Measuring dyspepsia-related health in randomized trials: the Severity of Dyspepsia Assessment (SODA) and its use in treatment with NSAIDs and COX-2-specific inhibitors

L. Rabeneck

Dyspepsia is a common problem that is important from the perspectives of both patient health and economics. While there has been variability in the definitions used to describe dyspepsia, there have also been few standardized outcomes tools designed to measure dyspepsia-related health, especially in relation to changes in dyspepsia over time. An evaluative tool was developed, the Severity of Dyspepsia Assessment (SODA), which takes into account the multidimensional nature of dyspepsia using three scales (Pain, Non-pain Symptoms, and Satisfaction with Dyspepsia-related Health) and demonstrates good psychometric properties with respect to validity, reliability and sensitivity to change in the measurement of dyspepsia-related health. Although originally developed for the assessment of uninvestigated dyspepsia, the validation of SODA for use in clinical trials suggested its ability to compare treatment effects of non-specific non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2-specific inhibitors. In comparative trials of celecoxib or valdecoxib with non-specific NSAIDs, COX-2-specific inhibitors were demonstrated to have superior dyspepsia tolerability than non-specific NSAIDs. These data demonstrate that SODA is an effective instrument for measuring dyspepsia-related health with a broad range of applications.

KEY WORDS: Dyspepsia, Gastrointestinal tolerability, Treatment outcomes, Outcomes assessment, SODA, NSAIDs, COX-2-specific inhibitors.
pain is often accompanied by non-pain symptoms such as nausea, vomiting, early satiety, and bloating. The symptoms used in a study may or may not be included in the study’s description of dyspepsia.

Dyspeptic symptoms can result from a variety of factors including acid-related disorders, the presence of *Helicobacter pylori* and/or ulcer-related disease, and the use of certain medications, such as non-specific NSAIDs, which have been shown to increase the risk of dyspepsia by almost 40% [12]. However, a review of endoscopic findings has determined that detectable organic disease, such as gastroduodenal ulcers or erosive oesophagitis, can be identified in only 30–50% of the patients recognized as having dyspepsia [4]. When dyspepsia is chronic and there is no biochemical or structural basis for the condition, it is referred to as functional dyspepsia [10].

From the economic perspective, dyspepsia is associated with high medical expenditures resulting from excess health-care resource utilization. A recent prospective study of dyspepsia in primary care determined that the mean outpatient charges among all patients with dyspepsia were 126% higher than for patients without this condition [13] and that a small percentage of patients (9%) accounted for a disproportionate share of charges (56%). These data are consistent with studies showing dyspepsia were 126% higher than for patients without the condition, it is referred to as functional dyspepsia [10].

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Arthritis patients with dyspepsia had significantly higher health-care resource utilization compared with patients who only have arthritis [14]. This increased use of medical resources included higher use of outpatient services (53.9 vs 32.5 claims per patient, \( P < 0.001 \)) and higher claim rates for endoscopic procedures (odds ratio 10.0, \( P < 0.01 \)) and hospitalization (odds ratio 1.4, \( P < 0.01 \)), all of which contribute to significantly higher inpatient and outpatient costs among this population. Likewise, patients using NSAIDs who had dyspepsia had significantly higher medical charges than those not using these drugs [13].

The magnitude of the economic burden of dyspepsia has been estimated for direct medical costs, which have been reported to be greater than US$2.5 billion in the USA and greater than £1 billion in the UK [15, 16].

Although similar estimations of indirect costs resulting from work absence and loss of productivity are lacking, these costs can be expected to increase the economic burden because of the significant prevalence of dyspepsia.

In terms of patient-centred outcomes, dyspepsia has been shown to be associated with reduction in functional status and a decreased patient quality of life [17, 18]. Additionally, among patients taking certain drugs, such as non-specific NSAIDs, dyspeptic symptoms putatively associated with these drugs may affect treatment outcomes since many patients will stop or switch their medication when these symptoms occur [19, 20].

The lack of a precise definition and the multidimensional nature of dyspepsia have compounded the inability to accurately and reliably measure dyspepsia-related health. An appropriate tool is required for assessing the effectiveness of clinical management strategies and comparing alternative approaches to treatment.

