but withdrawal signs are difficult to detect in rodents (Nakamura and Shimizu, 1983). Similarly, it is difficult to detect physiological withdrawal signs in rodents with the long-acting barbiturates and benzodiazepines (Emmett-Oglesby et al., 1988; Woods et al., 1992). There have been suggestions that precipitated withdrawal from long-acting benzodiazepines was much easier to detect in rats than spontaneous withdrawal (e.g., Emmett-Oglesby et al., 1988). These findings suggest that whereas signs of spontaneous withdrawal from carisoprodol may be difficult to detect, the ability to elicit antagonist-precipitated

withdrawal would be sufficient to establish a barbiturate- / benzodiazepine-like dependence liability.

Demonstrating the abuse liability of a compound involves testing several aspects of the compound including tests of self-administration, drug discrimination, tolerance and cross-tolerance and dependence (Balster, 1991). For carisoprodol, there is substantial evidence of abuse in humans (Bailey and Briggs, 2002; Hoiseth et al., 2009; Reeves and Burke, 2010); as well as confirmation that it is self-administered in monkeys (France et al., 1999). The discriminative stimulus effects of carisoprodol are similar to known GABAergic drugs of abuse (Gonzalez et al., 2009). However, there has not been convincing evidence that carisoprodol produces tolerance and/or dependence. Therefore, the purpose of this study was to assess the ability of carisoprodol to elicit tolerance and to test whether antagonists could precipitate withdrawal from carisoprodol. If carisoprodol produces effects mediated by the barbiturate- or benzodiazepine-sites on the GABA_A receptor, as suggested by our earlier research (Gonzalez et al., 2009), there should be a development of tolerance during repeated administration. It should also be possible to precipitate withdrawal following the benzodiazepine-site antagonist flumazenil, or the barbiturate-site antagonist, bemegride, in the carisoprodol-tolerant subjects. These antagonist compounds have been useful in dissociating the effects of benzodiazepines and barbiturates in drug discrimination testing (De Vry and Slangen, 1986; Herling and Shannon, 1982; Schechter, 1984). In these studies, bemegride blocked the discriminative stimulus effects of pentobarbital but not benzodiazepines, whereas flumazenil blocked the discriminative stimulus effects of benzodiazepines but not pentobarbital. Further, the antagonists also blocked cross-substitution, for example, bemegride blocked both the discriminative stimulus effects of pentobarbital and the ability of pentobarbital to substitute for chlordiazepoxide (Schechter, 1984). Further, bemegride fully blocked the discriminative stimulus effects of carisoprodol, and flumazenil produced a non-dose dependent partial antagonism (Gonzalez et al., 2009), which suggests at least one of these two compounds could potentially precipitate withdrawal from carisoprodol.

2. Methods

2.1 Animals

Male Swiss-Webster mice were obtained from Harlan Laboratories at approximately 8 weeks of age and tested at approximately 10 weeks of age. Mice were group-housed on a 12-/12-h light/ dark cycle and were allowed free access to food and water. All testing of mice was done during the light portion of the cycle. All housing and procedures were in accordance with the guidelines of the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1996) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

2.2 Experimental Design

For the tolerance and precipitated-withdrawal experiments, five groups of 24 mice were administered carisoprodol or vehicle twice daily for three days and on the morning of day 4. The mice were injected at 7:00 AM and 7:00 PM with vehicle (2% methylcellulose), 100, 200, 300 or 500 mg/kg carisoprodol. Loss-of-righting scores were determined 20 min after administration of carisoprodol. Loss-of-righting was scored as follows: 0=normal lands/ rights cleanly onto four feet; 1=slight change; 2=faltering on landing/righting, slight over-compensation; 3=failure of animal to right itself within 15 seconds (Colpaert, 1986; Gatch et al., 2000). On the morning of day 4, 30 min after the final carisoprodol administration, mice from the vehicle, 100, 300, or 500 mg/kg groups were administered either an antagonist (bemegride (20 mg/kg) or flumazenil (20 mg/kg)) or the appropriate vehicle. The doses of

the antagonists selected were those having maximal effect in earlier experiments (Gonzalez et al., 2009). The experimental design and the number of mice in each condition are shown in Table 1. Withdrawal signs were rated at 15 and 30 min after administration of the antagonist. The rating scale (Table 2) was adapted from a barbiturate withdrawal rating scale (Yutzenka, 1989; Yutzenka et al., 1996) and an alcohol withdrawal rating scale (Goldstein, 1972). Maximum score on the scale was 14. The observers were blind to the experimental conditions. The 200 mg/kg group was not tested for withdrawal.

