Clinical Significance of Common Cold Treatment: Professionals’ Opinions

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ABSTRACT

Background: Little is known about professionals’ knowledge and attitudes regarding the clinical significance of treatments for common cold (upper respiratory infection, presumed viral).

Methods: We surveyed university-associated family physicians and published common cold researchers (“experts”) regarding evidence-of-benefit and magnitude-of-benefit for 8 treatments: antihistamine, oral decongestant, nasal decongestant, nasal steroid, zinc lozenge, zinc nasal spray, vitamin C, and the herbal echinacea.

Results: Responding family physicians (N=89) and experts (N=45) agreed that cold remedies do not reduce illness duration. There was substantial disagreement, however, regarding the evidence for severity reduction. Decongestants were rated most favorably. Alternative therapies (zinc, vitamin C, and echinacea) were rated approximately as favorably as the other conventional treatments (antihistamine, decongestant, nasal steroid). Published experts and family physicians responded similarly, as did men (N=84) and women (N=49). Older respondents (age ≥45; N=67) were less likely to rate treatments as justifiable than were their younger counterparts (P-values ranged from 0.001 to 0.078).

Conclusions: Family physicians and common cold experts tend to agree that available cold remedies offer limited benefit, with conventional and alternative therapies rated similarly. Substantial disagreements exist, however, regarding strength-of-evidence, and over whether current evidence justifies treatment. Older professionals appear more skeptical.

INTRODUCTION

The broad purpose of medicine is to enhance health and prevent or reduce illness. While a few therapies may truly change the course of disease or even extend life, most are aimed at decreasing severity of symptoms or functional impairments, so as to improve quality of life. It is generally agreed that randomized controlled trials (RCTs) provide the best evidence regarding specific effects of treatments. Successful RCTs randomize sufficiently large numbers of participants to active treatment (intervention) and control groups, then assess and compare outcome measures, so as to conclude whether or not the intervention affects the outcome. When observed effects are unlikely to be due to chance, then the null hypothesis of “no effect” is rejected (usually at P≤0.05 or P≤0.01), and the treatment is accepted as effective. Statistical proof of some effect is not sufficient to warrant treatment, however. A large trial can demonstrate a very small effect, an effect that is not clinically significant, or an effect that is simply not worth the costs and side effect risks.

The question of how to assess and interpret clinical significant effect size was advanced when investigators at McMaster introduced “minimal important difference” (MID), a concept that was originally defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troubling side effects and excessive cost, a change in the patient’s management.” Since that time, MID has been accepted in mainstream medical research and theory. Believing that side effects and costs should be accounted for, we proposed the concept of “sufficiently important difference” (SID), defined as the “smallest amount of patient-valued benefit that an intervention would require in order to justify associated costs, risks, and other harms.” Our research assessing SID in the common cold has shown that (1) people have widely differing opinions of how much benefit is needed to justify...
costs and risks, and (2) these judgments are consistent within person, and largely independent of age, sex, income, education, and severity of illness at time of interview.7,9

The first phase of that research concluded that “people want the duration of their colds to be reduced by between 26 and 65 hours in order to justify potential harms of popular cold treatments.”8 A second study looking at SID in terms of reduction in symptom severity reports that people want a 25%-57% overall severity reduction in order to justify costs and risks of popular cold treatments.9 What these efforts have not included, however, is the knowledge and perspective of those best situated to understand and appreciate clinical evidence: family physicians and common cold researchers.

METHODS

The survey discussed here was designed to evaluate knowledge and attitudes in 2 somewhat different populations: common cold researchers (experts) and practicing family physicians. Family physician respondents came from a convenience sample of all physician faculty (N=160) and resident physicians (N=90) associated with the Department of Family Medicine at the University of Wisconsin-Madison (N=250 total). Expert researchers were identified using the following inclusion criteria: (1) first author of a randomized control trial of a common cold treatment, (2) any author of a systematic review of a common cold treatment, or (3) any member of a national or international committee empowered to review evidence and make recommendations regarding common cold treatments. Using search terms such as “common cold,” “upper respiratory infection,” “respiratory tract infection,” and “acute respiratory infection,” we searched on-line databases including MedLine, the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effectiveness, and the Cochrane Central Registry of Controlled Trials. We reviewed at least 206 randomized trial reports and 97 systematic reviews (loosely defined). We also searched our own professional library and contact list, and consulted colleagues with relevant expertise. All told, we identified 211 “experts” meeting inclusion criteria. Using the Community of Science database and various Internet search engines, we found e-mail addresses for 158 of these.

