

Objective validity of patient-reported symptoms in aspirin-exacerbated respiratory disease patients

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First published: 25 November 2021

<https://doi-org.bibliosan.clas.cineca.it/10.1111/cea.14062>

Clinical Trial Registration:: NCT02824523

Key Messages

Patient-reported respiratory and anosmia symptoms correlated with related objective outcome measures, indicating that self-reports of symptoms approximate objective physiologic changes.

This study supports the validity and utility of TNSS-Plus and SNOT-22 questionnaires as research and clinical tools for patients with AERD.

To the Editor,

Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP) and acute respiratory symptoms following exposure to aspirin and other cyclooxygenase-1 inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with AERD often have a high symptom burden and more severe and difficult-to-treat upper respiratory symptoms compared with patients with aspirin-tolerant CRSwNP.¹ Exposure to NSAIDs triggers acute upper and lower respiratory symptoms including nasal congestion, rhinorrhoea, anosmia, wheezing and bronchospasm. Paradoxically, desensitization to aspirin followed by daily aspirin therapy has been shown to lead to marked improvement in symptoms and reduction in corticosteroid use for many patients with AERD.²

The long-term management of the chronic symptoms of AERD, the monitoring of symptoms during aspirin desensitization and the evaluation of response to treatment are often guided by patient-reported symptoms captured by questionnaires such as the Total Nasal Symptom

Score with systemic symptoms (TNSS-Plus)³ and Sino-Nasal Outcome Test (SNOT-22).^{4, 5} However, data on the correlation between objective outcome measures of respiratory disease severity and related patient-reported symptom questionnaire scores for nasal congestion, sense of smell and pulmonary symptoms in AERD patients are sparse. A recent study of patients with aspirin-tolerant CRSwNP demonstrated a correlation between subjective reports of nasal blockage and peak nasal inspiratory flow (PNIF) readings and between report of sense of smell on the SNOT-22 questionnaire and scores on Sniffin' Sticks extended test, respectively; however, this study excluded patients with AERD.⁶ As patients with CRSwNP with concurrent AERD tend to have more severe disease, our current study aimed to investigate this group for relationship between patient-reported symptoms and objective outcome measures and to establish whether there was meaningful correlation between patients' perception of their symptoms and the objective measurement of those symptoms.

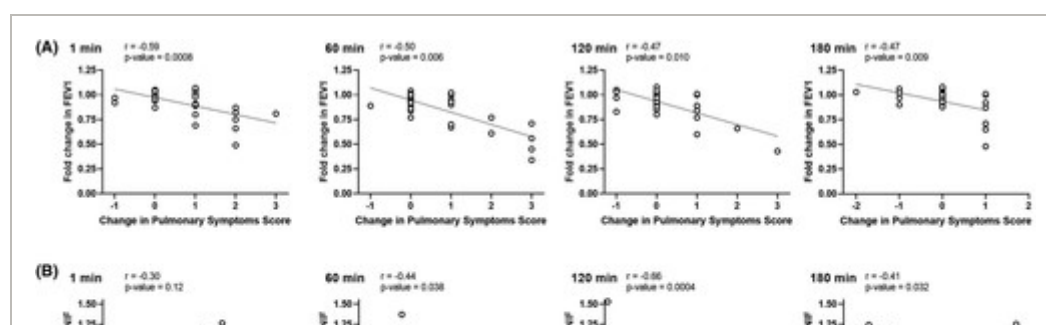
The data analysed and presented here were gathered as part of a prospective observational trial (NCT02824523) of twenty-nine adults with AERD who underwent an aspirin desensitization protocol with subsequent initiation of high-dose daily aspirin therapy at Brigham Women's Hospital. Aspirin desensitization was performed during a single-day oral protocol (Visit 1).⁷ Patients returned 8 weeks later while on daily high-dose aspirin (650 mg twice daily) (Visit 2) and again 2 weeks after that while on medium-dose aspirin (325 mg twice daily) (Visit 3). Inclusion criteria for this trial were a history of asthma, nasal polyposis and at least one historical respiratory reaction to aspirin or other nonselective COX inhibitor, stable asthma (post-bronchodilator FEV1 of $\geq 70\%$, no use of systemic steroids in the prior 1 month and no hospitalizations or emergency room visits for asthma in the prior 6 months) and current use of montelukast for at least 4 weeks before Visit 1. All participants in the study chose to enroll and undergo aspirin desensitization to initiate high-dose aspirin with the goal of preventing or delaying the regrowth of nasal polyps.