This article reviews a multidimensional tool that was initially developed to evaluate dyspepsia-related health in patients with uninvestigated dyspepsia (recent presentation of dyspeptic symptoms for which no diagnostic tests have yet been performed) but that has subsequently been validated for use in determining time-dependent changes in dyspepsia-related health in response to treatment. Consequently, it also provides a useful tool for comparing gastrointestinal tolerability of drugs such as non-specific NSAIDs and cyclooxygenase (COX)-2-specific inhibitors in clinical trials.

**Measurement of dyspepsia-related health: development of the Severity of Dyspepsia Assessment (SODA) scale**

Despite the clinical and economic importance of dyspepsia, no validated scoring system has yet been accepted for measuring its severity and impact in clinical trials. Although discriminative instruments are useful for identifying patients with dyspepsia in the population, an evaluative instrument that is responsive to clinically meaningful changes in the condition or that can measure treatment effects is also desirable. Pain scales, whether visual analogue or Likert-based, have been useful for the measurement of some types of pain, but for dyspepsia these single-item measures are less reliable than multiple-item scales, and they cannot adequately be used to measure a multidimensional construct such as dyspepsia-related health [21]. Multidimensional tools that sum scores across various domains are likewise impractical since arbitrary weights are ascribed to domains that may vary in clinical importance.

Generic instruments have often been employed to evaluate outcomes of dyspepsia, especially for measurement of functional status and quality of life, and the development of disease-specific instruments has been attempted.

Several assessment tools have been proposed and have shown limited usefulness in evaluating symptoms and/or the impact of dyspepsia on function or quality of life (Table 1). While some of these tools are not specific for dyspepsia, others do not provide the required multidimensionality, combine multidimensional aspects into a single evaluation, or have not been adequately validated for responsiveness (i.e. measurement of clinically meaningful changes) to treatment effects in clinical trials.

The SODA scale was developed to fulfil several needs in dyspepsia research and was especially designed for evaluating approaches to the management of uninvestigated dyspepsia. It was also necessary for SODA not only to be multidimensional, but also to have the psychometric properties of reliability, validity (including responsiveness to clinically meaningful changes), a broad effective measurement range, and equal-interval...
measurement scales. Equal increments on such a scale denote equal changes (up or down) and are less subject to ambiguity among patients with different baseline levels than ordinal-level scales, which express direction but not magnitude of change [22, 23].

The multidimensional nature of dyspepsia was addressed by evaluating three separate domains that were identified as important attributes of uninvestigated dyspepsia: Pain Intensity, Non-pain Symptoms, and Satisfaction with Dyspepsia-related Health [21]. Each domain consists of multiple items, six items for Pain Intensity, seven items for Non-pain Symptoms, and four items for Satisfaction. Furthermore, each domain generates a separate score that is calculated using an algorithm for conversion to equal-interval scores [24, 25]. Higher scores on the Pain Intensity and Non-pain Symptoms scales indicate greater symptoms or symptom severity, while higher scores on the Satisfaction scale indicate greater satisfaction.

The reliability and validity of SODA was evaluated in a trial of 98 outpatients with uninvestigated dyspepsia who were randomized in double-blind fashion to 6-week treatment with placebo or the proton pump inhibitor omeprazole 20 mg twice daily [25]. SODA was administered at baseline and at follow-up at 1, 2 and 6 weeks and 3, 6, 9 and 12 months. Reliability for each scale was tested using standardized Cronbach’s α, which requires a value >0.7 to demonstrate acceptable reliability [26]. To test for validity, the ability to discriminate between patients who self-reported improvement from baseline at their first follow-up visit and those who reported having an unchanged condition was determined by comparing mean change scores for the two populations.

As shown in Table 2, all three SODA scales demonstrated reliability, with Cronbach’s α that exceeded the required value for comparison of groups of patients [25]. Also shown in Table 2 is the ability to significantly discriminate between responders and non-responders, thereby demonstrating the validity of SODA. Responsiveness to effect sizes, an aspect of validity that is important in detecting changes that are clinically meaningful [27], was greatest for the Pain Intensity and Satisfaction scales [25]. This responsiveness suggests the value of these scales in evaluating treatment effects in clinical trials. The smallest effect size was for the Non-pain Symptoms, but since treatment with proton pump inhibitors such as omeprazole is targeted towards relief of dyspepsia pain, this was not unexpected [25].