For the spontaneous-withdrawal experiment, 4 groups of mice were administered vehicle (n=8), 100 (n=14), 300 (n=7), or 500 (n=8) mg/kg carisoprodol twice daily for 4 days as in the precipitated-withdrawal experiment. Withdrawal signs were rated at 6, 12 and 24 hr after administration of the last dose of carisoprodol.

2.3. Drugs

Bemegride was obtained from Pfaltz and Bauer Ltd. (Waterbury, CT) and was dissolved in 0.9% saline. Flumazenil and carisoprodol were obtained from Tocris Bioscience (Ellisville, MO) and were suspended in 2% methylcellulose. All drugs were injected intraperitoneally.

2.4. Data Analysis

Loss-of-righting scores were analyzed by two-way, analysis of variance with carisoprodol dose as a between groups factor and treatment time as a within-groups factor, precipitated-withdrawal scores were considered in separate 4×2 , between groups analyses of variance (carisoprodol dose X antagonist dose) at the 15- and 30-min time periods, and spontaneous-withdrawal scores in 4×3 analyses of variance (carisoprodol dose X time), with time as a within-groups factor. In the context of a significant overall effect, individual doses were compared to the appropriate control using individual F tests. The criterion for significance was set a priori at $p < 0.05$.

3. Results

Carisoprodol produced a substantial and dose-dependent loss of motor coordination as measured by the loss-of-righting reflex [$F(4,99)=103.606$, $p < .001$], as shown in Figure 1. Tolerance to this effect of carisoprodol occurred over the 4 days, as evidenced by a decrease in the loss-of-righting score over time [$F(6,594)=38.915$, $p < .001$]. There was a dose by time interaction [$F(24,594)=8.561$, $p < .001$], as the decrease in loss-of-righting reflex occurred in the groups receiving 200, 300 and 500 mg/kg, but not the groups receiving vehicle or 100 mg/kg. The loss-of-righting score increased in the 500 mg/kg group between the morning and evening sessions on the first day.

There was a significant main effect of bemegride on withdrawal signs 15 min after administration [$F(1,36)=28.733$, $p < .001$]. As shown in Figure 2, this outcome reflected the significantly higher withdrawal scores in the 100 and 500 mg/kg carisoprodol-treated mice receiving bemegride when compared to their matching vehicle-injected controls. Although there was no main effect of carisoprodol dose [$F(3,36)=0.939$, $p=0.432$], there was a significant interaction effect [$F(3,36)=20.870$, $p=0.013$], which suggests that the degree of withdrawal increased as dose of carisoprodol increased. The interaction may also have been due to the small drop in withdrawal signs in the vehicle group, although this further adds to the appearance of a dose-dependent effect. Withdrawal signs remained elevated 30 min after administration [$F(1,38)=48.03$, $p < .001$], as evidenced by significant differences from treatment-matched control in the mice that had received bemegride, for the 100, 300 and 500 mg/kg carisoprodol groups. There was no main effect of carisoprodol dose [$F(3,36)=1.995$, $p=0.132$], and no interaction effect [$F(3,36)=0.908$, $p=0.447$].

There was a significant main effect of flumazenil on withdrawal signs 15 min after administration [$F(1,39)=8.682$, $p=0.005$]. This outcome was driven mainly by the significantly higher withdrawal scores in the flumazenil-injected versus vehicle-injected mice of the 500 mg/kg carisoprodol group (Figure 2). There was no main effect of carisoprodol dose [$F(3,39)=2.752$, $p=0.055$], and no interaction effect [$F(3,39)=1.563$, $p=0.214$] at the 15-min time period. At 30 min after administration, there was also a significant effect of flumazenil on withdrawal signs [$F(1,39)=20.263$, $p<0.001$], and there were significant differences from treatment-matched control in the number of withdrawal signs after flumazenil for the mice receiving the 100, 300 and 500 mg/kg carisoprodol doses. There was a main effect of carisoprodol dose [$F(3,39)=4.272$, $p<0.011$] which reflected the observation that flumazenil-associated withdrawal scores increased with the dose of carisoprodol. However, there was no interaction effect [$F(3,39)=1.946$, $p<0.138$].