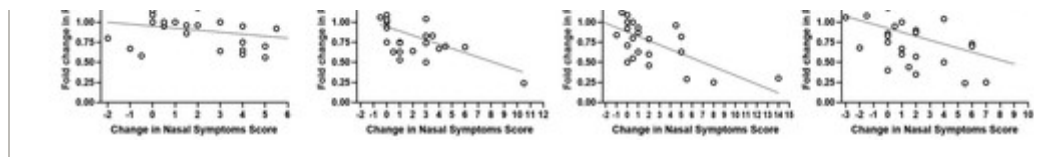
Patient-perceived sense of smell ("Sense of taste/smell" question within SNOT-22, rated on a scale of 0–5) and objective smell identification with the Sniffin' Sticks Screening 12-odour test were captured longitudinally over the three study visits. During the aspirin-induced reaction at Visit 1, we recorded the acute change in patient-perceived nasal and pulmonary symptoms, PNIF and forced expiratory volume in 1 s (FEV1). Baseline values were measured prior to aspirin administration and then repeated at the onset of aspirin-induced reaction and at 30-min intervals for a 3-h period of observation during the reaction. Patients filled out the TNSS-Plus questionnaire (a scoring tool for both nasal and systemic symptoms during aspirin challenge described previously)³ every 30 min and performed PNIF and FEV1 every 60 min. The portion of the TNSS-Plus questionnaire that related to nasal symptoms (questions on nasal congestion, runny nose, itchy nose and sneezing responses (questions 1–5 on the TNSS-Plus), rated on a summed scale of 0–20) served as a patient-reported symptom questionnaire for nasal symptoms, with nasal airflow measured objectively by PNIF, while the TNSS-Plus pulmonary question (which asks about presence of symptoms of

cough, wheezing, chest tightness or shortness of breath, rated on a scale of 0–5) served as a patient-reported symptom questionnaire for pulmonary function, measured objectively by FEV1. At each time-point, participants were asked to complete the symptom questionnaires prior to performing lung function testing (FEV1) or the PNIF manoeuvre, to prevent potential bias introduced by changes noted in the objective measurements. The onset of reaction was defined as per study protocol as the time-point at which either a decrease in FEV1 of $\geq 15\%$ from baseline, and/or an increase in TNSS total questionnaire score of ≥ 2 points from baseline first occurred.

For the acute reaction-related changes at Visit 1, we compared the aspirin-induced change in patient-reported TNSS-Plus nasal symptoms and pulmonary question scores, PNIF, and FEV1 from baseline. The raw SNOT-22 and Sniffin' Sticks test scores were compared at all three study visits separately. Data were analysed using SAS with Spearman's correlation coefficient generated for each pair of patient-reported symptoms and objective outcome measures.

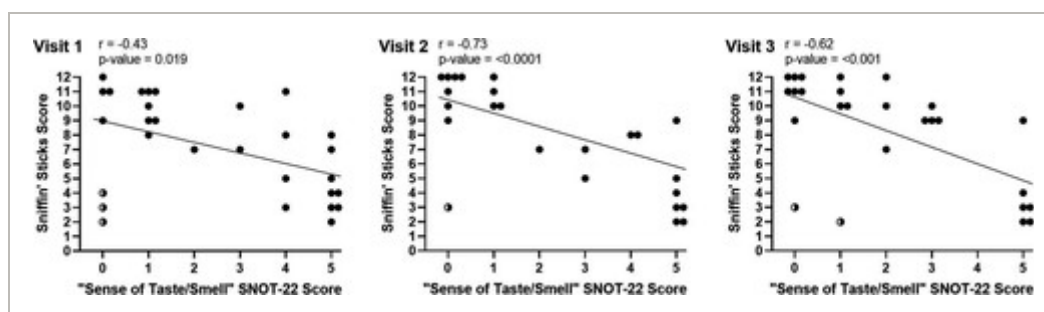
Of the 29 patients included in the study, 45% were male and the average age was 47.1 years (SD 11.0). Overall, the aspirin-induced fall in FEV1 tended to nadir at the 60 min post-onset of reaction time-point, with a mean change in FEV1 of -15% (range $+4\%$ to -66%) at that time-point. The change in pulmonary symptoms score correlated strongly and significantly with the fold change in FEV1 from baseline at all matched time points (1, 60, 120 and 180 min after the onset of reaction) with the first measurement 1 min after the onset of reaction being the most highly correlated ($r = -0.59$, $p < 0.001$) (Figure 1A). Overall, the aspirin-induced decrease in PNIF tended to nadir at the 120 min-post onset of reaction time-point, though was widely variable between patients, with a mean change in PNIF of -23% (range of $+53\%$ to -75%) at that time-point. The change in nasal symptom score correlated strongly and significantly with the change in PNIF at 60, 120 and 180 min after the onset of reaction, with the measurement at 120 min being the most highly correlated ($r = -0.66$, $p < 0.001$) (Figure 1B). Interestingly, there was less association between the change in PNIF and the change in response to just the nasal congestion question. This parallels the recent findings by Ta, et al.⁶ that showed only a weak correlation between PNIF readings and the single SNOT-22 question for “nasal blockage”, suggesting that the additional questions about rhinorrhea, nasal itching and sneezing add value to the patient-reported symptom questionnaire measurement and more accurately reflect the patient's perceived sense of decreased airflow.



