Regulatory Analysis Form

(Completed by Promulgating Agency)

(All Comments submitted on this regulation will appear on IRRC's website)

INDEPENDENT REGULATORY REVIEW COMMISSION
RECEIVED
IRRC
2012 FEB 22 A 10: 33

(1) Agency:
Department of State, Bureau of Professional and Occupational Affairs, State Board of Medicine

(2) Agency Number: **16A**
Identification Number: **4933**

IRRC Number: 2931

(3) PA Code Cite: **49 Pa. Code § 16.92**

(4) Short Title: **Prescribing**

(5) Agency Contacts (List Telephone Number and Email Address):

Primary Contact: **Teresa Lazo, Regulatory Unit Counsel, Department of State; (717)783-7200; P.O. Box 2649, Harrisburg, PA 17105-2649; (717)787-0251; tlazo@pa.gov**

Secondary Contact: **Cynthia K. Montgomery, Regulatory Counsel, Department of State; (717)783-7200; P.O. Box 2649, Harrisburg, PA 17105-2649; (717)787-0251; cymontgome@pa.gov**

(6) Type of Rulemaking (check applicable box):

- X Proposed Regulation
- ☐ Final Regulation
- ☐ Final Omitted Regulation
- ☐ Emergency Certification Regulation;
  - ☐ Certification by the Governor
  - ☐ Certification by the Attorney General

(7) Briefly explain the regulation in clear and nontechnical language. (100 words or less)

The rulemaking rewrites § 16.92 (related to prescribing, administering and dispensing controlled substances) for clarity and will expand the provisions of the current section to three non-controlled substances (drugs of abuse).

(8) State the statutory authority for the regulation. Include specific statutory citation.

This rulemaking is authorized by section 8 of the Medical Practice Act of 1985 (act) (63 P.S. § 422.8).

(9) Is the regulation mandated by any federal or state law or court order, or federal regulation? Are there any relevant state or federal court decisions? If yes, cite the specific law, case or regulation as well as, any deadlines for action.

No. The rulemaking is not mandated by Federal or state law, or court order.

(10) State why the regulation is needed. Explain the compelling public interest that justifies the regulation. Describe who will benefit from the regulation. Quantify the benefits as completely as possible and approximate the number of people who will benefit.

The proposed rulemaking is necessary to protect the public from unscrupulous practitioners who inappropriately prescribe and overprescribe drugs of abuse that are not controlled substances.

(11) If data is the basis for this regulation, please provide a description of the data, explain in detail how the data was obtained, and how it meets the acceptability standard for empirical, replicable and testable data that is supported by documentation, statistics, reports, studies or research. Please submit data or supporting materials with the regulatory package. If the material exceeds 50 pages, please provide it in a searchable electronic format or provide a list of citations and internet links that, where possible, can be accessed in a searchable format in lieu of the actual material. If other data was considered but not used, please explain why that data was determined not to be acceptable.

A literature search was performed on MedLine and other medical research database search engines available at the medical library of Harrisburg Hospital. Articles that discuss the three drugs to be added to the regulation were presented to the Board and approved as appropriate to cite in the Preamble. The articles are attached. The articles meet the acceptability standard as they were published in peer-reviewed medical journals. One article is an editorial piece.

Additional articles were considered and the data was consistent with the articles cited. The articles were determined to be duplicative.

(12) Describe who and how many people will be adversely affected by the regulation. How are they affected?

The Board does not foresee any groups being adversely affected by the rulemaking.

(13) List the persons, groups or entities that will be required to comply with the regulation. Approximate the number of people who will be required to comply.

All physicians licensed by the Board of Medicine and other practitioners licensed and authorized to prescribe drugs by the Board will be required to comply with the regulation.

(14) Provide a specific estimate of the costs and/or savings to the **regulated community** associated with compliance, including any legal, accounting or consulting procedures which may be required. Explain how the dollar estimates were derived.

The Board does not anticipate either costs or savings to the regulated community associated with compliance with the rulemaking.

(15) Provide a specific estimate of the costs and/or savings to **local governments** associated with compliance, including any legal, accounting or consulting procedures which may be required. Explain how the dollar estimates were derived.

The Board does not anticipate either costs or savings to local governments associated with compliance with the rulemaking.

(16) Provide a specific estimate of the costs and/or savings to **state government** associated with the implementation of the regulation, including any legal, accounting, or consulting procedures which may be required. Explain how the dollar estimates were derived.

The Board anticipates some savings to state government associated with the implementation of the regulation. The savings will result from an anticipated decrease in accidents and overdose fatalities. The Board does not anticipate any costs to state government associated with compliance with the rulemaking.

(17) In the table below, provide an estimate of the fiscal savings and costs associated with implementation and compliance for the regulated community, local government, and state government for the current year and five subsequent years.

	Current FY Year	FY +1 Year	FY +2 Year	FY +3 Year	FY +4 Year	FY +5 Year
SAVINGS:	$	$	$	$	$	$
Regulated Community						
Local Government						
State Government						
Total Savings	NA	NA	NA	NA	NA	NA
COSTS:						
Regulated Community						
Local Government						
State Government						
Total Costs	NA	NA	NA	NA	NA	NA
REVENUE LOSSES:						
Regulated Community						
Local Government						
State Government						
Total Revenue Losses	NA	NA	NA	NA	NA	NA

(17a) Provide the past three year expenditure history for programs affected by the regulation.

Program	FY -3	FY -2	FY -1	Current FY
Pa. State Board of Medicine	$5,790,741.22	$4,850,758.87	$5,571,463.51	$6,665,000.00

(18) Explain how the benefits of the regulation outweigh any cost and adverse effects.

No adverse effects or costs are associated with compliance with the rulemaking. Therefore, the benefits identified herein and in the Preamble to Proposed Rulemaking outweigh any costs.

(19) Describe the communications with and input from the public and any advisory council/group in the development and drafting of the regulation. List the specific persons and/or groups who were involved.

The Board's allied health committee discussed this proposed rulemaking at a series of public meetings, during which representatives from interested parties, including the Pennsylvania Medical Society, attended and participated in the discussions. Additionally, the Board discussed the proposed rulemaking at public meetings of the Board, which are routinely attended by members of the regulated community and their professional associations.

(20) Include a description of any alternative regulatory provisions which have been considered and rejected and a statement that the least burdensome acceptable alternative has been selected.

No alternative regulatory schemes were considered.

(21) Are there any provisions that are more stringent than federal standards? If yes, identify the specific provisions and the compelling Pennsylvania interest that demands stronger regulations.

This proposed rulemaking would be more stringent than federal requirements. The Federation of State Medical Boards and National Association of Boards of Pharmacy have encouraged their member boards to develop regulations to monitor and restrict inappropriate prescribing and overprescribing. Most states have done so; however, Pennsylvania lags behind the rest of the nation in regulating this area and has become one of the largest providers of prescription drugs of abuse to individuals in states across the United States. The Pennsylvania Board of Medicine, which already regulates physician prescribing of controlled substances, had not updated its prescribing regulations since 1998 and currently does not directly address the standards for prescribing drugs that are not controlled substances. Under the current regulations, it is extremely difficult to hold unscrupulous physicians accountable for inappropriate prescribing or overprescribing of drugs that are not controlled substances.

(22) How does this regulation compare with those of other states? How will this affect Pennsylvania's ability to compete with other states?

The regulation is consistent with regulations adopted in every other state that restrict the prescription of drugs over the Internet in a variety of ways, including by requiring pre-prescription physical examination and prohibiting prescribing based on a questionnaire. The Board's proposal requires a physician to obtain objective data related to a patient's specific complaint. In this manner, it is narrowly tailored and will not provide a prohibitive restriction on legitimate uses of telemedicine technology in medical practice.

Delaware provides that a practitioner, whether acting within or outside Delaware, shall not issue a prescription drug order, by email or otherwise, to or on behalf of a Delaware patient through an internet pharmacy unless the person is a licensed practitioner who has a patient-practitioner relationship with the Delaware patient. "Patient-practitioner" relationship includes that the practitioner has conducted at least one in-person medical evaluation of the patient and performed a medical history and physical examination sufficient to establish a diagnosis and to identify underlying conditions of, or contraindications to, the treatment recommended or provided. 16 Del. Code § 4743(12) and 4744(c)(1).

