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Review of Nicotine nasal spray neither effective nor well-tolerated by adolescent smokers

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for increasing time without fever and the relief of fever-associated discomfort?

Design Randomized, blinded, 3-arm trial.

Setting Primary care settings in Bristol, England.

Participants A total of 156 children, ages 6 months to 6 years with axillary temperatures of at least 37.8° C and up to 41.0° C.

Intervention Advice on physical measures to reduce temperature and the provision of, and advice to give, acetaminophen plus ibuprofen, acetaminophen alone, or ibuprofen alone.

Outcomes Primary outcomes were the time without fever (<37.2° C) in the first 4 hours after the first dose was given and the proportion of children reported as being normal on the discomfort scale at 48 hours. Secondary outcomes were time to first occurrence of normal temperature (fever clearance), time without fever over 24 hours, fever-associated symptoms, and adverse effects.

Main Results On an intention to treat basis, acetaminophen plus ibuprofen were superior to acetaminophen for less time with fever in the first four hours (adjusted difference 55 minutes, 95% confidence interval 33 to 77; $P < .001$) and may have been as good as ibuprofen (16 minutes, -7 to 39; $P = 0.2$). For less time with fever over 24 hours, acetaminophen plus ibuprofen were superior to acetaminophen (4.4 hours, 2.4 to 6.3; $P < .001$) and to ibuprofen (2.5 hours, 0.6 to 4.4; $P = .008$). Combined therapy cleared fever 23 minutes (2 to 45; $P = .025$) faster than acetaminophen alone but no faster than ibuprofen alone (-3 minutes, 18 to -24 ; $P = .8$). No benefit was found for discomfort or other symptoms, although power was low for these outcomes. Adverse effects did not differ between groups.

Conclusions Parents, nurses, pharmacists, and doctors wanting to use medicines to supplement physical measures to maximize the time that children spend without fever should use ibuprofen first and consider the relative benefits and risks of using acetaminophen plus ibuprofen over 24 hours.

Commentary Fever is common in children and causes parents to worry. Most febrile children have self-limiting infections and will get better without treatment. But young children who are febrile are usually uncomfortable and miserable. It is standard practice for doctors to recommend, and parents to administer, antipyretic treatment. The 2 most widely used drugs are acetaminophen and ibuprofen. Recently it has become increasingly common for doctors to recommend a combination of both drugs, so this primary care study randomizing feverish young children to either drug alone or a combination of the 2 drugs is timely. The authors report 2 primary outcomes: time without fever in first 4 hours and fever-associated discomfort after 48 hours. The first could be argued to represent a proxy of parental concern, but it is fever-associated discomfort that is the key outcome. And for this outcome, the study is underpowered. One hundred fifty-

six children were recruited and randomized from 1038 potentially eligible participants. Despite this, their results suggest no additional improvement in fever-associated discomfort or activity levels in the combined medication group at 24 hours, 48 hours, and 5 days. Their data confirm that ibuprofen is faster acting and has a longer duration than acetaminophen but that a combination of drugs has little advantage. Of some concern is their report of 31 children in the combined group receiving an overdose of medication even in clinical trial conditions. A larger trial is required to confirm their findings, but for now, I am not persuaded that prescribing a combination of acetaminophen and ibuprofen for the treatment of feverish young children has any advantage over use of either drug alone.

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Nicotine nasal spray neither effective nor well-tolerated by adolescent smokers

Rubinstein ML, Benowitz NL, Auerback GM, Moscicki A. A randomized trial of nicotine nasal spray in adolescent smokers. *Pediatrics* 2008;122:e595-e600.

Question Among adolescent smokers who wanted to quit smoking, is nicotine nasal spray effective at increasing cessation rates?

Design Randomized, open-label, 12-week trial.

Setting Five San Francisco Bay Area high schools.

Participants Forty adolescents, ages 15 to 18 years of age, who smoked ≥ 5 cigarettes daily for at least 6 months.

Intervention Participants were assigned to receive either weekly counseling alone (control) for 8 weeks or 6 weeks of nicotine nasal spray along with 8 weeks of counseling.

Outcomes Self-reported smoking abstinence, as verified by both expired-air carbon monoxide and salivary cotinine levels.