In general, the bemegride- and flumazenil-associated withdrawal scores did not differ qualitatively and involved caudal posture, tremor, and enhanced startle response. In contrast, mice receiving the same regimens of carisoprodol showed very few signs when tested for spontaneous withdrawal from 6 to 24 hours following the last dose (Figure 3). While there was indeed a statistically significant main effect of carisoprodol dose [$F(3,33)=4.024$, $p=0.013$], this outcome reflected a time- and dose-independent trend involving relatively small differences between carisoprodol (100 and 500 mg/kg) and vehicle-treated mice. The increase in withdrawal signs at the 100 and 500 mg/kg doses could not be confirmed by comparisons with control at the individual time points. There was also neither a main effect of time [$F(2,66)=0.270$, $p=0.765$] nor a dose by time interaction [$F(6,66)=0.570$, $p=0.753$]. Weights did not change over the course of the experiment [$F(4,132)=1.941$, $p=0.107$].

4. Discussion

In the present study, tolerance and dependence developed during the 4 days of repeated administration of carisoprodol. Tolerance to the loss of motor coordination induced by carisoprodol was observed within 3 days of subchronic administration. This finding agrees with case reports of tolerance to the clinical effects of carisoprodol (Heacock and Bauer, 2004; Reeves et al., 2004).

Little sign of spontaneous withdrawal was observed during this study and the effects were not dose dependent, which agrees with an earlier study that carisoprodol did not produce overt signs of withdrawal in humans (Eddy, 1969). However, there are indeed case reports of withdrawal following repeated exposure to very high doses of carisoprodol (Eleid et al., 2010; Morse and Chua, 1978; Rohatgi et al., 2005), and thus it is possible that observable signs of spontaneous withdrawal may have been detected had higher doses been tested in the present study, or had more lengthy treatment regimens been used. However, substantial toxic effects were reported in the earlier studies. Similarly, in the present study, attempts to use higher doses or longer periods of exposure in mice led to substantial morbidity and mortality (data not shown).

Although the current study did not establish an animal model of spontaneous withdrawal, repeated treatment with carisoprodol did result in a robust antagonist-precipitated withdrawal following administration of either bemegride or flumazenil. In this regard, it is noteworthy that spontaneous withdrawal from meprobamate (the major metabolite of carisoprodol), and long-acting benzodiazepines, all of which are scheduled owing to their dependence liability in humans, is often difficult to detect in rodents (Emmett-Oglesby et al., 1988; Nakamura and Shimizu, 1983; Woods et al., 1992), yet, at least for the benzodiazepines, antagonist-precipitated withdrawal can be readily detected. In this study, we report that antagonist-precipitated withdrawal could be detected in the context of a wide

range of carisoprodol treatment regimens. The lower doses (100 and 200 mg/kg b.i.d.) used in the present study were selected to be comparable to those used clinically in humans (350 mg t.i.d.), whereas the higher doses are comparable to those used recreationally. People self-report taking as many as nine or ten 350 mg tablets on experience-sharing sites such as Erowid.com or Bluelight.ru.

Based on the pharmacokinetic properties of carisoprodol and its metabolite meprobamate, it is likely that the withdrawal detected in this study is primarily attributable to chronic exposure to meprobamate. Meprobamate has a half-life that is nearly 8-fold longer than carisoprodol (Bramness et al., 2005; Olsen et al., 1994), the latter being undetectable in plasma of mice 2 hr following a 600 mg/kg dose (National Toxicology Program, 2000). Thus, accumulation of carisoprodol under any condition in the current study is unlikely, whereas a continuous exposure to meprobamate would be expected throughout the studies. Moreover, chronic dosing may result in a 3- to 4-fold increase in the plasma half life of meprobamate (Harvey, 1985), further promoting its accumulation in plasma. This is plausible, as high levels of meprobamate were found during blood testing of a woman who had been taking large doses of carisoprodol (Littrell et al., 1993). In this case report, the woman was subsequently treated for meprobamate dependence.

The barbiturate and benzodiazepine receptor antagonists, bemegride and flumazenil, were selected for use in these studies because they at least partially blocked the behavioral effects of carisoprodol in a previous study (Gonzalez et al., 2009). A high dose (20 mg/kg) was selected to maximize the likelihood of a robust response, since flumazenil had equivocal effects at blocking the discriminative stimulus effects of carisoprodol. Whereas the current study outcomes would tend to support the view that both barbiturate and benzodiazepine receptor sites on the GABA_A receptor may be involved in the neuroadaptive process underlying carisoprodol tolerance and withdrawal, without additional studies it would be premature to attribute such adaptations solely to carisoprodol's activity at the GABA receptor complex. These findings agree with earlier behavioral and electrophysiological research indicating that neither the barbiturate nor the benzodiazepine sites are the sole site for the mechanism of action of carisoprodol (Gonzalez et al., 2009).