Maryland allows a physician to prescribe medication after conducting a patient evaluation, and provides that if the evaluation does not include a face-to-face interaction with the patient, the physician must incorporate real-time auditory communications or real-time visual and auditory communications with the patient. Code of Maryland Regulations 10.32.05.05.

New Jersey requires that a physician must perform a physical examination of a patient before issuing prescriptions. New Jersey does not specify the character of the physical examination. N.J. Admin. Code tit. 13, 13:35-7.1A.

New York provides that a physician must conduct a physical examination before prescribing controlled substances and has specifically stated that online questionnaires are not a sufficient substitute for a physical examination. 10 NYCRR 80.63

Regulations of the Ohio Board of Medicine prohibit a physician from presdribing any dangerous drug to a person the physician has not personally examined. Ohio Code of Regulations 4731-11-09.

In Virginia, a physician may prescribe medications only if there is a bona-fide physician-patient relationship. To have this relationship, the physician must conduct a physical examination, which can take place "physically or by the use of instrumentation and diagnostic equipment through which images and medical records may be transmitted electronically." Va. Code Ann. § 54.1-33.3.

By definition, West Virginia deems it unprofessional for a physician to issue a prescription via electronic or other means without establishing an on-going physician-patient relationship. W. Va. Code St. R. § 11-1A-12.

(23) Will the regulation affect any other regulations of the promulgating agency or other state agencies? If yes, explain and provide specific citations.

This proposed rulemaking would not affect other regulations of the Board or other state agencies.

(24) Submit a statement of legal, accounting or consulting procedures and additional reporting, recordkeeping or other paperwork, including copies of forms or reports, which will be required for implementation of the regulation and an explanation of measures which have been taken to minimize these requirements.

This proposed rulemaking would not require any legal, accounting or consulting procedures or any additional recordkeeping or other paperwork.

(25) Please list any special provisions which have been developed to meet the particular needs of affected groups or persons including, but not limited to, minorities, elderly, small businesses, and farmers.

The Board has determined that there are no special needs of any subset of its applicants or licensees for whom special accommodations should be made.

(26) Include a schedule for review of the regulation including:

A. The date by which the agency must receive public comments:	30 days after publication as provided
B. The date or dates on which public meetings or hearings will be held:	The Board meets in public session on the 4th Tuesday of each month.
C. The expected date of promulgation of the proposed regulation as a final-form regulation:	Spring 2012
D. The expected effective date of the final-form regulation:	Upon final promulgation Anticipated Spring 2012
E. The date by which compliance with the final-form regulation will be required:	Upon the effective date Anticipated Spring 2012
F. The date by which required permits, licenses or other approvals must be obtained:	N/A

(27) Provide the schedule for continual review of the regulation.

The Board continually reviews the efficacy of its regulations, as part of its annual review process under Executive Order 1996-1. The Board reviews its regulatory proposals at regularly scheduled public meetings, generally the fourth Tuesday of each month. More information can be found on the Board's website (www.dos.state.pa.us/med).

CDL-1

FACE SHEET
FOR FILING DOCUMENTS
WITH THE LEGISLATIVE REFERENCE BUREAU

(Pursuant to Commonwealth Documents Law)

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2012 FEB 22 A 10:33

DO NOT WRITE IN THIS SPACE

Copy below is hereby approved as to form and legality. Attorney General

BY: _____
(DEPUTY ATTORNEY GENERAL)

FEB 07 2012
DATE OF APPROVAL

Copy below is hereby certified to be a true and correct copy of a document issued, prescribed or promulgated by:

State Board of Medicine
(AGENCY)

DOCUMENT/FISCAL NOTE NO. 16A-4933

DATE OF ADOPTION: _____

BY: Carol E. Rose
Carol E. Rose, M.D.

TITLE: Chairperson
(EXECUTIVE OFFICER, CHAIRPERSON OR SECRETARY)

Copy below is approved as to form and legality. Executive or Independent Agencies.

Megan L. Consedine
Megan L. Consedine

JAN 18 2011
DATE OF APPROVAL

(Deputy General Counsel (~~Chief Counsel~~, Independent Agency. Strike inapplicable title)

[ ] Check if applicable Copy not approved. Objections attached.

[ ] Check if applicable. No Attorney General approval or objection within 30 day after submission.

PROPOSED RULEMAKING
COMMONWEALTH OF PENNSYLVANIA
DEPARTMENT OF STATE
BUREAU OF PROFESSIONAL AND OCCUPATIONAL AFFAIRS
STATE BOARD OF MEDICINE
45 PA. CODE § 16.92
PRESCRIBING

The State Board of Medicine (Board) proposes to amend § 16.92 (relating to prescribing, administering and dispensing controlled substances), to read as set forth in Annex A.

Effective date

The amendments will be effective upon publication of the final-form rulemaking in the *Pennsylvania Bulletin.*

Statutory Authority

The amendments are authorized under section 8 of the Medical Practice Act of 1985 (act) (63 P.S. § 422.8).

Background and Need for the Amendment

The problems caused by inappropriate prescribing and overprescribing have been compounded in recent years by "rogue online pharmacies." Because of the severity of these problems, most states and the Federal government have promulgated regulations to place reasonable restrictions on prescribing drugs that will protect the public from unscrupulous practitioners. Nevertheless, instances of a single practitioner and single pharmacy dispensing hundreds of thousands of doses of dangerous drugs to patients virtually unknown to the practitioner or pharmacist persist. Pennsylvania's regulations must be reformed to address this threat to public health and safety.

Some of the attempts at regulation include the following: In 2006, the United States Department of Justice's Drug Enforcement Administration required practitioners to register in every state in which they prescribe in order to monitor and reduce inappropriate prescribing and overprescribing of controlled substances. In 2008, the United States Congress passed the Ryan Haight Online Pharmacy Consumer Protection Act, Pub.L. 110-425, which amended the Drug Abuse Prevention and Control Act, 21 U.S.C. § 801 *et seq.*, to address the alarming growth in prescription drug abuse by minors purchasing drugs over the internet. It requires online pharmacies to have a valid prescription, preceded by a physical examination, in order to dispense controlled substances. However, this law has failed to address drugs of abuse that are not listed as Federally-controlled substances. Rogue online pharmacies coupled with unscrupulous prescribers have turned to drugs of abuse that are not on the Federal controlled substance list.

The Federation of State Medical Boards and National Association of Boards of Pharmacy have encouraged their member boards to develop regulations to monitor and restrict inappropriate prescribing and overprescribing. Most states have done so; however, Pennsylvania lags behind the rest of the nation in regulating this area and has become one of the largest providers of prescription drugs of abuse to individuals in states across the United States. The Pennsylvania Board of Medicine, which already regulates physician prescribing of controlled substances, had not updated its prescribing regulations since 1998 and currently does not directly address the standards for prescribing drugs that are not controlled substances. Under the current regulations, in order to hold a

physician licensee accountable for inappropriate prescribing or overprescribing of a drug that is not a controlled substance, the Commonwealth must allege and prove that a practitioner's prescribing deviated from the standard of care. In order to demonstrate the inappropriate prescribing or overprescribing, the Commonwealth must have access to the medical records of thousands of patients spread across the United States as well as the records of pharmacies that are frequently located offshore. Using the tools currently available under the Board's regulations, it is extremely difficult to hold unscrupulous physicians accountable for inappropriate prescribing or overprescribing of drugs that are not controlled substances.

Three drugs that are not controlled substances, but which share serious potential for addiction and abuse (butalbital, carisoprodol and tramadol hydrochloride) are being prescribed by Pennsylvania-licensed physicians and sold by rogue pharmacies at alarming rates in this Commonwealth. The Board therefore proposes to expand its regulation of prescribing, administering and dispensing of controlled substance to include these three drugs. The Board had drafted a proposed revision of § 16.92 (relating to prescribing, administering and dispensing controlled substances), which would have applied to all drugs and provided its stakeholders with a draft of its proposal. The Board received many comments opining that its draft was overly inclusive and would have a negative impact on accessible health care. The Board then revised its draft to its current form, which is narrowly focused to address these three drugs, which are not controlled substances, but which are currently being inappropriately prescribed and overprescribed. The Board spoke with representatives of its stakeholders regarding this revision; the revision met with unanimous approval.

