If the Internet contains information of variable quality, perhaps carefully regulated direct-to-consumer advertising, for example on television, may be a better approach? Just two countries (the United States and New Zealand) permit direct-to-consumer television advertising, and in this issue of the *Journal*, Daubresse and colleagues (pp. 40–46) have reported how such advertising might impact prescription rates for four controller asthma medications and healthcare use for patients with asthma in the United States (4). Using a complex methodology, the authors first defined direct-to-consumer advertising exposure based on household television viewing and then related this to both pharmacy sales of medications and outpatient visits, emergency room visits, and hospitalizations (with asthma). The advertising seemed to work in that pharmacy sales of the advertised products increased, but unlike other forms of advertising, the increase here reflects not direct consumer demand but demand via a physician. The increase in sales is unlikely to reflect brand switching, because the introduction of a new inhaled steroid/long-acting β -agonist inhaler during the course of this study did not appear to reduce sales of a preexisting similarly advertised product. However, there was a strong correlation between exposure to advertising and new prescriptions for the new product. Less easy to explain was the association observed between viewing the television advertisements and the greater number of emergency room visits (for asthma).

Like all research involving interrogation of databases, the results are useful in hypothesis generation rather than for providing definitive answers. For example, it may be that advertisements lead to a search for convenient sources of more medication, or perhaps the advertisement reminds patients or carers of signs that suggest poor control of their condition, and this initiates healthcare attendances. If so, the fact that emergency room attendances but not hospitalizations increased with increased exposure to advertising suggests that the attendances were not necessarily for severe disease. Other unanswered questions also arise from the present study. Do we know that the expensive advertising is leading to an increase in *necessary* medication, or is it resulting in overtreatment? Patients' requests for medication have been shown to be a powerful driver of prescribing decisions, but the appropriateness of such prescriptions may suffer (5). Similarly, how certain are we that the content of advertisements is balanced, informative, and helpful? Marketing legislation requires advertisements to contain information regarding side effects. Although the same information is contained within patient information leaflets (which have been shown to lead to better informed and more satisfied patients [6]), there might be a difference between choosing to read a package insert and the same information displayed on television screens. Not taking medication in the manner previously discussed with a doctor is a major problem in the

management of most long-term conditions (7), and real or imagined side effects or fear of side effects can play a significant part in this nonadherence.

More work is needed before we know whether direct-to-consumer advertising of medications is a welcome source of information central to shared decision making and partnership medicine or whether it unnecessarily increases medication usage and cost, encourages emergency room attendance that could potentially have been avoided by different anticipatory prior care, and raises fears regarding side effects. Definite benefits in terms of health outcomes currently seem to be missing. ■

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Stress, *ADCYAP1R1*, and Childhood Asthma No Sigh of Relief

Children with asthma in the United States continue to experience suffering and diminished quality of life (1). Despite decades of

research, the precise genetic and environmental factors giving rise to asthma and its phenotypic characteristics have remained elusive. Children from Puerto Rico in particular have a greater asthma prevalence (8–49%) (2) and disease burden compared with children from other ethnic groups (2, 3). The exposure to early-life

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psychosocial stress (PSS) (4, 5) and an increased susceptibility to PSS among Puerto Ricans (6) may contribute to these disparities. These themes of PSS and asthma-related genetic predisposition are presented in a series of interesting analyses in this issue of the *Journal*, presented by Brehm and colleagues (pp. 47–56) (7).

More broadly, research has clearly demonstrated that children exposed to PSS more often suffer from a variety of long-term health problems ranging from cancer to depression to asthma (8). Sources of PSS often include child neglect or abuse, extreme poverty, and family violence (9), which appear to disrupt the coordinated development of the central nervous system and the neuroendocrine and immune systems (9). Specifically, the hypothalamic–pituitary–adrenal axis, which is important in regulating stress, appears to be dysfunctional in humans born into and experiencing high PSS (10).

PSS clearly increases the risk for asthma diagnosis (4) and can worsen existing disease (11). In fact, before asthma was understood as an inflammatory disease of the airways, “asthma nervosa” was largely seen as a somatic manifestation of stress and of the psyche. Maimonides first described the important role of emotion and psychology in asthma (12). Later, Sir William Osler agreed with this view and described asthma as a “neurotic affliction” (13).

The gene *ADCYAP1R1*, which encodes for pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1) and binds pituitary adenylate cyclase activating peptide, may play a role in stress and asthma among Puerto Ricans. *ADCYAP1R1* functions along with the hypothalamic–pituitary–adrenal axis to regulate stress responses and has been associated with risk for post-traumatic stress disorder (14), childhood anxiety, and childhood asthma (15). Recently, several of the current authors found that children exposed to violence had greater DNA methylation of *ADCYAP1R1* and that this greater methylation was also associated with asthma risk. Few previous studies have examined the role of genetic and molecular mechanisms linking PSS and asthma outcomes, and the recent results linking PSS, asthma, and *ADCYAP1R1* are important but require replication and further study. The study performed by Brehm and colleagues presented here provides exciting new information about these links (7). They assessed whether stress or *ADCYAP1R1* variation was associated with bronchodilator response (BDR) in children with asthma. BDR is important because it associates with clinical outcomes, airway inflammation, and response to inhaled corticosteroid therapy (16). The researchers performed a cross-sectional analysis of 6- to 14-year-old children with physician-diagnosed asthma from Puerto Rico. Replicate cohorts included similar-aged children from Rhode Island and Puerto Rico and a nonasthmatic cohort of children with reduced FEV₁/FVC (to address nonadherence as a potential confounder).