A further psychometric property demonstrated in this study was the lack of a floor or ceiling effect in this population (outpatients with uninvestigated dyspepsia who were enrolled at a VA medical centre) for the Pain Intensity and Non-pain Symptoms scales [25]. The lack of such an effect is important for allowing measurement across a broad range of possible outcomes. However, the Satisfaction domain did not discriminate well among patients with very low levels of satisfaction, and this may need to be considered in trials measuring dyspepsia treatment effects in patients with poor dyspepsia-related health.

| Table 1. Commonly used assessment scales for evaluating dyspepsia or dyspepsia outcomes |
|---------------------------------------------|---------------------------------------------|
| Glasgow Dyspepsia Severity Scale (GDSS) [36] | Impact of dyspepsia (function)            |
| Aberdeen Dyspepsia Questionnaire (ADQ) [37] | Impact of dyspepsia (symptoms/function)     |
| Gastrointestinal Rating Scale (GSRS) [38]   | Symptoms/function                           |
| Dyspepsia Symptom Severity Index (DSSI) [39]| Symptoms/function                           |
| Nepean Dyspepsia Index (NDI) [40]           | Quality of life                             |
| Quality of Life in Reflux and Dyspepsia [41]| Impact of dyspepsia (quality of life)         |
| Functional Digestive Disorders Questionnaire [44] | Quality of life (FDDQL) questionnaire       |

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Application of SODA in the measurement of dyspepsia-related health among NSAID and COX-2-specific inhibitor users

**Validation in NSAID trials**

Although a correlation between the use of non-specific NSAIDs and dyspepsia has always been empirically suggested, confirmation of the association has been lacking. A recent study was conducted to explore and confirm this relationship. Straus *et al.* [12], in their retrospective meta-analysis of randomized clinical trials, determined that the correlation is dependent upon the definition of dyspepsia. When a strict definition of dyspepsia was used, based on the presence of epigastric pain or discomfort, a risk ratio of 1.36 (95% confidence interval 1.11, 1.67) was calculated. In contrast, using a loose definition of dyspepsia that included heartburn, nausea, vomiting and anorexia, the relative risk was only 1.13 (95% confidence interval 0.98, 1.32). However, it should be noted that although a strict definition was needed for a clear association, this does not preclude the presence or potential importance of non-pain symptoms in an overall assessment of dyspepsia-related health. Furthermore, as pointed out by the authors, since this study was a meta-analysis of randomized controlled trials, it may not accurately reflect clinical practice.

The presence of dyspepsia and other gastrointestinal symptoms is not considered to be predictive of more serious gastrointestinal events, since several studies have determined that many patients with NSAID-associated ulcers or life-threatening events are asymptomatic [28–30]. Furthermore, the severity of gastrointestinal symptoms has also been determined to be a poor predictor of future hospitalization [31]. NSAID-associated dyspepsia is important from the aspect of QOL [18, 31] and has been recognized as an important factor in patient withdrawal from clinical trials and for non-compliance in clinical practice [19].

Currently, dyspepsia is evaluated in clinical trials and outcomes studies based on incidence of symptoms and withdrawals due to these symptoms, with little consideration of the subjective nature of the condition from the patient’s perspective.

The psychometric attributes of SODA suggested its usefulness in measuring dyspepsia-related health in trials of NSAIDs and COX-2-specific inhibitors.

The responsiveness of SODA suggested that it may be a valuable tool in clinical trials of non-specific NSAIDs to evaluate changes in dyspepsia-related health over time or with different treatments. When any assessment instrument is proposed for use in a population different from the one it was validated for, evidence is required that the tool is equally valid in the new population. For evaluation of dyspepsia-related health from the patient’s perspective in clinical trials of non-specific NSAIDs or COX-2-specific inhibitors, it was required that SODA demonstrate validity, reliability, and responsiveness to changes in the population taking these drugs. The validity of this use of SODA was tested and confirmed using the population in the Celecoxib Long-term Arthritis Safety Study (CLASS), a randomized double-blind outcomes study that compared a supratherapeutic dose of celecoxib (400 mg twice daily) with diclofenac 75 mg twice daily in patients with arthritis [32].

