

Reporting of Harm in Randomized, Controlled Trials of Nonpharmacologic Treatment for Rheumatic Disease

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Background: Reports of clinical trials usually emphasize benefits and give less attention to harms.

Purpose: To compare the reporting of harm in trials of pharmacologic and nonpharmacologic treatment.

Data Sources: MEDLINE and the Cochrane Central Register of Controlled Trials.

Study Selection: Reports of randomized, controlled trials assessing treatment of rheumatic disease that were published between January 1999 and January 2005.

Data Extraction: A standardized abstraction form was used to extract data.

Data Synthesis: 193 articles were analyzed. After adjustment for medical area, sample size, funding source, and multicenter

trials, data on harm were more often described in pharmacologic treatment reports than in nonpharmacologic treatment reports in reporting adverse events (odds ratio, 5.2 [95% CI, 2.1 to 12.9]), reporting withdrawals due to adverse events (odds ratio, 4.6 [CI, 2.0 to 10.9]), reporting severity (odds ratio, 3.7 [CI, 1.5 to 9.1]), and allocating space for describing harm (odds ratio, 1.6 [CI, 1.2 to 2.3]).

Limitations: Extrapolating results to trials in areas other than rheumatic disease is questionable.

Conclusions: The lack of reporting harm in trials assessing nonpharmacologic treatment in rheumatic disease is an important barrier to evaluating the benefit-harm balance of nonpharmacologic treatments.

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Evidence across diverse medical fields suggests that the reporting of harm in clinical trials is inadequate and receives less attention than efficacy outcomes (1–5). Studies assessing the reporting of harm have focused mainly on pharmacologic treatment, whereas nonpharmacologic treatment (such as surgery, technical interventions, technical devices, rehabilitation, behavioral interventions, and psychotherapy) represents a wide range of treatments proposed to patients. Only 1 study focusing on the reporting of harm in randomized, controlled trials of mental health interventions found that no report of nonpharmacologic treatment trials adequately reported harm (6).

Our goal was to compare the reporting of harm in reports of trials of pharmacologic and nonpharmacologic treatment. We focused on reports of randomized, controlled trials assessing treatment for rheumatoid arthritis and hip or knee osteoarthritis because these treatments cover many pharmacologic treatments (for example, oral drug administration; topical treatment; and subcutaneous, intravenous, or intra-articular injection) and nonpharmacologic treatments (for example, surgery, arthroscopy, joint lavage, exercise, physiotherapy, orthosis, spa therapy, acupuncture, and education).

METHODS

Search Strategy and Study Selection

We identified and selected all randomized, controlled trials published between 1 January 1999 and 31 January 2005 that assessed pharmacologic and nonpharmacologic treatment for rheumatoid arthritis and hip or knee osteoarthritis.

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (Issue 1, 2005) by using the search terms *rheumatoid arthritis* OR ([*osteoarthritis* OR *osteoarthritic*] AND [*hip* OR *knee*]), with a limitation to clinical trials in the following journals with a high impact factor (2002 Science Citation Index): 10 general and internal medicine journals (*The New England Journal of Medicine*, *The Journal of the American Medical Association*, *The Lancet*, *Annals of Internal Medicine*, *Annual Review of Medicine*, *Archives of Internal Medicine*, *British Medical Journal*, *American Journal of Medicine*, *Medicine*, and *Annals of Medicine*); 6 rheumatology journals (*Arthritis and Rheumatism*, *Seminars in Arthritis and Rheumatism*, *Annals of the Rheumatic Diseases*, *Rheumatology* [Oxford, United Kingdom], *The Journal of Rheumatology*, and *Arthritis Care and Research*); 6 orthopedic journals (*Osteoarthritis and Cartilage/OARS*, *Arthroscopy*, *Journal of Orthopaedic Research*, *The Journal of Bone & Joint Surgery, American Volume*, *Gait and Posture*, and *Spine*); and 6 rehabilitation journals (*Archives of Physical Medicine and Rehabilitation*, *Supportive Care in Cancer*, *Journal of Electromyography and Kinesiology*, *Physical Therapy*, *Journal of Rehabilitation Research and De-*

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velopment, and *Scandinavian Journal of Rehabilitation Medicine*).

We chose these journals because a high impact factor is a good predictor of high methodologic quality of journal articles (8).

