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LETTER TO THE EDITOR

Anxiety/depression and impaired asthma control in adolescents. Is an increased basal cholinergic tone a possible link ?

G. Liccardi ¹, L. Calzetta ^{1,2}, M. Milanese ³, MB Bilò ⁴, MV Liccardi ⁵, MG Matera ⁶, I. Baiardini ⁷ and P. Rogliani ^{1,2}

¹ Postgraduate School of Respiratory Medicine. Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy

² Department of Experimental Medicine, Unit of Respiratory Medicine. University of Rome "Tor Vergata", Rome, Italy

³ Division of Pulmonology, S. Corona Hospital, Pietra Ligure, Italy.

⁴ Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti - Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy.

⁵ Psychologist

⁶ Department of Experimental Medicine. Second University of Naples, Naples, Italy.

⁷ Department of Biomedical Science Humanitas University, Milan, Italy

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Short title: Increased cholinergic tone as possible link between anxiety/depression and asthma in adolescents

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Summary statement: The impaired control of asthma symptoms in adolescent with anxiety/depression could be related to an anxiety/stress-induced increased cholinergic tone.

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Corresponding author

Gennaro Liccardi, MD

-Postgraduate School of Respiratory Medicine. Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy

Phone : +39 081 5780554; E-mail gennaro.liccardi@tin.it

To the Editor

We read with interest the excellent article of Licari et al. (1) reporting that anxiety and depression are regulated with the perception of asthma control in adolescents. Since asthma control grade significantly correlated with emotional scoring, the authors show that optimal asthma management improves both asthma control and anxiety / depression. However, they did not provide comments on the causal and temporal association between anxiety and asthma outcomes. From a general point of view, it is not clear if a poor asthma control worsens patient's psychological status or vice-versa. Otherwise, both hypotheses are possible. A fundamental premise is that asthmatic adolescents may experience a period of physical and psychosocial changes that affect their health and well-being. Overall, adolescents with asthma are at increased risk for asthma morbidity, asthma death and even suicidal behaviour. Increased rates of depression and anxiety, in adolescents and their caregivers, can lead to non-adherence to their medical regimens, poor symptom control and poor treatment outcomes. Asthma during adolescence impairs health-related quality of life, especially in the case of uncontrolled symptoms (2). It has been demonstrated that parental stress and air pollution were synergistically associated with increased childhood asthma, indicating a common biological effect of parental stress and air pollution during both prenatal and postnatal periods. Therefore, we would like to suggest some potential mechanisms to explain the correlation between stress/anxiety and asthma in adolescents. We have previously shown that about 63% of asthmatic patients reported the usual appearance of at least one non-respiratory symptom (n-RS) before an asthma attack (3). Anxiety and, to a lesser extent depression, represented the most common n-RSs in our study, suggesting that both anxiety and depression may have a possible role in the development and trigger of an asthma attack. Several studies have shown that psychological stress may enhance bronchial hyperreactivity through different mechanisms such as mast cell activation, mediator release, inflammation, impairment of respiratory tolerance. Moreover, Ritz. et al. (4) reported a significant correlation between psycho-social stress and stimulation of the cholinergic system, resulting in an increased airway resistance. Visual stimulations (i.e. bloody films) can rapidly induce (after 1-2 minutes) vagal-mediated responses associated with airway resistance increase. Therefore, we suggest that attention should be focused on the potential role of the parasympathetic system as a trigger of bronchial obstruction in asthmatic adolescents reporting the usual onset of cholinergic-related n-RSs (i.e. stress and/or anxiety) before an asthma attack. Indirectly, the results of our study (5), confirm a significant role of the cholinergic pathway in the enrolled asthmatic subject.

The vagal hyperactivity induced by anxiety and stress in asthmatics also represents the basis of important considerations by a therapeutic point of view, such as the use of anticholinergic agents.

94 Considering this background, we suggest the need of an adequate phenotyping of asthmatic adolescents
95 who could exhibit an increased basal cholinergic tone (6,7). The effect of oxygen and methacholine
96 inhalation, neck suction, slow deep breathing assessed by multiple frequency forced oscillation
97 technique (FOT) as well as measurement of resting heart rate and pupillometry represent the most
98 effective methods for evaluating the level of vagal tone (8) (figure 1).

99 According to our previous study (5), a simple question exploring the presence of vagal-related n-RSs
100 during the collection of anamnestic data could help to identify asthmatics with imbalance between
101 sympathetic and parasympathetic systems who could benefit of further diagnostic evaluation of vagal
102 tone. Since the degree of cholinergic tone is likely to be different among asthmatics, we believe it is not
103 possible to rule out that the effectiveness of anticholinergic agents such as tiotropium could be greater
104 in patients with an increased degree of cholinergic tone (9). This possible increased responsiveness to
105 tiotropium may be usefully exploited also in the event of poor efficacy or occurrence of adverse events
106 with the use of long-acting β_2 agonists (LABAs) (figure 1).

107 In conclusion, the currently available literature indicates that anxiety and related psychological
108 disorders should be considered as mechanisms that might trigger the airway inflammation, the onset of
109 asthma attacks, and the severity of respiratory symptoms. We concur with Licari et al (1) and others
110 (10) that adequate educational programs should be planned for those asthmatic patients suffering from
111 psychological disorders (both in adults and minors). We believe that this approach requires a peculiar
112 attention in adolescents in order to obtain a better control of respiratory symptoms in the short term, a
113 delay in asthma progression, and a reduced airway remodeling in the long term.

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164 **Legends:**
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166 **Figure 1.** Suggested flow-chart for a better phenotyping of asthmatic adolescents suffering from
167 anxiety / depression.
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