In the CLASS trial, dyspepsia was captured as an adverse event based on a combined set of terms for pain and non-pain symptoms using the World Health Organization Adverse Reaction Terminology (WHOART) [32]. These dyspepsia adverse events were used as the gold standard for measuring clinically meaningful changes in dyspepsia-related health. During the trial, 39.4% of patients reported a dyspepsia adverse event, and 7.0% of patients withdrew for this reason [32].

The SODA scale was completed by 3607 patients at baseline and 4, 13, 26 and 52 weeks, with baseline and the 4-week time-point serving as the test for validation of SODA.

As in the original SODA validation study, standardized Cronbach’s α was used as a test of reliability. The baseline and 4-week scores both had α values that exceeded the 0.7 value required to demonstrate acceptable reliability for group-level comparisons [32]. For baseline, these values were 0.93, 0.82 and 0.89 for the Pain Intensity, Non-pain Symptoms and Satisfaction scales respectively. There was little change at 4 weeks, with values of 0.95, 0.83 and 0.91 for the corresponding SODA scales.

The most critical parameter required by SODA for evaluation and comparison of treatments is the ability to respond to changes in health status. Responsiveness and longitudinal construct validity of SODA were explored using analysis of trend for the correlation between dyspepsia adverse event severity and mean change in score (i.e. follow-up score minus baseline score) for each SODA scale during the first 4 weeks. As shown in Fig. 1, there was good correlation between these parameters. Additionally, for all three SODA scales there was good discriminative ability between each successive level of severity (severe > moderate > mild > none; $P < 0.05$) except for the two most severe levels of Non-pain Symptoms (severe = moderate; $P = 0.11$).

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*Table 2. Reliability and validity of SODA scales*

<table>
<thead>
<tr>
<th>SODA scale</th>
<th>Reliability (Cronbach’s α)</th>
<th>Improved patients</th>
<th>Unchanged patients</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td>0.97</td>
<td>10.6</td>
<td>2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-pain Symptoms</td>
<td>0.90</td>
<td>3.6</td>
<td>1.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>0.92</td>
<td>-6.9</td>
<td>-0.5</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*Mean change score is enrolment score minus follow-up score, and was determined separately for patients who stated that they were ‘improved’ and those who stated they were ‘unchanged’ at follow-up. For Pain Intensity and Non-pain Symptoms, a higher scale score indicates greater symptoms or symptom severity; for Satisfaction, a higher scale score indicates greater satisfaction.

Adapted with permission from Rabeneck *et al.* [25].
In a further test of the discriminative ability of SODA, the changes in SODA scale scores were compared between patients who withdrew due to a dyspepsia-related event and those who did not withdraw due to dyspepsia [32]. Table 3 shows that the mean change scores for all three SODA scales were significantly worse among patients who withdrew compared with those who did not withdraw. These data were then used to plot a receiver operating characteristic (ROC) curve (withdrawal score minus baseline score), which can provide a quantitative estimation of responsiveness and discriminative ability. In this plot (Fig. 2), sensitivity (true positive proportion) is plotted on the y-axis, the false-positive proportion (1 minus specificity) is on the x-axis, and the dotted diagonal line represents a non-discriminative ability. The clustering of points in the upper left quadrant suggests good discriminative ability that can be further quantitated by calculating the area under the curves (AUCs). The AUCs for all three scales, 0.78, 0.75 and 0.74 for Pain Intensity, Satisfaction, and Non-pain Symptoms respectively, fell between perfect discriminating ability (1.0) and non-discrimination (0.5) [32].