Because earlier work indicated that carisoprodol produced effects mainly through the barbiturate site on the the GABA_A receptor (Gonzalez et al., 2009), a barbiturate withdrawal scale (Yutzenka, 1989; Yutzenka et al., 1996) was used as the primary model for the scale used in the present study. Carisoprodol may have other mechanisms of action, so a ethanol-withdrawal scale (Goldstein, 1972) was also used, since ethanol is also a depressant and has multiple sites of action. Any signs on either scale that were scored 0 on all time points were discarded. It is possible that the scale may have missed some signs of carisoprodol withdrawal and may need to be refined. The items on the scale are similar to some of the signs reported in case reports of carisoprodol withdrawal including tremors, restlessness, psychomotor agitation, twitching and seizures (Reeves et al., 2004; Rohatgi et al., 2005). Other signs reported in humans such as insomnia, heart palpitations and stomach cramps (Heacock and Bauer, 2004; Morse and Chua, 1978; Reeves et al., 2004; Rohatgi et al., 2005) are difficult to measure in mice. Overall, the rating scale is sensitive to carisoprodol withdrawal and appears to have external validity.

In conclusion, repeated administration of carisoprodol led to development of tolerance as evidenced by the decrease in loss-of-righting reflex, and to dependence as evidence by withdrawal precipitated by GABA_A antagonists. Both the barbiturate antagonist bemegride and the benzodiazepine antagonist flumazenil precipitated withdrawal from carisoprodol, which suggests that both the barbiturate and benzodiazepine sites are involved in the neuroadaptive process underlying carisoprodol withdrawal. In combination with the findings

that carisoprodol acts at the GABA_A receptor in a barbiturate-like manner and produces subjective effects similar to those of barbiturates (Gonzalez et al., 2009), is self-administered in monkeys (France et al., 1999), as well as an increasing number of clinical case studies of carisoprodol overdose and dependence in humans (Reeves and Burke, 2010), these findings further support concerns that carisoprodol has a substantial liability for abuse. In addition, these findings suggest that meprobamate, a psychoactive metabolite of carisoprodol, may be sufficient to account for the chronic effects of carisoprodol, including tolerance and withdrawal. Meprobamate is a scheduled compound, due to its high abuse potential, and there is clinical evidence that dependence to meprobamate may result from chronic use of carisoprodol (Littrell et al., 1993). Taken together, these findings strongly support scheduling carisoprodol at the same level as its metabolite, meprobamate.

Acknowledgments

Role of funding source

Funding for this study was provided by NIDA grant R01DA022370. NIDA had no further role in the design, analysis or publication of this report.