The on-line survey instrument was created to efficiently seek opinions regarding common cold treatments. We were interested in perspectives regarding both degree of benefit (reduction in duration and/or severity of illness) and strength of evidence behind the judgments. Aiming to broadly represent popular cold remedies, we selected 8 different treatments: antihistamine pill, decongestant pill, nasal decongestant, nasal steroid, zinc lozenge, zinc nasal spray, vitamin C, and echinacea. Questionnaire items asked respondents to evaluate each treatment’s ability to reduce the duration of a cold. Response options for duration reduction were 3 days, 2 days, 24 hours, 12 hours, 6 hours, or no duration reduction at all. We also asked about overall severity reduction benefits, with 50%, 33%, 25%, 20%, 15%, 10%, 5%, and no severity reduction as response options. In order to standardize and frame the questions, we suggested that colds on average last for 7 days, and provided a graphic portraying what we meant by duration reduction and overall severity reduction benefit. We asked respondents to “consider overall severity reduction as area-under-the-curve,” and to assume “optimal dosing and timing.” A copy of the entire questionnaire can be found at: http://www.coldstudy.org/expected-benefits/.

After providing opinions on expected duration and severity benefits, respondents were asked to rate the strength of evidence behind these judgments. Response options for strength of evidence were very strong, moderately strong, reasonable, moderately weak, very weak, or no evidence whatsoever. Next, respondents were asked to give their opinion of whether or not the expected benefits were sufficient to justify associated costs and risks (which we did not describe). Every questionnaire item included a “no response” option and a free text comment box. Finally, we asked for age and gender, area of research interest (experts), and length of time in practice (physicians). After pilot testing of several iterations, we were satisfied with a 42-item questionnaire, which took an estimated 5-10 minutes to complete.

An e-mail inviting recipients to participate in this survey was first sent on November 1, 2005. Three follow-up reminder e-mails were sent at 2-week intervals to non-respondents. Using PHP Surveyor software, an information systems specialist in our university-based Family Medicine Department coded the returned surveys so as to maintain the anonymity of respondents and non-respondents. Data were direct-entered by respondents, then compiled into the final database. The UW Institutional Review Board reviewed the protocol and granted an exemption from continuing IRB review and monitoring.

Data were first inspected for missing and outlying values, and for overall patterns of central tendency and distribution. The direct entry data capture system precluded any values outside the listed response range.
Patterns of outlying data suggested these were choices, not errors. For example, the nasal zinc item showed the highest rate of “non response.” Nasal zinc preparations are relatively recent additions to the cold treatment market and scientific literature, hence choices not to respond to this item make sense, especially for those not aware of the few studies available. A decision was made not to impute values, as there was very little missing data.

RESULTS

Of 250 e-mails sent to family physicians, 89 responded to our survey (response rate 35.6%). Of the 158 e-mails addressed to experts, 32 bounced back as undeliverable, leaving 126 experts who may have received our invitation. Of these, 45 responded to the survey. This suggests a 35.7% response rate. We expect that actual response rates were somewhat higher, as outdated or incorrect e-mail addresses do not always have working “returned undeliverable” return-to-sender message systems. This would be more likely for experts, whose e-mails we obtained from various sources, some dating back several years. Figure 1 shows distribution of age, gender, and professional status of respondents. We have no similar data for non-respondents.

Overall, response patterns were consistent with expectations. The majority of respondents felt the 8 cold treatments represented did not provide much in the way of expected duration reduction benefit. (See Figure 2.) Of those who felt that there was some duration benefit, 12-hour and 24-hour duration benefits were most likely to be selected. These were reported slightly more often for vitamin C, zinc, and echinacea than for antihistamines, decongestants, and nasal steroids.