One author assessed the retrieved articles and screened the titles and abstracts to identify the relevant studies. We included articles only if the study was identified as a randomized, controlled trial, was published as a full-text article, and assessed pharmacologic or nonpharmacologic treatment of rheumatoid arthritis or hip or knee osteoarthritis. We excluded case series, uncontrolled studies, articles published as abstracts only, editorials, news, or correspondence sections. We screened articles for duplicate publication (that is, the same trial published with results from different lengths of follow-up), and in these cases, we selected only the initial article. We excluded articles assessing treatment of both rheumatoid arthritis and osteoarthritis or both pharmacologic and nonpharmacologic treatment.

Data Extraction

We collected general data on trials: year of publication, funding source, multicenter trials (at least 2 centers), sample size, treatment classification (nonpharmacologic and pharmacologic), and methodologic quality (Jadad scale [7] and Delphi list [8]).

We checked for indexing terms, such as *adverse effects* or *safety*, in the title, in the abstract, and in MEDLINE (3).

Data collected on reporting harm included methods used to collect harm-related information and the reporting of adverse events, adverse events causally related to treatment, and the severity of adverse events, even if these criteria were mentioned minimally.

We also used a qualitative and quantitative component of the reporting of harm previously validated (1, 2, 6). The qualitative component included the reporting of frequency and reasons for withdrawal due to adverse events per study group and use of an adequate definition of the severity of adverse events. We measured the quantitative component by the space allocated to adverse events in the results sections (that is, proportion of lines allocated to reporting adverse events).

One author extracted all the data. In addition, a second reviewer evaluated a computer-generated random sample of reports ($n = 30$) to determine interobserver reproducibility.

Statistical Analysis

We reported descriptive statistics by means and SDs or median (lower quartile; upper quartile), frequencies, and percentages. To compare pharmacologic and nonpharmacologic treatments, we analyzed categorical data by using the chi-square test or Fisher exact test as appropriate and continuous data by using the Student *t*-test or unpaired Wilcoxon test as appropriate.

We compared data on reporting harm by using a mul-

Context

We need rigorous randomized, controlled trial evaluations of nonpharmacologic, as well as pharmacologic, treatments.

Contribution

This analysis of 193 treatment trials for rheumatic disease found that trials evaluating pharmacologic therapies reported data about potential adverse events and harm more often than trials evaluating nonpharmacologic treatments. Fewer than half of the nonpharmacologic treatment trials reported any harm data.

Cautions

Generalizing these findings to areas other than rheumatic disease is difficult.

Implications

Trials of nonpharmacologic therapies must report data about harm so that clinicians and patients can make informed decisions about these therapies.

—The Editors

iple logistic regression equation adjusted for the following confounding variables: medical area (that is, rheumatoid arthritis or osteoarthritis), sample size, funding source, and multicenter trials. We created separate models for each of the following data related to adverse events: collection methods; blinded assessment; reporting of the nature of adverse event, frequency of adverse event, withdrawals due to adverse events, severity of adverse event, and adequate definition of the severity; and space allocated to reporting harm. We used SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina), for all data analyses. We determined the degree of agreement between the 2 reviewers by using the κ coefficient for categorical variables or the intraclass correlation coefficient for continuous variables.