References

- Bailey DN, Briggs JR. Carisoprodol: an unrecognized drug of abuse. *Am. J. Clin. Pathol.* 2002; 117:396–400. [PubMed: 11888078]
- Bramness JG, Mørland J, Sørli HK, Rudberg N, Jacobse D. Carisoprodol intoxications and serotonergic features. *Clin. Toxicol. (Phila.)*. 2005; 43:39–45. [PubMed: 15732445]
- Bramness JG, Skurtveit S, Morland J. Impairment due to intake of carisoprodol. *Drug Alcohol Depend.* 2004; 74:311–318. [PubMed: 15194209]
- Colpaert FC. Effects of putative α -adrenoceptor antagonists and of other compounds on the loss of the righting reflex and on exophthalmia induced by zylazine in rat. *Drug Dev. Res.* 1986; 7:221–239.
- De Vry J, Slangen JL. Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. *Pharmacol. Biochem. Behav.* 1986; 24:999–1005. [PubMed: 3012604]
- Eddy NB. Codeine and its alternates for pain and cough relief. *Ann. Intern. Med.* 1969; 71:1209–1212. [PubMed: 5361414]
- Eleid MF, Krahn LE, Agrwal N, Goodman BP. Carisoprodol withdrawal after internet purchase. *Neurologist.* 2010; 16:262–264. [PubMed: 20592570]
- Emmett-Oglesby MW, Mathis DA, Harris CM, Idemudia SO, Lal H. Withdrawal from diazepam substitutes for the discriminative stimulus properties of pentylenetetrazol. *J. Pharmacol. Exp. Ther.* 1988; 244:892–897. [PubMed: 3150850]
- Fass JA. Carisoprodol legal status and patterns of abuse. *Ann. Pharmacother.* 2010; 44:1962–1967. [PubMed: 21062909]
- France, CP.; Gerak, LR.; Rowlett, JK.; Woolverton, WL.; Winger, G.; Briscoe, RJ. Progress report from the testing program for stimulant and depressant drugs (1998). In: Harris, LS., editor. NIDA Research Monograph 180: Problems of Drug Dependence; Proceedings of the 61st Annual Scientific Meeting; The College on Problems of Drug Dependence, Inc. U.S. Department of Health and Human Services, Government Printing Office, Washington, D.C.. 1999; p. 423-433.1999
- Fraser HF, Essig CF, Wolbach CF, J AB. Evaluation of carisoprodol and phenylramidol for addictiveness. *UNODC Bull. Narc.* 1961:1–5.
- Gatch MB, Wallis CJ, Lal H. Effects of ritanserin on ethanol withdrawal-induced anxiety in rats. *Alcohol.* 2000; 21:11–17. [PubMed: 10946153]
- Goldstein DB. Relationship of alcohol dose to intensity of withdrawal signs in mice. *J. Pharmacol. Exp. Ther.* 1972; 180:203–215. [PubMed: 5062297]

- Gonzalez LA, Gatch MB, Taylor CM, Bell-Horner CL, Forster MJ, Dillon GH. Carisoprodol-mediated modulation of GABAA receptors: in vitro and in vivo studies. *J. Pharmacol. Exp. Ther.* 2009; 329:827–837. [PubMed: 19244096]
- Harvey, SC. Hypnotics and sedatives. In: Gilman, AG.; Goodman, LS.; Rall, TW.; Murad, F., editors. *Pharmacological Basis of Therapeutics*. Macmillan Publishing; New York: 1985. p. 339-371.
- Heacock C, Bauer MS. Tolerance and dependence risk with the use of carisoprodol. *Am. Fam. Physician.* 2004; 69:1622–1623. [PubMed: 15086035]
- Herling S, Shannon HE. Ro 15-1788 antagonizes the discriminative stimulus effects of diazepam in rats but not similar effects of pentobarbital. *Life Sci.* 1982; 31:2105–2112. [PubMed: 6817002]
- Hoiseth G, Karinen R, Sorlid HK, Bramness JG. The effect of scheduling and withdrawal of carisoprodol on prevalence of intoxications with the drug. *Basic Clin. Pharmacol. Toxicol.* 2009; 105:345–349. [PubMed: 19663822]
- Littrell RA, Sage T, Miller W. Meprobamate dependence secondary to carisoprodol (Soma) use. *Am. J. Drug Alcohol Abuse.* 1993; 19:133–134. [PubMed: 8438828]
- Luo X, Pietrobon R, Curtis LH, Hey LA. Prescription of nonsteroidal anti-inflammatory drugs and muscle relaxants for back pain in the United States. *Spine (Phila, Pa.* 2004; 29:E531–537. 1976.
- Morse RM, Chua L. Carisoprodol dependence: a case report. *Am. J. Drug Alcohol Abuse.* 1978; 5:527–530. [PubMed: 755391]
- Nakamura H, Shimizu M. Physical dependence on meprobamate after repeated oral administration in rats. *Jpn. J. Pharmacol.* 1983; 33:1171–1176. [PubMed: 6686852]
- National Toxicology Program. NTP Technical Report on the Toxicity Studies of Carisoprodol (CAS No. 78-44-4) Administered by Gavage to F344/N Rats and B6C3F1 Mice. *Toxicol. Rep. Ser.* 1-G14. 2000
- Olsen H, Koppang E, Alvan G, Mørland J. Carisoprodol elimination in humans. *Ther. Drug Monit.* 1994; 16:337–340. [PubMed: 7974621]
- Reeves RR, Beddingfield JJ, Mack JE. Carisoprodol withdrawal syndrome. *Pharmacotherapy.* 2004; 24:1804–1806. [PubMed: 15585447]
- Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr. Drug Abuse Rev.* 2010; 3:33–38. [PubMed: 20088817]
- Rohatgi G, Rissmiller DJ, Gorman JM. Treatment of carisoprodol dependence: a case report. *J. Psychiatr. Pract.* 2005; 11:347–352. [PubMed: 16184075]
- Schechter MD. Specific antagonism of the behavioral effects of chlordiazepoxide and pentobarbital in the rat. *Prog. Neuropsychopharmacol. Biol. Psychiatr.* 1984; 8:359–364.
- Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies; Rockville, MD: 2001. NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549.
- Substance Abuse and Mental Health Services Administration. C.f.B.H.S.a.Q.. Drug Abuse Warning Network, 2008: National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: 2011.
- Woods J, Katz J, Winger G. Benzodiazepines: use, abuse, and consequences. *Pharmacol. Rev.* 1992; 44:151–347. [PubMed: 1356276]
- Yutzenka GJ. Intensity of the withdrawal syndrome varies with duration of pentobarbital administration. *Pharmacol. Biochem Behav.* 1989; 34:49–51. [PubMed: 2626453]
- Yutzenka GJ, Stone T, Anderson S. Ro 15-4513 alteration of pentobarbital dependence. *Pharmacol. Biochem Behav.* 1996; 55:379–386. [PubMed: 8951979]