Opinions regarding overall reduction in illness severity were more varied than those for illness duration. Figure 3 shows that diversity of opinion was especially pronounced for oral and nasal decongestants, where significant numbers of respondents selected nearly all of the options, ranging from no or very little (5%, 10%) overall severity reduction to substantial severity benefit (25%, 33%, 50%). Although antihistamines, nasal steroids and zinc lozenges received some severity-reduction support, decongestants stood out as receiving the
most favorable responses.

Figure 4 shows there was a wide variety of opinion regarding strength of evidence. Interesting to us, antihistamines and echinacea received the most favorable ratings, with the largest number of moderately strong or very strong ratings. Zinc nasal spray was rated most unfavorably, with about half of responses indicating no or very weak evidence. Decongestants, nasal steroids, vitamin C, and zinc lozenges received similar ratings regarding strength of evidence.

Figure 5 displays magnitude of expected benefit by whether or not the respondent thought the treatment was justified. While it is clear that people who think a treatment is justified also attribute that treatment greater benefit, there is also a fair amount of diversity in this regard. Expectation of overall severity reduction benefit appears to drive the opinion that treatment is justified, as very few people attribute duration reduction benefits to these treatments.

Table 1 displays the numbers of family physicians and expert researchers judging expected benefits sufficient to justify treatments. For all treatments except nasal decongestants, proportions of favorable responses were slightly higher among family physicians than for experts. Using conventional 2-sample Z-testing for binomial proportions, P-values ranged from 0.01 to 0.11, suggesting these tendencies may or may not be due to chance. On average, family physicians were 15% to
29% more likely to favorably rate the risk benefit profile than were these published respiratory infection researchers.

Women appeared to judge benefits of treatments favorably slightly more often than men, with 7 of 8 treatments receiving a more favorable response (nasal decongestant was the exception). However, as only 1 of these (nasal zinc) reached statistical significance, we conclude that apparent gender effects are not large, and may be due to chance. Response patterns, however, did seem to be influenced by the age of the respondent. Table 2 shows that respondents aged 44 and younger were 17%-33% more likely to rate a treatment favorably, compared with those aged 45 and older. Favorable responses to all 8 treatments trended in the same younger age direction, with 7 of 8 making statistical significance. We conclude that apparent age effects were unlikely to be due to chance.

DISCUSSION

As mentioned in the introduction, we feel this paper is best situated in the emerging discussion on clinical significance and important difference, within the now-established framework of evidence-based medicine. It is no longer acceptable for a treatment to simply demonstrate a statistically significant benefit in 1 or more randomized controlled trials. Instead, the magnitude of benefit (effect size) should be sufficient to justify associated costs and risks. In general, benefit harm trade-offs should be assessed from the individual patient’s perspective, as various outcomes may be valued differently by different people.

Our first publications on sufficiently important difference (SID) demonstrated that people with colds hold widely varying opinions on how much benefit a treatment should have in order to justify costs, risks, and other harms. Those data suggested that SID is influenced by individual values and treatment specifics, but not by age, gender, ethnicity, income, or tobacco use. Severity of illness at time of interview did not influence SID judgments. SID values followed predictable patterns, including a normally-shaped distribution of SID across a reasonable range of benefit magnitudes, with a few people rejecting—and accepting—treatments

Figure 5. Amount of expected benefit by whether or not respondents think treatment is justified. This figure displays expected degree of benefit for those answering “Yes” and “No” to “Is the benefit you selected sufficient to justify associated costs and risks?” for each treatment.
almost without regard to benefit.

Data from the current survey of health professionals suggests that diversity of opinion is not limited to patients, but instead is seen with both family physicians and expert researchers. Despite differences in opinion, however, there is some consensus. For instance, relatively few professionals think that existing cold treatments provide any duration reduction benefit. While severity reduction benefits received more favorable ratings (especially decongestants), benefit size was modest.