RESULTS

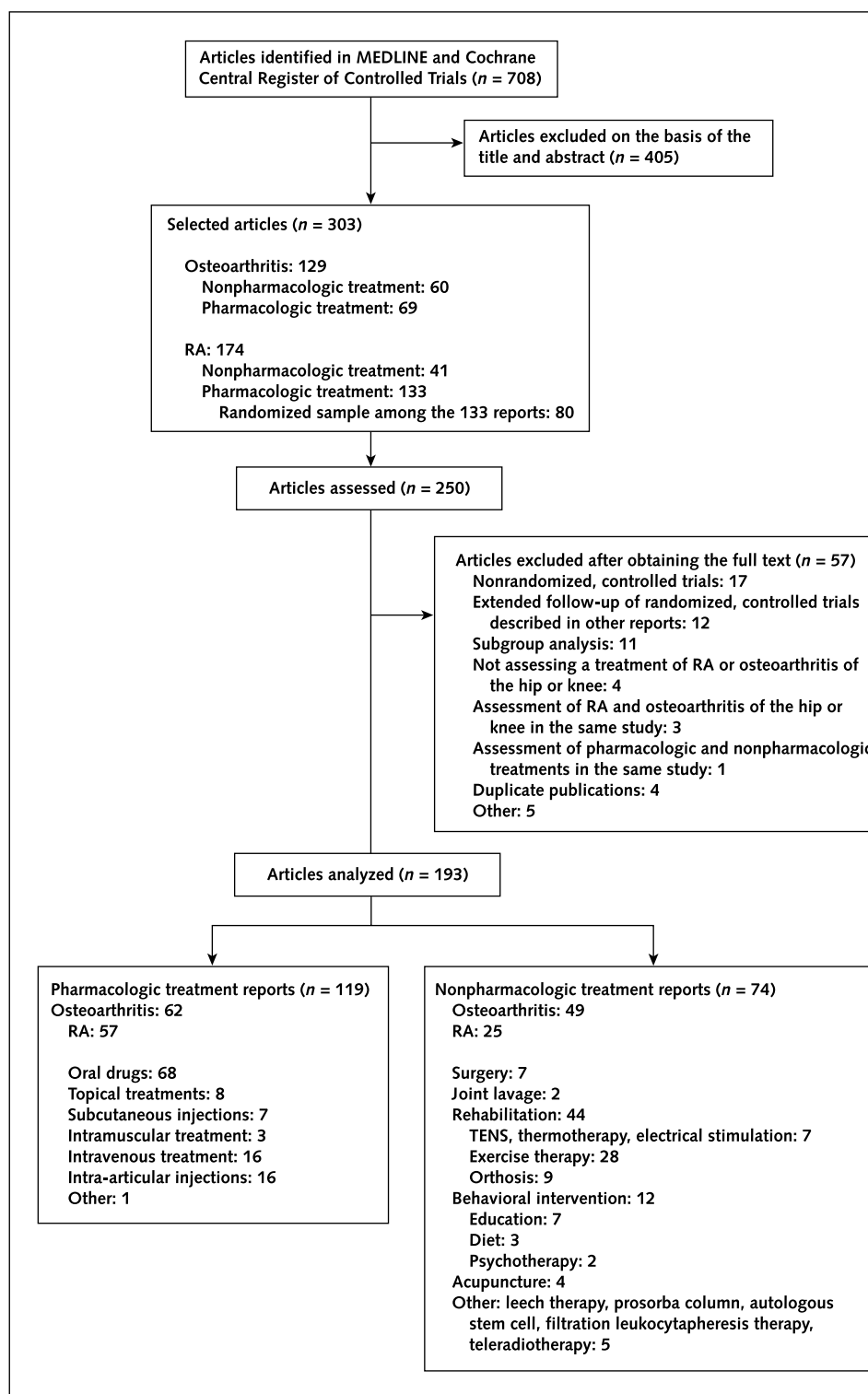
Selected Articles

Of 708 articles identified, we selected 193 for assessment (Figure). One hundred nineteen (61.7%) reports involved pharmacologic treatment, and 74 (38.3%) reports involved nonpharmacologic treatment.

Trial Characteristics

Only 24 (12.4%) articles were published in a general medical journal. When reported ($n = 74$), funding was more often reported as public in reports of nonpharmacologic (79.4%) than pharmacologic (23.3%) trials ($P < 0.001$). Trials were more often reported as multicenter for those assessing pharmacologic (69.7%) than those assessing nonpharmacologic treatment (36.5%) ($P < 0.001$). The median sample size was 118 patients (lower quartile, 61 patients; upper quartile, 250 patients); 163 (lower quartile, 62

Figure. Study screening process.



RA = rheumatoid arthritis; TENS = transcutaneous electrical nerve stimulation.

patients; upper quartile, 382 patients) for trials of pharmacologic treatment and 168 (lower quartile, 60 patients; upper quartile, 156 patients) for trials of nonpharmacologic treatment ($P = 0.005$). Whatever the tool used to assess quality,

the scores were better for pharmacologic treatment reports than for nonpharmacologic treatment reports (4.7, SD 2.1, vs. 3.0, SD 2.0, on the Jadad scale; $P < 0.001$).

Interobserver reproducibility was good for the main

items assessed, and κ coefficients were between 0.78 and 0.93.

Reporting of Harm: Indexing Terms

Among the 138 articles reporting adverse events, 105 (76.1%) articles dealing with harm contained indexing terms in the title, in the abstract, or in MEDLINE. Pharmacologic treatment reports used these terms significantly more often than nonpharmacologic treatment reports (85.4% vs. 48.6%; $P < 0.001$).

Reporting of Adverse Events

Pharmacologic treatment reports reported data on harm more often than nonpharmacologic treatment reports (Table 1) on collection methods (64.7% vs. 23.0%; $P < 0.001$); blinded assessment (68.1% vs. 23.0%; $P < 0.001$); and reporting of adverse events (86.5% vs. 47.3%; $P < 0.001$), causal relationship between the treatment and adverse events (33.6% vs. 1.3%; $P < 0.001$), withdrawals due to the events (82.3% vs. 43.2%; $P < 0.001$), and

severity of the events (59.7% vs. 16.2%; $P < 0.001$). Only 9.3% of reports (18 reports: 16 and 2 reports of pharmacologic and nonpharmacologic treatment, respectively) adequately defined severity according to the Ioannidis and Lau classification (2). The mean proportion of space allocated to describing harm in the results section was 22.5%, SD 71.0%. More space was allocated in pharmacologic than nonpharmacologic treatment reports (32.3% vs. 6.6%; $P = 0.002$).