The Board proposes to rewrite, simplify and update § 16.92 to expand it to include the following additional drugs that are not controlled substances in Pennsylvania: butalbital, carisoprodol and tramadol hydrochloride, including agents in which these drugs are an active ingredient. Butalbital is a barbiturate that is known to have addictive and abuse potential and is prone to overuse by the consumer. See, e.g. Charles E. Romero. MD; Joshua D. Baron MD; Antony P. Knox, MD, PhD; Judy A. Hinchey, MD; Allan H. Ropper, MD. Barbituate Withdrawal Following Internet Purchase of Fioricet, Archives of Neurology, 2004; 61: 1111-1112.

A metabolite of carisporodol is meprobamate, which is a controlled substance. Roy R. Reeves, DO, PhD; Jeffery S. Hammer, MD and Richard O. Pendarvis, PhD. Is the Frequency of Carisoprodoal Withdrawal Syndrome Increasing? Pharmacotherapy 2007; 27 (10): 1462-1466. Cases of dependence, withdrawal and abuse have also been reported with carisoprodol. Roy R. Reves, DO, PhD and Randy S. Burke, PhD. Is it Time for Carisoprodol to Become a Controlled Substance at the Federal Level? Southern Medical Journal. Vol. 101, No. 2, Feb. 2008, 127-128. The U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control lists carisoprodol as a "drug of concern" and notes that carisoprodol has been consistentlylisted in the top 25 most frequently identified drugs by state and local forensic laboratories since 2000, and that Florida reported a 100% increase in carisoprodol/meprobamate related deaths from 208 in 2003 to 415 in 2008, surpassing opioids such as heroin, fentanyl and hydromorphone. The drug has been added to the state controlled substances lists in Alabama, Arizona, Arkansas, Florida, Georgia, Hawaii, Indiana, Kentucky, Louisianna, Massachusetts, Minnesota, Nevada, New Mexico, Oklahoma, Oregon, Texas and West Virginia.

Tramadol is used to treat moderate to moderately severe pain and may induce psychic and physical dependence of the morphine-type; dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug; and withdrawal symptoms. Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, Feb. 2011 circular on Tramadol. Tramadol related incidents have dramatically increased by 165% from 1995 to 2002 in the Federal Drug Abuse Warning Network (DAWN). What is the addiction risk associated with tramadol? The Journal of Family Practice January 2005, vol. 54, no. 1: 72-73. Additional evidence that tramadol is a drug of abuse has led Arkansas and Kentucky to designate it a controlled substance under state law and Louisiana to list it as a drug of abuse. Anecdotal evidence from Pennsylvania suggests that tramadol is one of the most inappropriately and overprescribed drugs.

Description of the Proposed Amendments

The Board proposes to amend § 16.92 to expand its application to carisoprodol, butalbital and tramadol hydrocholoride, and agents in which these drugs are an active ingredient. The Board proposes to rewrite the section for clarity; however, no other substantive amendments are proposed.

Fiscal Impact and Paperwork Requirements

The proposed amendments will have no adverse fiscal impact on the Commonwealth or its political subdivisions. The amendments will impose no additional paperwork requirements upon the Commonwealth or its political subdivisions. Because the Board believes that the standard of medical care in the Commonwealth already requires an objective examination before prescribing the three additional drugs, practitioners who are already compliant with the standard of care will not be affected by the regulation.

Sunset Date

The Board continuously monitors the effectiveness of its regulations. Therefore, no sunset date has been assigned.

Regulatory Review

Under section 5(a) of the Regulatory Review Act (71 P.S. § 745.5(a)), on February 22, 2011, the Board submitted a copy of this proposed rulemaking and a copy of a Regulatory Analysis Form to the Independent Regulatory Review Commission (IRRC) and to the Chairpersons of the Senate Consumer Protection and Professional Licensure Committee and the House Professional Licensure Committee. A copy of this material is available to the public upon request.

Under section 5(g) of the Regulatory Review Act, IRRC may convey comments, recommendations or objections to the proposed rulemaking within 30 days of the close of the public comment period. The comments, recommendations or objections shall specify the regulatory review criteria which have not been met. The Regulatory Review Act specifies detailed procedures for review, prior to final publication of the rulemaking, by the Board, the General Assembly and the

Governor of comments, recommendations or objections raised.

Public Comment

Interested persons are invited to submit written comments, suggestions or objections regarding this proposed rulemaking to Teresa Lazo, Assistant Counsel, Department of State, by mail at P.O. Box 2649, Harrisburg, PA 17105-2649, or by email at st-medicine@state.pa.us, within 30 days following publication of this proposed rulemaking in the *Pennsylvania Bulletin*. Please reference No. 16A-4933 (Prescribing), when submitting comments.

ANNEX A

TITLE 49. PROFESSIONAL AND VOCATIONAL STANDARDS

PART I. DEPARTMENT OF STATE

Subpart A. PROFESSIONAL AND OCCUPATIONAL AFFAIRS

CHAPTER 16. STATE BOARD OF MEDICINE—

GENERAL PROVISIONS

* * * * *

Subchapter F. MINIMUM STANDARDS OF PRACTICE

* * * * *

§ 16.92. Prescribing, administering and dispensing [controlled substances].

(a) [A person licensed to practice medicine and surgery in this Commonwealth or otherwise licensed or regulated by the Board, when prescribing, administering or dispensing controlled substances , shall carry out, or cause to be carried out, the following minimum standards:

(1) *Initial medical history and physical examination.* In a health care facility regulated by the Department of Health, the Department of Public Welfare or the Federal government, an initial medical history shall be taken and an initial physical examination shall be conducted to the extent required by the Department of Health in 28 Pa. Code (relating to health and safety) or Department of Public Welfare in 55 Pa. Code (relating to public welfare) or the Federal government in appropriate Federal regulations, whichever is applicable, and bylaws of the health care facility and its medical staff. In other practice settings, before commencing treatment that involves prescribing, administering or dispensing a controlled

substance, an initial medical history shall be taken and an initial physical examination shall be conducted unless emergency circumstances justify otherwise. Alternatively, medical history and physical examination information recorded by another health care provider may be considered if the medical history was taken and the physical examination was conducted within the immediately preceding 30 days. The physical examination shall include an evaluation of the heart, lungs, blood pressure and body functions that relate to the patient's specific complaint.

(2) *Reevaluations*. Among the factors to be considered in determining the number and frequency of follow-up evaluation that should be recommended to the patient are the condition diagnosed, the controlled substance involved, expected results and possible side effects. For chronic conditions, periodic follow-up evaluations shall be recommended to monitor the effectiveness of the controlled substance in achieving the intended results.

(3) *Patient counseling*. Appropriate counseling shall be given to the patient regarding the condition diagnosed and the controlled substance prescribed, administered or dispensed. Unless the patient is in an inpatient care setting, the patient shall be specifically counseled about dosage levels, instructions for use, frequency and duration of use and possible side effects.

(4) *Medical records*. In a health care facility regulated by the Department of Health, the Department of Public Welfare or the Federal government, information pertaining to the prescription, administration or dispensation of a controlled substance shall be entered in the medical records of the patient and the health care

facility under 28 Pa. Code or 55 Pa. Code or appropriate Federal regulations, whichever is applicable, and bylaws of the health care facility and its medical staff. In other practice settings, certain information shall be recorded in the patient's medical record on each occasion when a controlled substance is prescribed, administered or dispensed. This information shall include the name of the controlled substance, its strength, the quantity and the date it was prescribed, administered or dispense. On the initial occasion when a controlled substance is prescribed, administered or dispensed to a patient, the medical record shall also include a specification of the symptoms observed and reported, the diagnosis of the condition for which the controlled substance is being given and the directions given to the patient for the use of the controlled substance. If the same controlled substance continues to be prescribed, administered or dispense, the medical record shall reflect changes in the symptoms observed and reported, in the diagnosis of the condition for which the controlled substance is being given and in the directions given to the patient.