Figure 1. Loss-of-Righting Reflex Score

Swiss Webster mice were injected i.p. with vehicle (2% methylcellulose) or carisoprodol i.p. administration (100, 200, 300, or 500 mg/kg) during the morning (M) and evening (E) of 3 consecutive days and on the morning of day 4. Each point depicts the mean loss-of-righting reflex score ($\pm$ SEM) of 12 mice, 20 min after carisoprodol administration. * indicates points different from time-matched vehicle control ($p < 0.05$). # indicates points different from M1 at the matching dose ($p < 0.05$).

Figure 2. Precipitated Withdrawal Scores Following Bemegride or Flumazenil

Mice were injected i.p. with vehicle (2% methylcellulose) or carisoprodol (100, 300, or 500 mg/kg) during the morning (M) and evening (E) of 3 consecutive days and on the morning of day 4. Bemegride (left panels) or flumazenil (right panels) was administered 20 min following the last carisoprodol injection and withdrawal was scored 15 min (top panels) and 30 min later (bottom panels). * indicates points different from treatment-matched vehicle control ($p < 0.05$). Each bar depicts the mean withdrawal score ($\pm$ SEM) of 5-6 mice.

Figure 3. Spontaneous Withdrawal Scores

Mice received carisoprodol twice via daily i.p administration (0, 100, 300, 500 mg/kg) as indicated in Figure 2, and spontaneous withdrawal scores were recorded at 6, 12 and 24 hours following the last dose of carisoprodol. Each bar depicts the mean (+SEM) of 7-14 mice.

Table 1

Experimental conditions.

Antagonist Dose	Carisoprodol Dose*			
	Vehicle (Methylcellulose)	100 mg/kg	300 mg/kg	500 mg/kg
Vehicle (Saline)	n=6	n=6	n=6	n=5
Bemegride 20 mg/kg	n=4	n=6	n=6	n=5
Vehicle (Methylcellulose)	n=6	n=6	n=6	n=5
Flumazenil 20 mg/kg	n=6	n=6	n=6	n=6

* A 200 mg/kg dose of carisoprodol was tested in the tolerance experiments (n=12) but not evaluated for bemegride- or flumazenil-precipitated withdrawal.

Table 2**Carisoprodol Withdrawal Rating Scale**

Withdrawal Signs	PT
1. Response to air puff	0-2
0= No response	
1= Jumps	
2= Jumps and vocalizes	
2. Response to being picked up and held	0-3
0= No response	
1=Struggles or vocalizes	
2=Struggles and vocalizes	
3= Struggles, vocalizes, scratches, bites	
3. Caudal Posture	0-3
0= limp or normal tail	
1= stiff, curls around finger	
2= stiff, curls around finger, stays elevated after released	
3= spontaneous abnormal posture of tail such as severe deviation or lift above back, stiff, curls around finger, and stays elevated after released.	
4. Tremor	0-3
0= no tremor,	
1= mild tremor in one portion of body,	
2= occasional generalized tremor,	
3= constant generalized tremor.	
5. Startle	0-3
0= none,	
1= twitch,	
2= jump or freeze,	
3= exaggerated jump or freeze.	