Table 2 contains the multivariate analysis for reporting harm. Whatever the item assessed, odds ratios were higher for reports of pharmacologic treatment trials than for reports of nonpharmacologic treatment trials. With adjustment for sample size, medical area, funding, and multicenter trials, all odds ratios decreased but remained significantly higher for pharmacologic than nonpharmacologic treatment reports for collection methods (odds ratio, 5.2 [95% CI, 2.2 to 12.2]); reporting of harm (odds ratio,

Table 1. Data on Adverse Events in Published Randomized, Controlled Trials of Pharmacologic and Nonpharmacologic Treatment

| Data on Adverse Events Reported | All Reports, n (%) (n = 193) | Pharmacologic Treatment Reports, n (%) (n = 119) | Nonpharmacologic Treatment Reports, n (%) (n = 74) | P Value |
|---|---------------------------------|---|---|---------|
| Collection methods | 94 (48.7) | 77 (64.7) | 17 (23.0) | <0.001 |
| Blinded assessment | 98 (50.8) | 81 (68.1) | 17 (23.0) | <0.001 |
| Reporting of harm | | | | |
| Any reporting | 138 (71.5) | 103 (86.5) | 35 (47.3) | <0.001 |
| Reporting with numerical data | 134 (69.4) | 101 (84.9) | 33 (44.6) | |
| Reporting with generic statement | 4 (2.1) | 2 (1.7) | 2 (2.7) | |
| Nature | | | | |
| Any reporting | 125 (64.8) | 97 (81.5) | 28 (37.8) | <0.001 |
| Reporting per trial group | 111 (57.5) | 92 (77.3) | 19 (25.7) | |
| Reporting for all trial groups combined | 12 (6.2) | 4 (3.4) | 8 (10.8) | |
| Reporting in only 1 group | 2 (1.0) | 1 (0.8) | 1 (1.3) | |
| Frequency | | | | |
| Any reporting | 137 (71.0) | 103 (86.5) | 34 (45.9) | <0.001 |
| Reporting per trial group | 121 (62.7) | 97 (81.5) | 24 (32.4) | |
| Reporting for all trial groups combined | 15 (7.8) | 6 (5.0) | 9 (12.2) | |
| Reporting in only 1 group | 1 (0.5) | 0 (0.0) | 1 (1.3) | |
| Treatment-related event | | | | |
| Any reporting | 41 (21.2) | 40 (33.6) | 1 (1.3) | <0.001 |
| Withdrawals due to the event | | | | |
| Any reporting | 130 (67.4) | 98 (82.3) | 32 (43.2) | <0.001 |
| Reporting per trial group | 126 (65.3) | 95 (79.8) | 31 (41.9) | |
| Reporting for all trial groups combined | 4 (2.1) | 3 (2.5) | 1 (1.3) | |
| Reporting in only 1 group | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Reporting of each type of event leading to withdrawal | 53 (27.5) | 42 (35.3) | 11 (14.9) | |
| Severity | | | | |
| Reporting severity | 83 (43.0) | 71 (59.7) | 12 (16.2) | <0.001 |
| Reporting with generic statement only | 18 (9.3) | 15 (12.6) | 3 (4.0) | |
| Reporting with numerical data | 65 (33.7) | 56 (47.1) | 9 (12.2) | |
| Reporting life-threatening event separately per group | 42 (21.8) | 40 (33.6) | 2 (2.7) | |
| Reporting the type of life-threatening event | 31 (16.1) | 28 (23.5) | 3 (4.0) | |
| Definition of severity | | | | |
| Adequate | 18 (9.3) | 16 (13.4) | 2 (2.7) | 0.01 |

Table 2. Data on Adverse Events in Published Randomized, Controlled Trials of Pharmacologic and Nonpharmacologic Treatment

| Data on Adverse Event Reported | Crude Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* |
|---|---------------------------|-------------------------------|
| Collection methods | 6.1 (3.2–11.9) | 5.2 (2.2–12.2) |
| Blinded assessment | 7.1 (3.7–13.9) | 4.7 (2.0–11.1) |
| Reporting of harm | 7.2 (3.6–14.4) | 5.2 (2.1–12.9) |
| Nature | 7.2 (3.7–14.0) | 3.5 (1.5–8.2) |
| Frequency | 7.6 (3.8–15.2) | 5.2 (2.1–12.8) |
| Reporting of withdrawals due to the event | 6.1 (3.2–11.8) | 4.6 (2.0–10.9) |
| Severity | 7.6 (3.7–15.7) | 3.7 (1.5–9.1) |
| Definition of severity adequate | 5.6 (1.2–25.5) | 1.3 (0.2–7.2) |
| Space allocated to describing adverse events (per 10-fold increase) | 2.2 (1.7–3.1) | 1.6 (1.2–2.3) |

* Adjusted for sample size, medical area, funding, and multicenter trial.