(5) *Emergency prescriptions.* In the case of an emergency phone call by a known patient, a prudent, short-term prescription for a controlled substance may be issued. Neither a refill nor a consecutive issuance of this emergency prescription may be given unless a physical examination and evaluation of the patient are first conducted. The results of this examination and evaluation shall be set forth in the patient's medical record together with the diagnosis of the condition for which the controlled substance is being prescribed. An emergency oral prescription for a Schedule II controlled substance shall be covered by a written prescription

delivered to the pharmacist within 72 hours. In certain health care facilities regulated by the Department of Health, the Department of Public Welfare or the Federal government, orders for the immediate, direct administration of a Schedule II controlled substance to a patient are not considered prescriptions and are, therefore, not subject to the requirements in this paragraph. Further information regarding this exclusion can be found in The Controlled Substance, Drug, Device and Cosmetic Act (35 P.S. §§ 780-101—780-144) and 28 Pa. Code Chapter 25 (relating to controlled substances, drugs, devices and cosmetics).

(b) This section establishes minimum standards for the prescription, administration and dispensation of controlled substances by persons licensed to practice medicine and surgery in this Commonwealth or otherwise licensed or regulated by the Board. This section does not restrict or limit the application of The Controlled Substance, Drug, Device and Cosmetic Act or of another statute or regulation, and does not relieve a person from complying with more stringent standards that may be imposed by another statute or regulation.

(c) Compliance with this section will not be treated as compliance with the standards of acceptable and prevailing medical practice when medical circumstances require that the practitioner exceed the requirements of this section.]

For purposes of this section, "drug" includes the following:

(1) Controlled substances under The Controlled Substance, Drug, Device and Cosmetic Act (35 P.S. §§ 780-101—780-144) or substances that are controlled substances under Federal law.

(2) Carisoprodol or agents in which carisoprodol is an active ingredient.

(3) Butalbital or agents in which butalbital is an active ingredient.

(4) Tramadol hydrochloride or agents in which tramadol hydrochloride is an active ingredient.

(b) When prescribing, administering or dispensing drugs regulated by this section, a person licensed to practice medicine and surgery in this Commonwealth or otherwise licensed or regulated by the Board shall carry out, or cause to be carried out, the following minimum standards:

(1) *Initial medical history and physical examination.* An initial medical history shall be taken and an initial physical examination shall be conducted unless emergency circumstances justify otherwise. Medical history and physical examination information recorded by another licensed health care provider may be considered if the medical history was taken and the physical examination was conducted within the immediately preceding 30 days. The physical examination shall include an objective evaluation of the heart, lungs, blood pressure and body functions that relate to the patient's specific complaint.

(2) *Reevaluations.* Reevaluations of the patient's condition and efficacy of the drug therapy shall be made consistent with the condition diagnosed, the drug or drugs involved, expected results and possible side effects.

(3) *Patient counseling.* The patient shall be counseled regarding the condition diagnosed and the drug prescribed, administered or dispensed. Unless the patient is in an inpatient care setting, the patient shall be specifically counseled about dosage levels, instructions for use, frequency and duration of use and possible side effects.

(4) *Medical records.* Accurate and complete medical records shall document the evaluation and care received by patients.

(i) On the initial occasion when a drug is prescribed, administered or dispensed to a patient, the medical record shall include the following:

(A) A specification of the symptoms observed by the health care provider and reported by the patient.

(B) The diagnosis of the condition for which the drug is being given.

(C) The directions given to the patient for the use of the drug.

(ii) After the initial occasion when a drug is prescribed, administered or dispensed, the following information shall be recorded in the patient's medical record:

(A) The name of the drug.

(B) The strength of the drug.

(C) The quantity of the drug.

(D) The date the drug was prescribed, administered or dispensed.

(E) Any changes to the information recorded under subparagraph (b)(4)(i).

(5) *Emergency prescriptions.* In the case of an emergency contact from a known patient, a prudent, short-term prescription for a drug may be issued. Neither a refill nor a consecutive issuance of this emergency prescription may be given unless a physical examination and evaluation of the patient is first conducted by a licensed health care provider. The results of this examination and evaluation shall be set forth in the patient's medical record together with the diagnosis of the condition for which the drug is being prescribed. An emergency oral prescription for a Schedule II controlled substance shall be covered by a written prescription delivered to the pharmacist within 72 hours.

(6) *Compliance with other laws.*

(i) Nothing in this section may be construed as restricting or limiting the application of The Controlled Substance, Drug, Device and Cosmetic Act or statutes or regulations of the Pennsylvania Departments of Health and Public Welfare that govern the prescription, administration and dispensation of drugs and medical recordkeeping in certain health care facilities.

(ii) Nothing in this section may be construed as restricting or limiting the application of Federal laws or regulations that govern the prescription, administration and dispensation of drugs and medical recordkeeping in certain health care facilities.

(iii) Nothing in this section relieves a person from complying with more stringent standards that may be imposed by another statute or regulation.

(7) *Compliance with facility policy.* Nothing in this section relieves a person from complying with more stringent standards that may be imposed by the health care facility in which the person practices or by the person's employer.

(8) *Adherence to standards of practice.* Compliance with this section will not be treated as compliance with the standards of acceptable and prevailing medical practice when medical circumstances require that the practitioner exceed the requirements of this section.

* * * * *

ARCHIVES OF
NEUROLOGY

Vol. 61 No. 7, July 2004

Observation

Barbiturate Withdrawal Following Internet Purchase of Fioricet

Charles E. Romero, MD; Joshua D. Baron, MD; Anthony P. Knox, MD, PhD; Judy A. Hinchey, MD; Allan H. Ropper, MD

Arch Neurol. 2004;61:1111-1112.

ABSTRACT

Background The Internet enables businesses to advertise their pharmaceutical products and services without medical supervision. The Internet also allows for the unsupervised purchase of medications that may have neurologic consequences.

Objective To describe acute withdrawal delirium following the abrupt discontinuation of Fioricet.

Patient The patient was a 37-year-old woman with a history of depression and migraine headaches but not drug abuse. She developed a florid withdrawal delirium following the discontinuation of a drug she purchased online. The medication, which contained butalbital, was self-administered in escalating doses for the treatment of chronic headaches. Daily doses of up to 750 mg to 1000 mg were reported.

Results The patient was admitted to the hospital for the treatment of unexplained seizures that were followed by several days of an intense withdrawal syndrome. Little improvement was noted after the administration of benzodiazepines and phenothiazine. After parenteral phenobarbital administration, her symptoms resolved.

Conclusions The withdrawal state from barbiturates is similar to that from ethanol. Tolerance can develop with prolonged abuse, leading to escalating drug doses to achieve the desired effect. The suggested management of both types of withdrawal syndromes is similar, but the relative resistance of the behavioral and autonomic features in patients was remarkable. Physicians should be aware of the ease with which medications can be purchased without supervision from Internet pharmacies. The magnitude of the number of drugs that are made available through this means creates a proclivity to withdrawal states.

INTRODUCTION

Several authors have commented on the vast "underground drug information" the Internet can provide.[1-3] The World Wide Web can be used to obtain data on drug dosing, adverse effects, overdose, warnings, pharmacology, and current patient information.[4-6] It also allows completely unfettered purchases of medications that may have neurologic consequences. We treated a patient who had repeated seizures followed by several days of an intense withdrawal delirium. The patient described a massive and prolonged daily ingestion of Fioricet (a combination drug composed of acetaminophen, butalbital, and caffeine) that she had purchased without a prescription, through the

Online Only
- Online First Table of Contents
- Online Features

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- PDF
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- Save in My Folder
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- Neurology
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Social Bookmarking
What's this?

Jump to Section
- Top
- Introduction
- Report of a case
- Comment
- Author information
- References

Internet, for the unsupervised treatment of headaches. This observation highlights the need for physicians to understand alternative means by which patients may obtain medications with serious neurologic sequelae.

REPORT OF A CASE

Jump to Section
- Top
- Introduction
- Report of a case
- Comment
- Author information
- References

A 37-year-old woman was brought to the emergency department after 3 consecutive grand mal seizures. She had a history of depression and migraine headaches but not of drug abuse. A large tongue laceration was evident, as were bruises and abrasions on her face, arms, and trunk. The patient was calm but intermittently disoriented and easily distracted, with incoherent and pressured speech containing paraphasic errors. A urine toxicology screen detected the presence of barbiturates. She was able to relate that she had periodic migraine, recurring a few times per year since the age of 21 years. The frequency of headaches had increased during the past year, as did her reliance on Fioricet to control them. During the 3 months before her seizures, she reported consumption of 15 to 20 tablets a day. The medication had been prescribed once by a neurologist years earlier, and she subsequently obtained the medication from multiple Web sites, including http://rx-refills.net/_buy_migraine_relief_prescriptions.html. A computed tomographic scan revealed a small epidural hematoma with an overlying temporal bone fracture. She was treated with phenytoin in the neurologic intensive care unit.