**FIGURE 1**[Open in figure viewer](#) | [PowerPoint](#)

Scatter plots comparing the change from baseline in pulmonary symptom score and FEV1 (A) and the change in baseline in nasal symptom score and PNIF (B). Spearman r values are shown for each time-point

The SNOT-22 smell/taste score strongly correlated with the Sniffin' Sticks score at each of the three visits, with Visit 2 having the highest correlation ($r = -0.73$, $p < 0.0001$) (Figure 2). Of note, there was quite a bit of variability in these data, and as other studies have also found,⁶ there were a number of outliers. Specifically, we noted three patients whose SNOT-22 smell/taste scores appeared to be incongruent with their results on the Sniffin' Sticks test. Their SNOT-22 scores of 0 at Visit 1 indicated that they did not have a problem with smell/taste; however, they were only able to correctly identify 2–4 out of the 12 odours tested (Figure 2, half-filled circles). We did not exclude these patients from our analyses but we were curious about the possible causes of their contrasting answers to the subjective smell/taste question and their objective ability to identify odours. The formal instructions at the top of the SNOT-22 questionnaire ask patients to rate “how severe the problem is”. We hypothesize that these patients were either unaware of their olfactory dysfunction or did not consider this deficit to be a problem in their lives and therefore marked “0” or “No problem”. This information may be helpful for assessing patient symptoms and designing questionnaires in the future.

**FIGURE 2**[Open in figure viewer](#) | [PowerPoint](#)

Scatter plot comparisons of individual patient Sniffin' Sticks test odour identification scores and response to “Sense of taste/smell” question from SNOT-22 questionnaire at baseline (Visit 1), after 8 weeks of high-dose aspirin therapy (Visit 2) and then after 2 weeks of medium-dose aspirin therapy (Visit 3). Spearman r values are shown for each time-point. Half-filled circles identify patients whose SNOT-22 smell/taste scores appeared to be incongruent with their score on the Sniffin' Sticks test

Overall, all the patient-reported symptoms we studied correlated with their related objective

outcome measures, indicating that patient self-reports of symptoms closely approximate objective physiologic changes, and confirming the suitability of both the TNSS-Plus and the SNOT-22 for use during clinical trials and routine clinical care of patients with AERD. Put simply, our AERD patients generally have a good awareness of their own symptoms and can accurately recognize and report on acute changes in their respiratory function. Our findings support the use of these patient-reported symptom questionnaires both for acute changes in nasal and pulmonary symptoms (repeated use of the TNSS-Plus during aspirin challenges) and for monitoring baseline sense of smell/taste (SNOT-22) as valuable tools for clinicians and researchers to aid in estimating disease severity, assessing response to therapy and titrating medications in patients with AERD.

ACKNOWLEDGEMENTS

TL Laidlaw participated in study design, data collection and analysis and manuscript preparation. KN Cahill participated in study design, data collection and manuscript preparation. PP Patel participated in data analysis and manuscript preparation. J Cui participated in data analysis and manuscript preparation.

CONFLICT OF INTEREST

TM Laidlaw has served on scientific advisory boards for GlaxoSmithKline, Sanofi-Genzyme and Regeneron. KN Cahill has severed on scientific advisory boards for Teva, GlaxoSmithKline, Blueprint Medicines, Regeneron, Genentech, Sanofi-Pasteur and reports personal fees from Novartis, Third Harmonic Bio, Ribon Therapeutics and Verantos outside the submitted work. PP Patel and J Cui have no conflicts.

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