Taken together, the above data provide evidence that SODA can be used as a valid, sensitive and responsive tool for subjective assessment of treatment effects. While the Pain Intensity scale, consistent with the observed correlation between non-specific NSAIDs and dyspepsia defined by pain symptoms [12], was demonstrated to provide the best discriminative ability, the Satisfaction scale also provided good sensitivity and responsiveness to treatment effects. These results suggest that the Satisfaction scale will be useful for evaluating a subjective patient-centred outcome, and by implication, satisfaction with specific treatments that affect dyspepsia-related health [33]. Data from all time-points for which SODA data were available in the CLASS study (baseline, 4, 13, 26 and 52 weeks or early withdrawal) were analysed for change from baseline for the three SODA domains. Analysis was performed for the entire population as well as a subset of patients who self-reported an upper gastrointestinal complaint.

As shown in Table 4, patients taking celecoxib at a supratherapeutic dose reported superior dyspepsia-related health compared with diclofenac for all three SODA domains and at all evaluated time-points. Patients taking celecoxib reported less pain and greater satisfaction than with diclofenac, and this was reflected by the significantly superior scores on the Pain Intensity and Satisfaction scales in the celecoxib group ($P < 0.001$). Both of these domains had previously been shown to be good indicators of dyspepsia adverse event severity and withdrawal status [32]. Consistent with their predictive value, withdrawals due to abdominal pain or any gastrointestinal adverse event were significantly lower in the celecoxib group (3.9 and 8.9% respectively) than in the diclofenac group (6.6 and 12.8% respectively; $P < 0.001$). These observed differences may be important determinants of outcomes in the clinical setting by affecting patient compliance or physician response in the form of additional healthcare resource utilization.
FIG. 2. Receiver operating curve (ROC) for multiple change scores (4-week score minus baseline score) for the three SODA scales. Clustering of points in the upper left quadrant indicates good discriminative ability. Reprinted with permission from Rabeneck et al. [32].

TABLE 4. Mean scores (adjusted for baseline and centre) on the SODA for celecoxib 400 mg twice daily and diclofenac 75 mg twice daily in the CLASS trial

<table>
<thead>
<tr>
<th>Scale score (range) *</th>
<th>Total population</th>
<th>Patients with self-reported gastrointestinal complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib (n = 1791)</td>
<td>Diclofenac (n = 1816)</td>
</tr>
<tr>
<td><strong>Pain intensity (2–47)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.18 ± 9.53</td>
<td>11.34 ± 9.32</td>
</tr>
<tr>
<td>Change at week 4</td>
<td>0.99 (0.50, 1.48)</td>
<td>2.76 (2.28, 3.25)</td>
</tr>
<tr>
<td>Change at week 13</td>
<td>1.25 (0.73, 1.77)</td>
<td>3.03 (2.51, 3.55)</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>1.29 (0.75, 1.83)</td>
<td>2.87 (2.34, 3.40)</td>
</tr>
<tr>
<td>Change at week 52</td>
<td>1.32 (0.78, 1.86)</td>
<td>2.89 (2.35, 3.43)</td>
</tr>
<tr>
<td><strong>Non-pain symptoms (7–35)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.00 ± 3.73</td>
<td>12.16 ± 3.66</td>
</tr>
<tr>
<td>Change at week 4</td>
<td>−0.09 (−0.26, 0.08)</td>
<td>0.21 (0.04, 0.37)</td>
</tr>
<tr>
<td>Change at week 13</td>
<td>0.05 (0.13, 0.24)</td>
<td>0.21 (0.03, 0.39)</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>0.11 (0.08, 0.29)</td>
<td>0.18 (0.00, 0.37)</td>
</tr>
<tr>
<td>Change at week 52</td>
<td>0.03 (0.16, 0.22)</td>
<td>0.16 (−0.01, 0.36)</td>
</tr>
<tr>
<td><strong>Satisfaction (2–23)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>18.07 ± 5.43</td>
<td>17.83 ± 5.40</td>
</tr>
<tr>
<td>Change at week 4</td>
<td>0.02 (−0.26, 0.29)</td>
<td>−0.72 (−1.00, −0.45)</td>
</tr>
<tr>
<td>Change at week 13</td>
<td>−0.29 (−0.58, 0.00)</td>
<td>−0.97 (−1.26, −0.69)</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>−0.26 (−0.55, 0.04)</td>
<td>−0.95 (−2.34, −0.66)</td>
</tr>
<tr>
<td>Change at week 52</td>
<td>−0.30 (−0.59, 0.00)</td>
<td>−0.93 (−1.22, −0.63)</td>
</tr>
</tbody>
</table>

Baseline values are mean ± S.D.; other values are mean change from baseline (baseline minus follow-up) with 95% confidence intervals.