The following day, 48 hours after her last ingestion of Fioricet, she became agitated, tachycardic, and had a low-grade temperature of 37.2°C. Her blood pressure was 133 mm Hg/77 mm Hg. Her electroencephalogram showed no abnormalities. Visual hallucinations, insomnia, diaphoresis, hyperreflexia, and intense psychomotor agitation followed; however, she was not tremulous. Phenobarbital sodium (100 mg by mouth [PO] 3 times a day), lorazepam (2 mg intravenously every 4 hours), haloperidol lactate (5 mg intravenously every 6 hours), oxazepam (30 mg PO every hour), and olanzapine (5 mg PO 2 times a day) were administered without effect. Her agitation was so intense that she became tangled in her bedsheets and repeatedly attempted to climb over the bedrails. Intravenous midazolam hydrochloride (0.05 mg/kg per hour) was required to sedate her; reducing the dose exposed a hyperkinetic-delirious state. On the fifth day, she was cognitively normal. Treatment with phenobarbital sodium (100 mg PO 3 times a day) was continued through her hospitalization and was slowly withdrawn.

COMMENT

Jump to Section
- Top
- Introduction
- Report of a case
- Comment
- Author information
- References

The withdrawal state from barbiturates is similar to that from ethanol.[7-8] Tolerance can develop with prolonged abuse and lead to escalating drug doses in order to achieve the desired effect. In the withdrawal syndromes, removal of GABA (γ-aminobutyric acid)-ergic inhibitory tone in the central nervous system has been proposed to cause hypertension, tachycardia, diaphoresis, tremors, hyperthermia, and seizures. Seizures followed by a confusional state that progresses to a hyperkinetic and hypersympathetic delirium with hallucinosis are common to both barbiturate and alcohol withdrawal syndromes, including a rapid resolution. We only comment that our patient notably lacked the tremulousness that is so characteristic of alcohol withdrawal.

The suggested management of both types of withdrawal syndromes is similar, but the relative resistance of the behavioral and autonomic features in patients was remarkable. Symptoms of psychomotor agitation and tachycardia are treated with sedative-hypnotic agents. Benzodiazepines are used for ethanol withdrawal, and phenobarbital has been suggested for barbiturate withdrawal with a dose reduction of 10% per day once the patient's condition is stabilized while the medications are taken.[8] It is possible that high doses of benzodiazepines address both withdrawal syndromes. Delirium continued in our patient despite the administration of phenobarbital; perhaps higher doses or a loading dose was required.[9]

Butalbital, a component of Fioricet, is an intermediate-acting (3-6 hours) barbiturate. It binds to the GABA

receptor complex and prolongs the opening of the chloride channels in response to GABA, thereby inhibiting excitable cells of the nervous system.[8] Butalbital is a weak acid with a volume of distribution of 0.8 L/kg of body weight and 26% protein binding in the plasma. With therapeutic doses, plasma concentrations generally peak in 40 to 60 minutes. Butalbital is metabolized by the liver and has a half-life elimination of 1.6 to 5.8 days. It is excreted in the urine.[10]

Ethanol also binds to the GABA receptor complex. Activation of the postsynaptic $GABA_A$ receptor and prolonged chloride influx lead to cell hyperpolarization and a decrease in the firing rate of neurons. The result is an overall clinical effect of sedation.[7-8] In the withdrawal state, patients can experience tremors, hallucinations, seizures, and delirium tremens. The hallucinations that result from alcohol abstinence typically have an onset of 7 to 48 hours after the last drink. This is similar to the time of onset of withdrawal seizures, although the peak seizure incidence is between 12 and 24 hours. Lastly, delirium tremens can occur 48 to 72 hours after cessation of drinking, with a peak incidence on the fourth day of abstinence. The symptoms are characterized by autonomic instability, diaphoresis, fever, tremulousness, and profound confusion.[7-8]

After a rudimentary investigation, we are able to report that Internet search engines can be easily used to locate numerous merchants who readily provide a steady supply of medication on demand to any customer wishing to buy Fioricet or a host of other medications. These online merchants claim "no prescription required, because the online pharmacy will provide a quick and easy online doctor's consultation, free of charge, when you order Fioricet on-line."[11] Our patient reported purchasing 500 pills per order without difficulty.

Physicians may wish to be aware of the ease with which certain medications can be purchased from "online pharmacies." Various Web sites we visited offered zolpidem (Ambien), zaleplon (Sonata), orlistat (Xenical), sibutramine hydrochloride monohydrate (Meridia), tramadol (Ultram), cyclobenzaprine (Flexeril), tizanidine (Zanaflex), carisoprodol (Soma), and many other medications that are subject to abuse and to withdrawal states. Furthermore, patients may suffer either somatic withdrawal effects or rebound headaches that only reinforce further self-medication.

Unrestricted access to pharmacological products such as narcotics, sedatives, or drugs with other psychotropic effects or otherwise habituating or addicting properties may cause serious adverse effects if used incorrectly.[7-10,12-13] The magnitude of the number of drugs that are made available through this means creates a proclivity to withdrawal states.

AUTHOR INFORMATION

Jump to Section
- Top
- Introduction
- Report of a case
- Comment
- Author Information
- References

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From the Neurology Service, St Elizabeth's Medical Center, Boston, Mass.

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Jump to Section
- Top

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• Introduction
• Report of a case
• Comment
• Author information
• References

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Need for Analgesics/drugs of Abuse: A Comparison Between Headache Patients and Addicts by the Leeds Dependence Questionnaire (LDQ)
Ferrari et al.
Cephalalgia 2006;26:187-193.
ABSTRACT | FULL TEXT

Is the Frequency of Carisoprodol Withdrawal Syndrome Increasing?

Roy R. Reeves, D.O., Ph.D., Jeffrey S. Hammer, M.D., and Richard O. Pendarvis, Ph.D.

Carisoprodol is a commonly used centrally acting muscle relaxant. A number of case reports have suggested that the drug may have abuse potential, presumably because it is metabolized to the anxiolytic drug, meprobamate, which is a controlled substance at the federal level. Two recent case reports described symptoms of withdrawal after the cessation of carisoprodol. We present two additional cases that support the concept of a withdrawal syndrome with this drug. Symptoms of carisoprodol withdrawal include anxiety, tremulousness, insomnia, jitteriness, muscle twitching, and hallucinations. These symptoms are most likely caused by withdrawal from the meprobamate that accumulates after large amounts of carisoprodol are ingested. Although carisoprodol is not a controlled substance at the federal level, clinicians should be aware of its significant potential for abuse.

Key Words: carisoprodol, withdrawal, carisoprodol withdrawal syndrome, meprobamate, substance abuse, drug abuse.
(Pharmacotherapy 2007;27(10):1462–1466)

Carisoprodol (*N*-isopropyl-2 methyl-2-propyl-1,3-propanediol dicarbamate [*N*-isopropyl-meprobamate]) is a centrally acting skeletal muscle relaxant marketed in the United States as Soma (MedPointe Healthcare Inc., Somerset, NJ) and in the United Kingdom as Carisoma (Forest Laboratories UK Limited, Kent, United Kingdom). The drug is a congener of meprobamate and has been available in the United States since the U.S. Food and Drug Administration approved it in 1959. Carisoprodol is widely used in primary care settings for the treatment of musculoskeletal conditions associated with muscle spasms and back pain. After its introduction, a number of reports have suggested that the drug may have a potential for abuse.[1–9] However, carisoprodol is not a controlled substance at the federal level.

The diversion and abuse of carisoprodol and its adverse health effects have substantially increased over the last several years. According to the Drug Abuse Warning Network, the numbers of emergency department episodes involving carisoprodol were 6569 in 1994, 7771 in 1995, 11,239 in 2001, 10,094 in 2002, 17,366 in 2004, and 19,513 in 2005.[10, 11] These figures represented an almost 300% increase from 1994 to 2005. According to data from the National Survey on Drug Use and Health from 2002–2005, the occurrence of misuse of carisoprodol was approximately equal to that of clonazepam.[12]

In 2004, a case report described a patient who had significant symptoms of withdrawal after abrupt cessation of carisoprodol.[13] In 2005, another case report described a patient who had similar symptoms during gradual tapering and after discontinuation of carisoprodol.[14] Since then, we encountered two additional cases of this syndrome, raising the issue of whether carisoprodol withdrawal is becoming more frequent, or at least more readily recognized by clinicians, now than ever before.