5.2 [CI, 2.1 to 12.9]), withdrawals due to the events (odds ratio, 4.6 [CI, 2.0 to 10.9]), and severity of adverse events (odds ratio, 3.7 [CI, 1.5 to 9.1]); and space allocated to reporting adverse events (odds ratio, 1.6 [CI, 1.2 to 2.3]). After adjustment, the odds ratios for adequate definition of severity did not differ between the 2 types of reports. Among the articles describing adverse events, pharmacologic treatment reports included indexing terms dealing with harm more often than nonpharmacologic treatment reports (odds ratio, 6.2 [CI, 2.6 to 14.7]), but the odds ratio decreased after adjustment for confounding variables (odds ratio, 3.1 [CI, 0.9 to 10.4]).

DISCUSSION

We assessed the reporting of harm in published randomized, controlled trials of pharmacologic and nonpharmacologic treatment for rheumatoid arthritis and hip or knee osteoarthritis during a 6-year period. Our results highlight that harm was described less in reports of nonpharmacologic treatment trials than in reports of pharmacologic treatment trials. These results remained true after adjustment for confounding factors and are consistent with those of a study of mental health interventions (6).

Presupposed lower toxicity profiles of nonpharmacologic treatment, such as exercise therapy, complementary and alternative medicine, and behavioral interventions, could explain a lower interest in the evaluation of adverse events. However, most therapy entails the risk for adverse events, including serious events (9). For instance, vertebral artery dissection or the caudal equine syndrome was described after spinal manipulation and pneumothorax was described after acupuncture, although these treatments are usually considered low risk (10, 11). Furthermore, unexpected adverse events can be detected only if data on all events are systematically appraised and collected. Otherwise, a relationship between adverse events and the treatment may be missed, especially for events that occur belatedly or are not obviously related to the treatment. For instance, we cannot exclude, as a matter of principle, the possibility that intensive exercise therapy performed by elderly patients with osteoarthritis and rheumatoid arthritis could be responsible for rare cardiovascular adverse events.

Because data on such events are not systematically collected, the safety of intensive exercise therapy is questionable. Consequently, the systematic reporting of harm in published results of trials of nonpharmacologic treatment must follow the same rules as for those of pharmacologic treatment.

Our results are also probably linked to the differences in the regulatory mechanisms for drugs and nonpharmacologic treatment. Although new pharmacologic treatment must fulfill very strict regulatory requirements, with approved preclinical and clinical development, no requirement exists for nonpharmacologic treatment, except for technical devices. Postmarketing evaluation with a requirement of reporting adverse events to regulatory agencies and methods used to detect such events have focused primarily on pharmacologic treatment and neglected most nonpharmacologic treatments. Moreover, studies evaluating harm are largely based on private funding because drug manufacturers are responsible for collecting, evaluating, and reporting data from postmarketing studies of their product; the lack of funding for trials assessing nonpharmacologic treatment is probably responsible for the lack of harm-related reporting. Therefore, assessing the harm of nonpharmacologic treatment relies mainly on anecdotal data, such as a case report (12).

Our study has some limitations. First, we focused on only 2 medical areas (rheumatoid arthritis and hip or knee osteoarthritis) because treatments in this field cover a wide range of pharmacologic and nonpharmacologic treatment. Therefore, caution should be used in extrapolating results to trials in areas other than these rheumatic diseases. Second, some discrepancies may exist between reported methods and the real application. Harm may be reported well in case reports but poorly in articles. The Consolidated Standards of Reporting Trials (CONSORT) statement (13) and recent extension (14) should improve the reporting of harm. Finally, our search was limited to reports of journals with a high impact factor because some evidence suggests better methodologic quality in these journals (15). Reporting could consequently be poorer in journals with a low impact factor. However, previous work showed a trend between high impact factor and lower reporting of harm (2).

In conclusion, these results highlight the low interest in the safety of nonpharmacologic treatment and the need for changing attitudes in the assessment of safety of nonpharmacologic treatment.

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