They estimated child stress stemming from violence during the preceding 6 months (measured using the Checklist of Children’s Distress Symptoms questionnaire), maternal stress (measured using the Perceived Stress Scale), and a composite “household stress” score. Spirometry (before and 15 minutes after appropriate bronchodilation) and DNA analysis were performed. The researchers found that children in the highest-stress quartiles in the primary and replicate cohorts displayed a significantly diminished percentage BDR compared with children with lower stress. Interestingly, high maternal stress had an even greater

negative effect on BDR than did child stress. However, BDR was lowest among children who had both high stress themselves and had mothers with high stress (i.e., high household stress). These children had a BDR that was more than 10% lower than that of children without either high child or maternal stress, which is likely to be clinically meaningful.

Next, common single-nucleotide polymorphism (SNPs) near *ADCYAP1R1* were interrogated for association with reduced BDR. Six of 106 SNPs were found to be significant ($P < 0.05$) and were further tested in six appropriate replication cohorts. One SNP (rs34548976) was found to be highly associated with reduced BDR after correction for multiple testing. Using publically available data, the investigators further showed that the same rs34548976 SNP is associated with increased *ADCYAP1R1* (PAC1) expression in both human lung and brain. The investigators then posed the question of whether this SNP in *ADCYAP1R1* could cause reduced BDR mediated by greater anxiety leading to reduced *ADRB2* expression. They found that in unstimulated CD4⁺ T cells from children and adults with asthma, rs34548976 was associated with reduced *ADRB2* expression. However, it is unclear whether *ADCYAP1R1*-related BDR reductions are a result of reduced airway smooth muscle (ASM) *ADRB2* expression, as *ADCYAP1R1* is not expressed in ASM. BDR also can be reduced in children with greater airway collapsibility and closure after ASM relaxation (which could be affected by stress and *ADCYAP1R1*). However, the authors propose the more likely explanation for reduced BDR being from neurohormonal mechanisms under conditions of stress leading to *ADRB2* down-regulation in ASM.

Using functional magnetic resonance imaging data from adult African American women, the investigators showed that two copies of rs34548976 associated with greater connectivity between the amygdala and insula, a pathway that is influential in anxiety and dyspnea. Last, they showed that the rs34548976 SNP showed effect modification on BDR by child stress in those within the highest-stress group. Taken together, these inquiries are an important contribution to understanding how childhood stress in the setting of a genetic predisposition affects asthma pathogenesis. Future longitudinal studies will help establish whether stress antedates methylation changes and how acute versus chronic stress at different developmental ages affect asthma symptom control, exacerbations, and lung function over time. These intricate scientific findings are also of major public health significance, as they serve to underscore the importance of policies that support a safe and healthy family and community environment. Household stress is a modifiable risk factor our professions can help address. Protection of children from toxic stress by a nurturing adult caregiver backed by a supportive public health system is likely to protect millions of children from future disease. ■

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Ventilator-associated Pneumonia Prevention Is It Worth It?

Ventilator-associated pneumonia (VAP) continues to be a clinically important hospital-acquired infection. A recent prospective surveillance study found that VAP prevalence was 15.6% globally (13.5% in the United States, 19.4% in Europe, 13.8% in Latin America, and 16.0% in Asia Pacific), with a corresponding global *Pseudomonas aeruginosa* VAP prevalence of 4.1% (corresponding regional prevalence rates of 3.4, 4.8, 4.6, and 3.2%, respectively) (1). VAP is also associated with excess attributable mortality, although the magnitude of the mortality excess appears to be greatest for surgical patients and patients with midrange severity of illness (2). Hospital lengths of stay and medical care costs are also greater for critically ill patients who develop VAP (3). Most important, VAP is increasingly attributed to antibiotic-resistant bacteria including methicillin-resistant *Staphylococcus aureus*, nonfermenting gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*), and antibiotic-resistant *Enterobacteriaceae* (extended-spectrum β -lactamase and carbapenem-resistant strains).

There has been a sense in the United States that VAP is a “vanishing” infection with reported mean national rates within intensive care units (ICUs) of less than 4 per 1,000 ventilator days (4). This is in contrast to higher rates of VAP reported internationally (1, 4). An important explanation for this discrepancy regarding nationally reported rates of VAP is the method of surveillance

employed. The Centers for Disease Control and Prevention surveillance method markedly underestimates the occurrence of clinically and microbiologically confirmed VAP (5). This had led the Centers for Disease Control and Prevention and the National Health Safety Network to adopt ventilator-associated events as a new method of ICU surveillance, focusing on oxygenation parameters. Unfortunately, ventilator-associated events appear to underestimate the occurrence of VAP and often identify clinical events that are related to the underlying disease process and are not potentially preventable (6, 7). A deemphasis of the importance of VAP could motivate hospitals to reallocate funds and resources used for VAP surveillance and prevention to other clinical problems, especially if the latter are more closely tied to reimbursement. This could promote increasing future rates of VAP and greater overall healthcare costs.

In this issue of the *Journal*, Branch-Elliman and colleagues (pp. 57–63) performed a cost-benefit analysis using model inputs from the medical literature and the US Department of Labor to determine the preferred VAP prevention strategy, both from the hospital and societal perspectives (8). They attempted to identify the overall least expensive strategy and the strategy with the best cost-benefit ratio. The preferred strategies from the hospital perspective included the use of subglottic suction endotracheal tubes, probiotics, and the Institute for Healthcare Improvement VAP Prevention Bundle. The preferred strategies from the point of view of society also included oral care with chlorhexidine and selective oral decontamination. Several important limitations of this analysis should be noted. First, some of the assumptions on

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