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Case Reports

Patient No. 1

A 36-year-old woman with no history of mental illness was hospitalized because she was actively hallucinating and responding to internal stimuli. She reported hearing music that she enjoyed and hearing the voices of several individuals. She had visual hallucinations of animals and people, including an annoying cousin with whom she argued. She believed that her dreams continued after she awakened and that they were real. Her hallucinations were intense enough to compete with her actual environment for her attention.

The patient's history revealed that she had been taking approximately 25 tablets/day of carisoprodol for several months. She denied other drug or alcohol abuse except for occasional use of oxycodone. Results of her urine drug screen were negative. Three days before admission, she had abruptly stopped taking carisoprodol because she could no longer obtain it. The next day, she became anxious and jittery. The day after that, she was tremulous, and she began hallucinating in the evening. The night before her admission, she slept less than 1 hour.

The patient was hospitalized and given lorazepam and risperidone on an as-needed basis to control her symptoms, which gradually resolved over the next 3 days. She had no recurrence of her psychotic symptoms.

Patient No. 2

A 21-year-old woman had been taking approximately 20 tablets/day of carisoprodol tablets for over 3 months. She was taking no other drugs and decided to stop taking carisoprodol after her family confronted her. About 24 hours after she stopped, she developed anxiety, tremulousness, and muscle twitching. She was unable to sleep in the evening. About 36–48 hours after she ceased taking carisoprodol, she began to see insects and flying things. She became paranoid about the police and other authority figures. She resumed ingesting large doses of carisoprodol, and the symptoms rapidly resolved.

A month later, she entered a treatment program and underwent detoxification beginning with lorazepam 6 mg on the first day. The dose was decreased by 10–20% each subsequent day. During the next 3 days of detoxification, she had complaints similar to but less intense than those she reported before. After resolution of her symptoms, she had no further symptoms of this type.

Discussion

Pharmacologic Properties and Metabolism of Carisoprodol

Carisoprodol is available as 350-mg tablets with a recommended dosage of one tablet 3 or 4 times/day. The drug begins to act within 30 minutes of oral ingestion and has a half-life of approximately 1.5 hours.[15] Carisoprodol undergoes hepatic transformation to its primary metabolites hydroxycarisoprodol, hydroxymeprobamate, and meprobamate, which are excreted in the urine.[16] The pharmacologically active metabolite is meprobamate, which has a half-life of approximately 11 hours but may be as long as 48 hours with long-term use.[17] Carisoprodol produces muscle relaxation by blocking intraneuronal activity and by suppressing the transmission of polysynaptic neurons in the spinal cord and in the descending reticular system of the brain.[18] Thus, the effect of the drug may be sedation more than direct relaxation of the skeletal muscle.[16]

Abuse Potential of Carisoprodol

Abuse of carisoprodol was reported first in 1978.[1] By the 1990s, the drug began to be recognized as having abuse potential. Initial case reports described one patient who tried to obtain prescriptions for the drug from several physicians,[2] four patients who regularly obtained carisoprodol and used it in excessive amounts to achieve mind-altering effects,[3] 16 patients in India who attempted to use it as a substitute for opiates,[4] one patient who abused the drug after obtaining it through a veterinary mail-order service,[5] and one patient who faced legal charges for forging prescriptions for carisoprodol.[6] In 1997, three additional patients were described: one man took carisoprodol to calm himself after cocaine use, one young woman who appeared to use it as a substitute for more potent illicit drugs, and one patient who became dependent on the drug as a sleep aid.[7]

Carisoprodol has been used to augment the effect of sedatives, such as benzodiazepines or alcohol, and to curb the effects of stimulants such as cocaine.[8] Abuse of combinations of carisoprodol and tramadol have been reported, with euphoric and relaxing effects described.[9]

Patients abusing this combination stated that it was easier to obtain prescriptions for the two drugs than to acquire controlled substances, such as benzodiazepines.[9]

Investigators evaluated a series of patients who had positive results for carisoprodol during urine drug screening.[19] These patients were typically Caucasian men or women (with equal frequency) in their early 40s who abused carisoprodol or used it for medical purposes (with equal frequency). Other researchers surveyed 40 patients taking carisoprodol for 3 months or longer.[20] Among 20 patients who had a history of substance abuse, 40% admitted using the drug in larger-than-prescribed amounts, 30% reported taking it for an effect other than that for which it was prescribed, 10% used it to augment the effect of another drug, 5% used it to counteract the effect of another drug, 20% attempted to obtain extra carisoprodol by prescription, and 10% obtained carisoprodol by means other than legal prescriptions.

The proposed basis for carisoprodol abuse is to achieve the effects of its major metabolite, meprobamate. Meprobamate is a controlled substance at the federal level because of its known potential for inducing tolerance and dependence. The abuse potential of meprobamate is equal to, if not greater than, that of benzodiazepines.[21]

Carisoprodol Withdrawal Syndrome

Literature Search

The *Physicians Desk Reference* states that no withdrawal symptoms occurred in dogs after the abrupt cessation of carisoprodol that was given at doses as high as 1 g/kg/day.[22] However, in a study of people who abruptly stopped taking doses of 100 mg/kg/day (approximately 5 times the recommended daily dose), some subjects had withdrawal symptoms, such as abdominal cramps, insomnia, chilliness, headache, and nausea. Delirium and convulsions did not occur.[22]

Several of the case studies reporting carisoprodol abuse described withdrawal symptoms. A woman taking 13 tablets at bedtime had daytime abstinence anxiety and tremors, which resolved with the ingestion of additional tablets.[5] Among the 16 patients who abused carisoprodol in the report from India, 69% had withdrawal symptoms, including body aches, anxiety, restlessness, and insomnia.[4] A 44-year-old patient who reported taking 30–50 tablets/day experienced anxiety, tremulousness, and cravings during attempts at abstinence.[1] In a Norwegian study, carisoprodol was gradually withdrawn from prisoners who had been taking 700–2100 mg/day for at least 9 months.[23] Most of the patients reported having anxiety, insomnia, irritability, cranial and muscular pain, and vegetative symptoms. Investigators reported irritability, back pain, headache, and dysphoria in two patients after they stopped their daily intake of four to eight tablets of carisoprodol.[7] Complaints similar but more severe than these were noted in five patients who abruptly stopped their daily consumption of carisoprodol 2100–4200 mg.[24]

Carisoprodol withdrawal syndrome was described in 2004.[13] A 43-year-old man who had been abusing hydrocodone until he could no longer obtain it consumed 30 or more tablets of carisoprodol every day (≥ 10,500 mg/day) for several weeks, then abruptly stopped taking the drug when it was no longer available to him. Within 48 hours, he developed anxiety, tremors, muscle twitching, insomnia, auditory and visual hallucinations, and bizarre behavior. He had difficulty distinguishing the hallucinations from reality. His symptoms intensified and peaked on the fourth day after he ceased taking carisoprodol. The patient required brief treatment with olanzapine and tapering doses of lorazepam while the symptoms gradually resolved. He had no recurrence of psychotic symptoms.

A case in 2005 involved a 46-year-old man who took 10–12 tablets of carisoprodol tablets every day (3500–4200 mg/day).[14] During tapering of the drug, he had cardiac palpitations, diaphoresis, chills, stomach cramps, nausea, insomnia, myalgia, tremors, diarrhea, anxiety, psychomotor agitation, and feelings of depersonalization. He continued to have mild symptoms for over a week after complete cessation.

Clinical Implications

The presentations of the two patients we described were similar to those of patients from the first case reports and support the concept of a carisoprodol withdrawal syndrome. Symptoms in common among the patients were anxiety, tremulousness, insomnia, and muscle twitching or jitteriness, all of which are possible symptoms of meprobamate withdrawal. Of interest, three of the four cases of carisoprodol withdrawal involved psychotic symptoms, whereas psychotic symptoms were described in about one fifth of cases of meprobamate withdrawal.[25] The

importance of this difference is unclear and cannot be determined given the small number of cases.