Whether or not limited benefits justify treatment was more controversial. For all treatments considered, our sample was substantively divided in answering “Is the benefit you selected sufficient to justify associated costs and risks?” Each of the treatments considered was positively assessed by at least a quarter of respondents, with positive assessment ranging from 28% (zinc nasal spray) to 68% (nasal decongestant). While gender and profession did not greatly influence these judgments, age was predictive, with older physicians (and researchers) significantly less likely to endorse a treatment.

We were not surprised that cold treatments were attributed severity but not duration benefit, or that alternative treatments (vitamin C, zinc, echinacea) received as favorable ratings as did antihistamines and nasal steroids. In our view, this is consistent with evidence in the literature, which includes several positive RCT reports for each of the treatments named in our survey10-15 (except nasal zinc and nasal steroids, which have been reported in very few RCTs). Nevertheless, the magnitude of expected benefits indicated by these respondents may be somewhat optimistic. For example, nasal decongestants received the highest benefit ratings, and in our opinion may exhibit the most verifiable pharmacological actions. Nevertheless, best evidence suggests limited effects. Quoting from a Cochrane review of nasal decongestants for common cold: “Five studies involv-

### Table 1. Do Treatment Benefits Justify Associated Costs and Risks? Favorable Responses by Profession*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Physicians (N=89)</th>
<th>Experts (N=45)</th>
<th>Statistical Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (NR)</td>
<td>Yes (NR)</td>
<td>Z-score†</td>
</tr>
<tr>
<td><strong>Antihistamine Pill</strong></td>
<td>41/83 (49%)</td>
<td>9/38 (24%)</td>
<td>2.47</td>
</tr>
<tr>
<td><strong>Decongestant Pill</strong></td>
<td>62/83 (75%)</td>
<td>20/39 (51%)</td>
<td>2.36</td>
</tr>
<tr>
<td><strong>Nasal Decongestant</strong></td>
<td>54/82 (66%)</td>
<td>30/40 (75%)</td>
<td>0.816</td>
</tr>
<tr>
<td><strong>Nasal Steroid</strong></td>
<td>31/79 (39%)</td>
<td>8/37 (22%)</td>
<td>1.66</td>
</tr>
<tr>
<td><strong>Zinc Lozenge</strong></td>
<td>42/77 (55%)</td>
<td>10/39 (26%)</td>
<td>2.76</td>
</tr>
<tr>
<td><strong>Zinc Nasal Spray</strong></td>
<td>19/56 (34%)</td>
<td>6/32 (19%)</td>
<td>1.27</td>
</tr>
<tr>
<td><strong>Vitamin C</strong></td>
<td>42/85 (49%)</td>
<td>13/40 (33%)</td>
<td>1.58</td>
</tr>
<tr>
<td><strong>Echinacea</strong></td>
<td>34/75 (45%)</td>
<td>9/35 (26%)</td>
<td>1.75</td>
</tr>
</tbody>
</table>

NR=non response data are not included in denominators or in statistical testing.

* While family physicians appear to rate treatments a bit more favorably than experts, differences only reach statistical significance for 3 of 8 treatments.

†Z-scores and P-values are calculated using a 2-sample test for binomial proportions.

### Table 2. Do Treatment Benefits Outweigh Associated Costs/Risks? Favorable Responses by Age*

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Age ≤ 44 (N=67)</th>
<th>Age ≥ 45 (N=67)</th>
<th>Statistical Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (NR)</td>
<td>Yes (NR)</td>
<td>Z-score†</td>
</tr>
<tr>
<td><strong>Antihistamine Pill</strong></td>
<td>33/61 (54%)</td>
<td>17/60 (28%)</td>
<td>2.69</td>
</tr>
<tr>
<td><strong>Decongestant Pill</strong></td>
<td>48/63 (76%)</td>
<td>34/60 (57%)</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Nasal Decongestant</strong></td>
<td>48/61 (79%)</td>
<td>36/62 (58%)</td>
<td>2.26</td>
</tr>
<tr>
<td><strong>Nasal Steroid</strong></td>
<td>24/57 (42%)</td>
<td>15/60 (25%)</td>
<td>1.77</td>
</tr>
<tr>
<td><strong>Zinc Lozenge</strong></td>
<td>36/59 (61%)</td>
<td>16/58 (28%)</td>
<td>3.45</td>
</tr>
<tr>
<td><strong>Zinc Nasal Spray</strong></td>
<td>19/43 (44%)</td>
<td>6/45 (13%)</td>
<td>2.97</td>
</tr>
<tr>
<td><strong>Vitamin C</strong></td>
<td>36/63 (57%)</td>
<td>21/62 (34%)</td>
<td>2.43</td>
</tr>
<tr>
<td><strong>Echinacea</strong></td>
<td>27/55 (49%)</td>
<td>16/56 (29%)</td>
<td>2.02</td>
</tr>
</tbody>
</table>

