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Since publication of their article, the authors report no further potential conflict of interest.
DOI: 10.1056/NEJMc1209658

THE EDITORIALIST REPLIES: Rosen and Mayne describe the figure in my editorial as “unsupported,” which is not the case. The sigmoid curve was first used for nutrients by Mertz in his classic article on trace elements1 and was adopted by standard textbooks of nutritional epidemiology such as Willett’s.2 In inverse form, it appears twice in the IOM’s first book in the current series on dietary reference intakes.3 More basically, the sigmoid curve is the fundamental model of pharmacology, in which the biologic response typically spans three orders of dose magnitude. The sigmoid curve for nutrients (unlike that for drugs) is compressed into a narrow range of intakes, with the left and right terminal segments of the sigma varying in length and location according to substance. However, their length is not germane to the point I was making, which was that in order to detect efficacy, the contrasting nutrient exposures must span an appreciable part of the rising segment of the sigma. That will not happen if the control exposure is too high or if the treated exposure is too low.

Paterson disagrees with my statement that a large single dose of vitamin D may induce transient vitamin D intoxication. He is correct that the excess vitamin D is stored in fat but overlooks the fact that vitamin D is transported to fat on the vitamin D-binding protein (DBP). From available data, the concentration of vitamin D in serum after the administration of doses as high as 500,000 IU can be estimated to exceed 2500 nmol per liter, more than enough to saturate the DBP and to elevate free 25-hydroxyvitamin D and calcitriol by displacing them from their bound status.4 With high single doses of vitamin D, serum 25-hydroxyvitamin D does not measure intoxication. Only the free level is informative. Moreover, the fact that a large single dose of vitamin D is efficacious in managing osteomalacia is irrelevant to its potential for toxicity. It is not a question of “either/or” but of “both/and.” However, I certainly do agree that daily vitamin D supplementation in the elderly is both burdensome and probably less effective than infrequent, larger doses. Single doses of 100,000 IU are not high enough to saturate the DBP and can safely be given every month or two to produce the benefits that Paterson appropriately seeks.

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Since publication of his article, the author reports no further potential conflict of interest.
DOI: 10.1056/NEJMc1209658

Management of Opioid Analgesic Overdose

TO THE EDITOR: Boyer (July 12 issue)4 reports that use of naloxone to treat opioid overdose is logical because it is a direct antagonist of mu opioid receptors. Other strategies for treating opioid-induced respiratory depression and oversedation are now plausible and should be developed as alternatives to single-drug therapy with naloxone. Ampakines, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor agonists, have been shown in clinical studies to effectively antagonize opioid-induced respiratory depression.2 Dopaminergic agonists act directly in the respiratory centers to enhance respiration3 and presumably in the mesocortical pathways to induce arousal. Administration of amantadine is a common practice for enhancing arousal in patients in a coma.4 Methylphenidate, a standard treatment for attention deficit–hyperactivity disorder, has been shown in experimental models to induce emergence from general anesthesia.5 A key physiological response on emergence is a considerably enhanced respiratory rate. Administering one or more of these drugs with naloxone suggests a combination therapy for opioid overdose that involves direct respiratory and arousal stimulation along with opioid antagonism. Rationally designed combination therapies, as compared
with single-dose therapy with naloxone, could make drug treatments of opioid overdose more effective and hence obviate the considerably higher costs of management in the intensive care unit.

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Drs. Brown and Solt report applying for a patent on the use of methylphenidate to induce emergence from general anesthesia. No other potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMba1209707

TO THE EDITOR: Boyer emphasizes the value of naloxone in treating opioid overdose in medical settings such as ambulances and emergency departments. To help maximize the public health effect of naloxone, the Food and Drug Administration (FDA), Centers for Disease Control and Prevention, and National Institute on Drug Abuse recently convened a public meeting to discuss its availability outside conventional medical settings (e.g., for patients taking high doses of opioids, hospice residents, and injection-drug users). Although naloxone is currently FDA-approved for intravenous, intramuscular, and subcutaneous use, researchers from a variety of locations reported encouraging data on the ability of naloxone to reverse opioid overdose through intranasal administration in nonmedical settings. At the meeting, the FDA outlined regulatory pathways for approval of this potentially easier-to-use formulation. Depending on study outcomes, the additional required studies may be limited in number and of modest size. Administration of naloxone with the use of auto-injectors and switching naloxone from prescription to over-the-counter status to increase availability were also discussed. The FDA and National Institute on Drug Abuse welcome the opportunity to discuss this lifesaving medication further with researchers and with manufacturers interested in pursuing its development.