Symptoms of patients who took carisoprodol closely parallel those of patients withdrawing from meprobamate. The most common symptoms of meprobamate withdrawal are insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia. Hallucinations and delusions may occur in as many as 18% of patients and seizures in up to 7%.[25]

Because of these similarities, symptoms occurring during carisoprodol withdrawal may result from withdrawal from the accumulation of meprobamate due to excessive intake of carisoprodol. Supporting this hypothesis is the finding that serum concentrations of meprobamate (15–20 µmol/L) after an oral dose of carisoprodol 700 mg (two tablets)[26] are not considerably higher from the concentrations of 20–100 µmol/L observed after therapeutic doses of meprobamate 400–800 mg.[27] Because the half-lives of meprobamate and carisoprodol are approximately 11 and 1.5 hours, respectively,[15, 16] regular intake of carisoprodol may cause meprobamate—but not carisoprodol—to accumulate. Therefore, one may reasonably assume that meprobamate formed during the metabolism of carisoprodol substantially contributes to the effects of carisoprodol and to the effects of carisoprodol withdrawal. Such withdrawal has occurred only in patients taking large doses; therefore, use of carisoprodol at approved doses may result in low levels of meprobamate and a low risk of withdrawal.

These cases raise the concern that carisoprodol abuse may be increasing in frequency and severity and that, with increasing severity of abuse, withdrawal syndromes may also be seen with growing frequency. Carisoprodol withdrawal syndrome appears to be a valid phenomenon that can occur when an intake of large doses is rapidly stopped.

Symptoms observed during withdrawal from carisoprodol and meprobamate share many similarities with symptoms related to withdrawal from alcohol, benzodiazepines, and barbiturates, although the risk of seizures appears to be less than 10% with meprobamate and carisoprodol. Long-term consumption of large doses of drugs such as carisoprodol and meprobamate may induce neural adaptation to their presence, and rebound resurgence of neural electrical activity occurs during withdrawal.[25] This rebound leads to symptoms ranging from anxiety and jitteriness to delirium, depending on the severity of withdrawal and on the degree of neuronal hyperactivity. In the cases reported to date, treatment with brief courses of benzodiazepines has been the primary therapy, and antipsychotic agents have been used if needed to manage psychotic symptoms.

Many patients who abuse substances are aware of the potent effects of carisoprodol, but evidence suggests that many clinicians are not aware that carisoprodol is metabolized to meprobamate, a substance with widely recognized abuse potential.[20] Carisoprodol is classified as a controlled substance in several states, including Alabama,[28] Kentucky,[29] Arizona,[30] and Florida.[31] The fact that the drug is not a controlled substance at the federal level should not lead clinicians to be less cautious when prescribing carisoprodol for patients who are at risk for misusing it.

Conclusion

Several case reports indicate that carisoprodol has a potential for abuse, and withdrawal symptoms may occur when an individual stops ingesting large amounts of the drug. Therefore, appropriate caution should be exercised when prescribing the drug. Clinicians should be cautious about prescribing carisoprodol to individuals who have a history of abusing other drugs and prescribing carisoprodol if the drug is needed for a long duration.

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Editorial

Is It Time for Carisoprodol to Become a Controlled Substance at the Federal Level?

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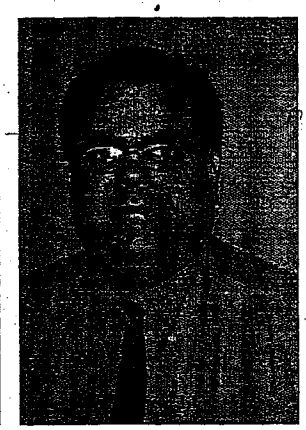

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Carisoprodol (N-isopropyl-2 methyl-2-propyl-1,3-propanediol dicarbamate; N-isopropylmeprobamate; Soma) is a commonly prescribed, centrally acting skeletal muscle relaxant. As the chemical nomenclature suggests, carisoprodol is structurally related to meprobamate. In fact, the primary active metabolite of carisoprodol *is* meprobamate. Meprobamate is a schedule IV controlled substance at the federal level with a known risk for causing addiction. Research has shown the abuse potential of meprobamate to be equal to, if not greater than, that of benzodiazepines.[1]

With meprobamate having this degree of abuse potential, one might expect a risk of misuse of carisoprodol. Indeed, a number of reports[2] suggest this to be a valid concern. Carisoprodol has been abused (usually in amounts much larger than the recommended daily dose of 350 mg three or four times daily) for its sedative and relaxant effects.[2] Carisoprodol has also been used to augment or alter the effects of other drugs (eg, to increase the sedating effects of benzodiazepines or alcohol, or to prevent jitteriness during cocaine use and help calm persons after its intake).[3] Abuse has also occurred by the intentional combination of carisoprodol and other noncontrolled medications because of the relative ease (as compared with controlled substances) of obtaining prescriptions. The combination of carisoprodol and tramadol has been reported by individuals misusing the two medications together to result in significant relaxation and euphoria.[4]

The diversion and abuse of carisoprodol and its adverse health effects appear to have dramatically increased over the last several years. According to the Drug Abuse Warning Network (DAWN), numbers of emergency department episodes involving carisoprodol were 6,569 in 1994, 7,771 in 1995, 11,239 in 2001, 10,094 in 2002, 17,366 in 2004, and 19,513 in 2005,[5,6] representing an almost 300% increase from 1994 to 2005.[6] According to the National Survey on Drug Use and Health (NSDUH) data from 2002 to 2005, the occurrence of misuse of carisoprodol was approximately equal to that of clonazepam.[7] Carisoprodol manufactured in Guadalajara and sold under the name Somacid is reported to be easily obtained in Mexico with the purchase of several thousand pills at a time possible. Workers in Mexican pharmacies near the US border have said they fill carisprodol orders several times per week for American teenagers, a trend they say has been going on for years.[8] According to the Los Angeles Police Department, carisoprodol is being diverted, trafficked, and abused nationwide, and is the pharmaceutical drug most frequently encountered at the US-Mexico border crossing.[9] In the US, the street value of Soma is $1 to $5 per 350 mg pill.[8]

Not only is the frequency of carisoprodol abuse increasing, in recent years clinicians have begun to see a withdrawal syndrome consisting of insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia in patients who abruptly cease intake of large doses of carisoprodol. Hallucinations and delusions also occur in some patients.[10] The withdrawal symptoms are very similar to those previously described for meprobamate withdrawal, suggesting that what is actually occurring is withdrawal from meprobamate accumulated as a result of intake of excessive amounts of carisoprodol. The incidence of this withdrawal syndrome also appears to be increasing.[10]

One might think that the medical community would be suspicious of a drug whose primary metabolite is a controlled substance. However, while most practitioners are aware that meprobamate is a controlled substance with a well-documented record of abuse, many are not aware that carisoprodol is metabolized to meprobamate, nor are they alert to the abuse potential of carisoprodol.[2] Some patients who abuse carisoprodol may be cognizant of this fact and attempt to take advantage of its noncontrolled status to obtain the drug because clinicians might feel more comfortable prescribing carisoprodol rather than a controlled substance such as a benzodiazepine. An excellent example of this phenomenon was described by Chop[11] who noted that some patients were "quite aggressive" in their attempts to procure carisoprodol, actually asking, in an agitated manner, questions like, "It's not even controlled, so why won't you give it to me, Doc?"

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All of this evidence has not gone unnoticed. Carisoprodol has been classified as a schedule IV controlled substance in several states, including Hawaii, Georgia, Kentucky, Massachusetts, New Mexico, Oklahoma, Alabama, Arizona, and Florida.[12–15] The Kentucky Board of Medical Licensure guidelines for prescribing controlled substances recommend that carisoprodol "should be prescribed with the same caution as opioids and other controlled substances."[16] However, no such action has been taken at the Federal level. This represents a curious inconsistency in drug enforcement policy between state and Federal administrations. Carisoprodol is metabolized to a controlled substance, has clear evidence of abuse potential and increasing incidence of abuse, has shown evidence of a withdrawal syndrome with abrupt cessation from intake of large amounts, and has been assigned a schedule IV controlled substance status in several states. Is it not time for carisoprodol to become a controlled substance at the Federal level?

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I am not afraid of death, I just don't want to be there when it happens.