Main Results There was no difference in cessation rates, the number of cigarettes smoked per day, or cotinine levels at 12 weeks. Fifty-seven percent of participants stopped using their spray after only 1 week. The most commonly reported adverse effect was nasal irritation and burning (34.8%), followed by complaints about the taste and smell (13%).

Conclusions The unpleasant adverse effects, poor adherence, and consequent lack of efficacy observed in this pilot study do not support the use of nicotine nasal spray as an adjunct to counseling for adolescent smokers who wish to quit.

Commentary This is an important and well-designed first study of the effect of nicotine nasal spray (NNS) on adolescent smoking cessation that supports current evidence-based guidelines that nicotine replacement therapy is neither effective nor recommended for adolescents.¹ NNS theoretically

could succeed for adolescents where other forms of nicotine replacement failed. Consistent with adolescent tobacco use patterns, potential benefits of NNS over other forms of nicotine replacement include the following: (1) NNS can be used intermittently, (2) in response to environmental influences, such as smoking to relieve stress, NNS has a relatively fast delivery of nicotine with reinforcing effects, and (3) compared with other forms of nicotine replacement, NNS allows greater self-control and ownership of the intervention, which adolescents prefer. Admirably, this study uses a validated nicotine dependence questionnaire for adolescents, a withdrawal symptom scale, biochemical validation of self-report, and an intention-to-treat analysis. Two noteworthy design limitations exist: First, this is an open-label trial without a placebo group. Second, although originally designed to be an effectiveness study, failure to meet sample size requirements forced the authors to truncate the study for feasibility. These limitations are relatively minor, however, because this study convincingly shows that NNS is not tolerated by adolescents. Although the delivery system holds promise for adolescent smokers, the negative side effects of the spray, in particular burning associated with use, led to such poor adherence that discussion of efficacy is moot. If future NNS preparations are better tolerated, this study deserves replication with adequate power to reexamine the issue of effectiveness for adolescents.

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Continuous glucose monitoring study does not demonstrate benefit in children and adolescents

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464-76.

Question Among patients with type 1 diabetes mellitus, does the use of continuous glucose monitoring result in improved glycemic control?

Design Randomized, controlled trial.

Setting Multiple centers in the United States.

Participants A total of 322 adults and children who were already receiving intensive therapy for type 1 diabetes.

Intervention Continuous glucose monitoring or a control group performing home monitoring with a blood glucose meter.

Outcomes Change in the glycated hemoglobin level at 26 weeks.

Main Results The changes in glycated hemoglobin levels in the 2 study groups varied markedly according to age group ($P = .003$), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change, -0.53% ; 95% confidence interval [CI], -0.71 to -0.35 ; $P < .001$). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08 ; 95% CI, -0.17 to 0.33 ; $P = 0.52$) or among those who were 8 to 14 years of age (mean difference, -0.13 ; 95% CI, -0.38 to 0.11 ; $P = .29$). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe hypoglycemia was low and did not differ between the 2 study groups; however, the trial was not powered to detect such a difference.

Conclusions Continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes, but was not effective in children and adolescents.

Commentary This is the largest, prospective, individually randomized unblinded controlled trial of continuous glucose monitoring (CGM). Use of CGM was associated with significantly improved glycemic control in adults with type 1 diabetes, but not children or adolescents. Between-group A1C levels fell by a mean of 0.53% in adults. Nonsignificant benefit of CGM was observed in subjects who were 8 to 14 years of age, and no benefit was observed among subjects who were 15 to 24 years of age. Why didn't children and adolescents benefit? The reasons might be related to adherence and to the study's method for randomization. Use of CGM is a tool for directing behavior on the basis of glucose levels. Adherence to a behavioral intervention is necessary for the intervention to be successful.¹ Adherence alone might account for the ranking of results between adults with the greatest compliance (80%) and greatest benefit, compared with children with the second-best compliance (50%) and second best results, and adolescents with the least compliance (33%) least benefit. The study used individual randomization, which is appropriate for a blinded trial, but in an unblinded trial of a behavioral intervention, cluster randomization of study sites is often used to prevent contamination of control subjects from knowledge of the intervention.² If control subjects learn about benefits of using CGM at the investigator's office, then they might monitor their glucose more frequently and artifactually improve their control. This behavior could improve the A1C outcome for controls and wash out the between-group benefit of the CGM intervention. Indeed, in this study the children and adolescent control subjects both had at least a