NR=non response data are not included in denominators or statistical testing.

* Respondents ≤ 44 years old are more likely to rate a treatment as justified than are their older counterparts. These tendencies reach statistical significance for all but 1 treatment.

† Z-scores and P-values were calculated using a 2-sample test for binomial proportions.
ing 286 adults were included, none in children. There was a significant 13% decrease in subjective symptoms after decongestants were compared with placebo.12 For comparison, our respondents estimated severity reduction benefits more in the 20%-50% range.

There is actually more trial data on alternative treatments, but the evidence is decidedly mixed. For example, in the 2006 Cochrane echinacea review, we examined 16 trials with 2601 participants, and concluded that some echinacea preparations “might be effective for the early treatment of colds in adults.”13 However, it is worth noting that some trials were reported quite positively, with both severity and duration benefits highlighted,16-19 while most recent trials have appeared flatly negative.20-23 Zinc and vitamin C share this history of multiple conflicting studies,13,14 while antihistamine trials are more uniform in suggesting minor nasal drying benefits, but no duration benefit and no reported overall severity reduction benefit.10,24 We were surprised to see nasal steroids receiving similar strength-of-evidence ratings, as we are not aware of an evidence base for nasal steroids for common cold.25-26 Perhaps our respondents were extrapolating from nasal steroids for allergic rhinitis, where multiple trials do suggest benefit.27 Despite these modest differences in interpreting evidence between our respondents and ourselves, we interpret overall response patterns as supportive of a reasonably well-informed population of physicians and researchers. Discrepancies regarding strength-of-evidence may have more to do with methodological limitations and lack of standards for interpretation rather than ignorance of evidence. Difference in opinion regarding whether treatments are justified is consistent with expected heterogeneity in health values. Doctors and researchers are people with personal health values, after all, and as such have different ideas of how much benefit justifies how much harm. Whether these results would apply to the non-respondents or to other populations is, of course, unknown.

One broad purpose of this work is to bring attention to diversity in health-related human values, when designing and interpreting medical research, and in clinical practice. Reasonable evidence of benefit may be necessary for a medical intervention to be considered, but it is not sufficient for recommendation. Instead, benefits should be considered in conjunction with potential harms. Even when benefits (positively valued outcomes) outweigh harms (negatively valued outcomes) in the mind of the medical professional, it is the patient’s value system that should be considered. A one-size-fits-

all approach to medicine is irrational in that it falsely assumes homogenous values, and unethical in that it displaces patient autonomy with implicit value judgments, even paternalism. While properly done randomized controlled trials can inform doctors and patients about treatment effects, they cannot be used as the sole basis of decision making. Instead, best evidence of risk and benefit should be considered when making individualized treatment decisions.

Acknowledgments: The Department of Family Medicine (DFM) at the University of Wisconsin–Madison has provided an institutional base and collegial support for this work. The Robert Wood Johnson Foundation Generalist Physician Faculty Scholars Program has more specifically supported this work through a career development grant to Dr Barrett. We would also like to acknowledge Eric Schoville at DFM, who masterfully managed the on-line survey, despite a few technical challenges. Perhaps most of all, we would like to thank the many professionals who took time out of their busy schedules to thoughtfully respond to our questionnaire.

Funding/Support: Support for this research project came from the Robert Wood Johnson Foundation Generalist Physician Faculty Scholars Program.

Financial Disclosures: None declared.

REFERENCES
The mission of the Wisconsin Medical Journal is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

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