—Woody Allen

What is the addiction risk associated with tramadol?

■ EVIDENCE-BASED ANSWER

Tramadol (Ultram, generic and with acetaminophen in Ultracet) carries a risk of substance abuse (strength of recommendation [SOR]: **B**, based on case report surveillance programs). While it appears that tramadol's risk of substance abuse is low (SOR: **B**, based on case report surveillance programs), tramadol is associated with a withdrawal syndrome usually typical of opioid withdrawal (SOR: **B**, based on case report surveillance programs, and a prospective descriptive study).

■ EVIDENCE SUMMARY

Tramadol is a novel, central-acting synthetic opioid with weak mu-opioid activity, and is approved for treatment of moderate to moderately severe pain in adults. Anecdotally, some clinicians have assumed this popular analgesic's nonscheduled status under the Controlled Substance Act (CSA) means tramadol has no substance abuse potential. (The term "abuse" herein denotes substance abuse or dependence.)

Evidence of tramadol abuse in the US comes primarily from federally operated programs collecting adverse drug event (ADE) data. The MedWatch program of the Food and Drug Administration (FDA) provides a central depository for receiving and compiling postmarketing voluntary case reports. While passive reporting systems can significantly underestimate serious ADE numbers, these reports are often the first evidence of an ADE after a new drug's release into the market.[1] MedWatch has received 766 case reports of abuse associated with tramadol, as well as 482 cases of withdrawal associated with tramadol from the drug's initial US marketing in 1995 through September 2004.[2,3]

The Drug Abuse Warning Network (DAWN) is a federally operated, national surveillance system that monitors trends in drug-related emergency department visits. Over the period from 1995 to 2002, DAWN reported drug-related emergency department visits mentioning tramadol in more than 12,000 cases. Tramadol case numbers significantly increased 165% during this time. For perspective, during the same period, DAWN found nalbuphine (Nubain, also not CSA scheduled) in 118 cases, propoxyphene drug combinations (CSA Class IV) in more than 45,000 cases, codeine drug combinations (CSA Classes III & V) in about 50,000 cases, and hydrocodone drug combinations (CSA Class III) in around 128,000 cases.[4]

Using data from observational postmarketing studies, investigators have extrapolated a tramadol abuse rate for the general tramadol-exposed population.[5,6] Ortho-McNeil, Ultram's manufacturer, funded a surveillance program that compiled tramadol abuse and withdrawal case reports from 2 sources: (1) periodic surveys for tramadol abuse case reports from a group of 255 substance abuse experts studying and caring for addiction communities, and (2) voluntary ADE case reports from health care professionals and consumers received by Ortho-McNeil. Over 3 years of surveillance, the program received 454 case reports classified as tramadol abuse. Over 5 years of surveillance, 422 cases of substance withdrawal, with primarily opioid withdrawal symptoms, were reported. There are significant threats to the validity and generalizability of the investigators' estimated abuse rate of 1 to 3 cases per 100,000 tramadol-exposed patients. The abuse cases were collected in nonrepresentative samples of the tramadol-exposed population. Tramadol exposure is likely suppressed in addiction communities with access to preferred, more potent or euphoriant opioids than tramadol. Voluntary case reports of tramadol abuse significantly underestimate the actual number of abuse cases in the tramadol-exposed population. In addition, the low survey return rate (49%) further decreases the accuracy of any estimation of tramadol abuse rates.

Prospective studies among patients with known abuse, or at high risk of abuse, reported a tramadol abuse rate, as well as subjective experiences of tramadol withdrawal. A 3-year post-mar-

keting cohort study measured tramadol's nonmedical misuse rates using urine drug testing for tramadol among 1601 participants in 4 US state monitoring programs for impaired healthcare professionals.[7] Tramadol exposure occurred in 140 (8.7%) participants. Thirty-nine (28%) were classified as extensive experimentation or abuse of tramadol. Overall, the rate of extensive experimentation or abuse was 18 cases per thousand person-years. The Hawthorne effect, where awareness of being monitored alters a subject's behavior, may threaten these measured frequency rates' generalizability. Another prospective study assessed the subjective tramadol withdrawal experience in 219 patients with a diagnosis of "Tramadol misuse" who were attending 6 drug detoxification centers in China.[8] Validated drug dependence symptom scales found that while the degree of physical dependence reported was uniformly mild, the majority of patients reported the psychic dependence symptom of tramadol craving.

The FDA's Drug Abuse Advisory Committee performed a formal review of the tramadol abuse evidence in 1998, including the data from Ortho-McNeil's surveillance studies and federal case reporting/surveillance programs. The FDA did not recommend changing tramadol's unscheduled status.[9] The FDA's considered decision to not schedule tramadol as a controlled substance implies its abuse risk to the general population is *low* in comparison to its novel analgesic benefit.

■ RECOMMENDATIONS FROM OTHERS

Ortho-McNeil's revised 2001 product package insert for Ultram states, "Tramadol may induce psychic and physical dependence of the morphine type (mu-opioid). *Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence*" (italics in original, emphasizing 2001 addition). The risk for patients with a history of substance abuse has been observed to be higher.[10]

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■ CLINICAL COMMENTARY

Though it may not have high abuse potential, prescribe tramadol cautiously

Although tramadol appears to have a low potential for abuse, the literature does reveal evidence of abuse, addiction, and withdrawal, even in patients without a history of such problems. We do not know if tramadol is less addictive than other narcotics in high-risk patients. For patients at risk for dependence, tramadol is a reasonable alternative to other opioids, but abuse appears more likely in these patients. Tramadol may be most appropriate for treatment of acute painful conditions, but it can be administered chronically under a watchful eye. Providers should prescribe it cautiously, particularly in patients with a history of abuse or addiction, at least until more definitive evidence surfaces.

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CONTINUED

COMMONWEALTH OF PENNSYLVANIA
DEPARTMENT OF STATE
BUREAU OF PROFESSIONAL AND OCCUPATIONAL AFFAIRS
STATE BOARD OF MEDICINE
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February 22, 2012

The Honorable Silvan B. Lutkewitte, III, Chairman
INDEPENDENT REGULATORY REVIEW COMMISSION
14th Floor, Harristown 2, 333 Market Street
Harrisburg, Pennsylvania 17101

Re: Proposed Regulation
State Board of Medicine
16A-4933: PRESCRIBING

Dear Chairman Lutkewitte:

Enclosed is a copy of a proposed rulemaking package of the State Board of Medicine pertaining to prescribing.

The Board will be pleased to provide whatever information the Commission may require during the course of its review of the rulemaking.

Sincerely,

James W. Freeman, M.D., Chairperson
State Board of Medicine

JWF/TL:klh
Enclosure
cc: Katie True, Commissioner
Bureau of Professional and Occupational Affairs
Rebecca Oyler, Director of Policy, Department of State
Steven V. Turner, Chief Counsel
Department of State
Cynthia Montgomery, Regulatory Counsel
Department of State
Teresa Lazo, Counsel
State Board of Medicine
State Board of Medicine

TRANSMITTAL SHEET FOR REGULATIONS SUBJECT TO THE REGULATORY REVIEW ACT

I.D. NUMBER: 16A-4933

SUBJECT: PRESCRIBING

AGENCY: DEPARTMENT OF STATE
STATE BOARD OF MEDICINE

TYPE OF REGULATION

X Proposed Regulation

Final Regulation

Final Regulation with Notice of Proposed Rulemaking Omitted

120-day Emergency Certification of the Attorney General

120-day Emergency Certification of the Governor

Delivery of Tolled Regulation
a. With Revisions b. Without Revisions

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IRRC
2012 FEB 22 A 10: 33

FILING OF REGULATION

DATE	SIGNATURE	DESIGNATION
		HOUSE COMMITTEE ON PROFESSIONAL LICENSURE
2/22/12	Michele Warren	MAJORITY CHAIRMAN Julie Harhart
2/22/12	Mary Walmer	SENATE COMMITTEE ON CONSUMER PROTECTION & PROFESSIONAL LICENSURE
		MAJORITY CHAIRMAN Robert M. Tomlinson
2/22/12	K. Cooper	INDEPENDENT REGULATORY REVIEW COMMISSION
		ATTORNEY GENERAL (for Final Omitted only)
2/23/12	Senator Hussa	LEGISLATIVE REFERENCE BUREAU (for Proposed only)