selective reporting bias. Skepticism of NRT's strong effectiveness (i.e., 50−70% increase in smoking cessation) need not depend on any meta-regression model, method, or assumption about publication bias.

Aside from clear evidence of publication bias ([4,6]; p.22), another important limitation of these 122 RCTs of NRT is that they are largely underpowered and thereby incapable of detecting the typical effect size that has been reported in the scientific literature. All but five of these 122 RCTs (or 96%) are underpowered [4]. That is, if we use the fixed-effect weighted average of these 122 RCTs as the proxy for "true" effect (log RR = 0.445; representing a 56% increase in quitting) and the widely accepted convention of 80% as adequate statistical power [7], then only five of these 122 (or 4%) have adequate power. This deficiency alone justifies skepticism about the strength of evidence that can be derived from this body of research on NRT's effectiveness. As all researchers know, statistical power is a key dimension to the validity of their research findings. "Unless (we) begin to incorporate methods for increasing the power of (our) studies, the published literature is likely to contain a mixture of apparent results buzzing with confusion. Not only do underpowered studies lead to a confusing literature but they also create a literature that contains biased estimates of effect sizes" [[8], p.161].

One sensible response to the power failure of the clinical investigation of NRT is to focus on only those studies which are adequately powered. The weighted least-squares weighted average of these five adequately powered studies is log RR = 0.366 (or a 44% increase in quitting) [9]. This weighted average of the adequately powered has recently been shown to be useful in reducing selective reporting bias among 159 areas of economics research [10]. However, Stead et al. (2012) judged the blinding integrity of two of these five studies to be at high risk. If we calculate the weighted average of the remaining adequately powered RCTS, we get a smaller effect size, log RR = 0.247 (or a 28% increase in quitting), which is about half the size reported by systematic reviews. Furthermore, the 95% confidence interval for this weighted average (−0.01; 0.50) contains zero; thus, it does not provide clear statistical evidence of the clinical effect from NRT. The advantage of this approach is that no assumption or model of selective reporting bias (aka publication bias and small-sample bias) is used. Merely concentrating on those studies with adequate statistical power and are not identified to be at high risk of bias is sufficient to question the strength of the clinical evidence for NRT.

Aside from the statistical issues that cast doubt on the quality of evidence contained among these 122 RCTs of NRT, it is important to put these numbers in context. Most smokers who use NRT do not successfully quit—84%, on average. Smokers in the control groups succeed in quitting about 10% of the time, whereas those receiving NRT have an average quit rate of approximately 16%. When power or selective reporting is considered along with identified risks of bias, this 6% effectiveness is reduced by half, or more. Thus, it seems clear that the vast majority of smokers will not be helped by NRT. What then should our health care systems do for them?

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The effectiveness of psychostimulants in ADHD treatment: Reversing parasympathetic promoting environmental influences?

To the Editor:

Punja et al. [1] recently published a meta-analysis which found that amphetamines and psychostimulants, such as methylphenidate, are effective in the treatment of pediatric

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attention-deficit hyperactivity disorder (ADHD). Part of the therapeutic benefit of these medications may lie in their role facilitating sympathetic mechanisms, including increasing heart rate and blood pressure [2,3] or reducing parasympathetic influences. In rat, amphetamines mydriasis was mediated at least in part by the inhibition of parasympathetic outflow [4]. If the pharmacologic benefit of psychostimulants in ADHD rests on the resuscitation of sympathetic mechanisms, these studies, therefore, imply that parasympathetic dominance may be an innate feature of medication-naïve ADHD.

Negrao et al. [5] studied autonomic correlates at rest in a sample of ADHD children, both medicated and nonmedicated, and reported that stimulant-free children experienced a parasympathetic overarousal in comparison to control subjects. Consistent with Punja's findings, methylphenidate use appears to correct this autonomic imbalance at rest. Kim et al. [6] also recently investigated the role of methylphenidate on heart rate variability in ADHD subjects. Heart rate variability parameters indicative of parasympathetic tone showed significant decreases after a 12-week treatment with methylphenidate. The authors suggested that parasympathetic dominance in ADHD was corrected with the use of methylphenidate.

It has been proposed elsewhere that exposure to the environmental pollutant, nitrous oxide (N_2O), may the principal etiological factor in the development of ADHD and related neuropathologies [7,8]. The pollutant is mostly associated with agricultural soil management and the increasing use of nitrogen fertilizers [9], and significant underestimations in pollutant burden have been reported [10]. Inhalational 30% exposure to N_2O in healthy humans was shown to impart a parasympathetic dominance via inhibition of sympathetic activity [11]. Chronic exposure to environmentally relevant concentrations (50, 500, 5000 ppm) of the compound has also been previously shown to significantly alter central neurotransmission in CD-1 mice [12]. Trace amounts (500 ppm) of N_2O in healthy adult men elicits cognitive impairment on the digit span test, a test of verbal working memory [13]. These studies suggest that trace levels of exposure to N_2O in humans may promote both cognitive deficits and autonomic imbalance in healthy humans. The role of psychostimulants in reversing these specific physiological changes may underlie their clinical benefit. Therefore, additional research is needed in understanding the role of environmental pollutants, specifically N_2O, in contributing to neurodevelopmental impairment in humans.

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