*For Pain Intensity and Non-pain Symptoms, a higher score indicates greater symptoms or symptom severity; for Satisfaction, a higher score indicates greater satisfaction.

Adapted with permission from Goldstein et al. [33].
In the above study, subset analysis was also performed in the 32% of celecoxib patients and 40.8% of diclofenac patients who reported an upper gastrointestinal complaint. This subset analysis controlled for potential differences in dyspepsia among patients with and without upper gastrointestinal disturbances and who were more likely to withdraw from the study. As shown in Table 4, results were consistent with those observed for the whole population; among the patients who self-reported upper gastrointestinal complaints, those taking diclofenac had significantly higher pain intensity and significantly lower satisfaction than those taking celecoxib. However, the magnitude of the differences between the groups was greater in the subset analysis than in the whole population. This difference in magnitude corroborates the more favourable gastrointestinal tolerability profile of celecoxib relative to diclofenac.

Two recent placebo-controlled studies of valdecoxib have similarly suggested its superior dyspepsia-related health at therapeutic doses compared with non-specific NSAIDs [34, 35]. In patients with rheumatoid arthritis, valdecoxib 10 mg daily demonstrated significantly superior dyspepsia-related health at the end of the study than naproxen 500 mg twice daily, as measured by the three SODA scales (P < 0.05) [34]. Furthermore, in contrast to naproxen, which resulted in deterioration of dyspepsia-related health over the 12 weeks of the study, patients receiving valdecoxib consistently reported improvements from baseline in Pain Intensity, Non-pain Symptoms and Satisfaction at all evaluated time-points (2, 6 and 12 weeks).

Patients with osteoarthritis receiving valdecoxib 10 mg daily also reported superior dyspepsia-related health compared with patients receiving ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily [35]. At 12 weeks, valdecoxib was numerically superior to the non-specific NSAIDs on all three SODA scales, but only showed significance against the non-specific NSAIDs for Pain Intensity.

**Conclusions**

Evaluation of dyspepsia from the patient’s perspective, whether in populations or in clinical trials, requires an appropriate multidimensional tool that can accurately measure clinically meaningful changes in dyspepsia-related health over time.

The Severity of Dyspepsia Assessment, originally developed and validated to evaluate uninvestigated dyspepsia, provides such a tool. Consisting of three evaluative scales, Pain Intensity, Non-pain Symptoms and Satisfaction, the high degree of reliability, validity and responsiveness of SODA suggests its usefulness for measuring treatment effects in clinical trials of NSAIDs.

In a validation study for use in clinical trials of non-specific NSAIDs and COX-2-specific inhibitors, all three scales demonstrated reliability and validity. However, Pain Intensity and Satisfaction were better discriminative scales for outcomes. Consistent with a recent study showing a stronger association between non-specific NSAIDs and dyspepsia when the definition of dyspepsia is based on pain rather than non-pain symptoms, the Pain Intensity scale of SODA showed the greatest sensitivity and responsiveness. The Satisfaction domain was also responsive, since satisfaction with health or treatment is often a function of pain relief.

Use of SODA in comparative studies of COX-2-specific inhibitors appears to confirm what has already been suggested in randomized clinical trials: that these drugs are associated with better dyspepsia tolerability than non-specific NSAIDs. Both celecoxib and valdecoxib demonstrated superior dyspepsia-related health in all three SODA domains compared with non-specific NSAIDs.

In conclusion, SODA represents a new and effective evaluative instrument for the measurement of clinically relevant outcomes of dyspepsia. The broad range of applications of this tool is only just beginning to be explored in its use for measuring treatment effects in clinical trials of drugs generally associated with gastrointestinal intolerance.

The author has received honoraria from Pfizer and Pharmacia.

**References**

Measuring dyspepsia-related health