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No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMcd1209707

TO THE EDITOR: Boyer promotes the use of low-dose naloxone (0.04 mg) instead of the conventionally recommended doses (0.4 or 2 mg). However, we wanted to clarify that his comment that naloxone can be administered “without compunction” applies specifically to the 0.04-mg dose, since, as suggested by the author, higher doses are associated with the risk of precipitating opioid withdrawal. Precipitated opioid withdrawal carries substantial risk, including agitated delirium, poor decision making, catecholamine storm, pulmonary edema, and aspiration pneumonitis in patients who are sedated from other intoxicants. A clear distinction should be made between precipitated opioid withdrawal induced by an opioid antagonist and spontaneous withdrawal from opioid abstinence, the latter of which is, as Boyer suggests, “unpleasant but not life-threatening.” Although we agree that in patients without opioid dependence, naloxone causes few if any adverse effects, its safe use in patients with profound opioid dependence, such as that induced by methadone or extended-release opioid analgesics, requires extreme caution. Titration with the use of a 0.04-mg aliquot may be a prudent course of action.

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TO THE EDITOR: Boyer states that naloxone “is active when the parenteral, intranasal, or pulmonary route of administration is used.” We think that another important route of administration is intramuscular. This route could be very advantageous for several reasons: in injecting drug users, it is often difficult to find a peripheral venous access; the personnel involved in the prehospital care may not be skilled in obtaining central venous access; and the intranasal formulation of naloxone is not available worldwide.

Intramuscular naloxone at a dose of 2 mg (the same dose that is given intranasally) has proved more effective than or equally effective as intranasal naloxone for heroin overdose. The mean time required to obtain a respiratory rate of 10 breaths per minute or more or a Glasgow Coma Scale score of 13 or more (on a scale of 3 to 15, with lower scores indicating reduced levels of consciousness) varies between 6 minutes and 8 minutes after the initiation of intramuscular naloxone. The reduced effectiveness of intranasal naloxone may be related to its lower bioavailability as compared with that of intramuscular naloxone.

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No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1209707

THE AUTHOR REPLIES: Brown and Solt propose replacing naloxone with a multidrug regimen. Whereas naloxone lacks substantial adverse effects, each drug in their proposed regimen has recognized toxic effects and drug interactions. Considerable justification will be needed before clinicians should consider replacing a proven, familiar, and inexpensive antidote with a convoluted regimen that increases the risk of preventable adverse events.

I, along with Throckmorton et al., await studies that extend encouraging data from studies of bystander-administered naloxone for heroin overdose. The brief duration of action of naloxone should impel investigators to protect study participants against recurrent respiratory depression, the risk of which is greater after opioid analgesic overdose that has been treated with naloxone than in heroin toxicity. Requiring patient transportation by ambulance to a health care facility after naloxone administration is a simple response that should improve patient safety. I speculate that it might also improve the validity of studies because investigators would be able to determine the type and dose of opioid ingested, the characteristics of the person who took the overdose, and the source of the naloxone.

I agree with Kim and Nelson that opioid withdrawal precipitated by naloxone is probably more severe than that from missed dosing, but I am unaware of supporting medical literature. Picetti et al. are correct that large intramuscular doses of the antidote will reverse intoxication in persons with opioid tolerance, but smaller doses are often sufficient in patients with opioid dependence. An initial dose of 0.04 mg of naloxone is a nuanced approach to overdose management, whereas injecting 2 mg of naloxone in selected patients may border on the cruel.

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Since publication of his article, the author reports serving as an expert witness in a class-action lawsuit against Watson Pharmaceuticals regarding fentanyl patches.
Four-Year Follow-up after Two-Year Dietary Interventions

TO THE EDITOR: Data from trials that compare the effectiveness of weight-loss diets are frequently limited to the intervention period. In our 2-year workplace-based study, called the Dietary Intervention Randomized Controlled Trial (DIRECT),\(^1,2\) we randomly assigned 322 moderately obese

Figure 1. Changes from Baseline in Diet-Related Measures.

Shown are mean changes from baseline in weight (Panel A), the ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol (Panel B), triglyceride levels (Panel C), and total cholesterol levels (Panel D) in 322 moderately obese participants who were assigned to one of three weight-loss plans: a low-fat, restricted-calorie diet (Low fat); a Mediterranean, restricted-calorie diet (Med); or a low-carbohydrate diet without calorie restriction (Low carb). The duration of the original study was 2 years (as indicated by the shaded portion of the graph). Four-year follow-up analyses were conducted in 259 of the original participants. LDL and HDL were measured in milligrams per deciliter. Asterisks denote \(P<0.05\) for the difference from baseline at 6 years. The bars indicate standard deviations.