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REVIEW

Scientific fraud

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SUMMARY

There is a heightening debate about the integrity of science, fuelled by a series of widely publicized cases of scientific fraud. Such cases have involved plagiarism, falsification of data, issues of reproducibility, study design (controls, blinding), sponsoring, ghost-writing, improper peer-review or publication procedures. Scientific publishers have also been criticized. In the biomedical sciences, these issues are equally relevant to both basic and clinical research. This article will describe challenges in evaluating and weighing the evidence from clinical studies. As a prominent example, meta-analyses of studies on chronic pain and its treatment by opioid analgesics will be described, because this topic is receiving increasing public attention. Both the medical community and policy makers have recognized that opioid use in chronic pain needs to be scrutinized with regard to analgesic effectiveness and adverse side effects, and clinical guidelines need to be revised. The development of an evidence-based guideline, reactions to its results by the media and by the opioid-producing pharmaceutical industry, as well as implications for scientific integrity will be discussed.

1. Introduction

There is a heightening debate about the integrity of science, fuelled by a series of widely publicized cases of scientific fraud.[1–5] Such cases have involved (but were not limited to) plagiarism, falsification of data, issues of reproducibility, study design (controls, blinding), sponsoring, ghost-writing, improper peer-review or publication procedures. Scientific publishers (e.g. Elsevier) have also been scrutinized.[6] In the biomedical sciences, these issues are equally relevant to both basic and clinical research, although some may believe that flaws in (pre-) clinical trials are more critical or have a higher impact on society than those in basic (experimental) research[7] (http://gesundheitsforschung-bmbf.de/_media/Leitfaden_Mustervorlage_Vollantrag_MSK.doc). This has lead to confusion and deterioration of medical and scientific ethical standards.[8–20]

This article will focus on challenges in evaluating and weighing the evidence from clinical studies. As a prominent example, meta-analyses of studies on chronic pain and its treatment by opioid analgesics will be described, because this topic is receiving increasing public attention. The most recent assessment of the global burden of disease has cited several chronic (non-cancer) pain syndromes (low back pain, musculoskeletal disorders, neck pain, arthritis) as well as drug-use disorders among the top 10 health problems in the United States and among the 25 leading diseases worldwide. Low back pain, for example, affects about 10% of the world population,[21] huge market sales (up to 50×10^9 US $) of analgesic drugs are quoted,[22] and the abuse of opioids (e.g. morphine) has lead to an epidemic of overdoses, death and abuse.[23–25] Thus, both the medical community and policy makers have recognized that opioid use in chronic pain needs to be scrutinized with regard to analgesic effectiveness and adverse side effects, and clinical guidelines need to be revised.[26,27] The development of an evidence-based guideline, reactions to its results by the media and by the opioid-producing pharmaceutical industry, as well as implications for scientific integrity will be discussed.

2. Opioid use in chronic pain

Opioids have been used for centuries and are generally considered the most potent pain killers.[28] Their application in acute and cancer pain is undisputed. However, the treatment of chronic non-cancer pain (CNCP) (e.g. low back pain, arthritis) with opioids is highly controversial. Major concerns include effectiveness, addiction potential and side effects. It is uncertain whether long-term application

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of opioids (or other analgesic drugs) produces clinically meaningful improvements in pain or day-to-day function, and which drug class is most effective. Opioids are limited by adverse central and intestinal effects (sedation, cognitive impairment, apnoea, nausea, addiction, constipation) and non-opioid analgesics (e.g. nonsteroidal anti-inflammatory drugs; NSAIDs) have gastrointestinal and cardiovascular side effects (bleeding, ulcers, stroke, heart attack).[26,29] In the case of opioids there has been a tremendous increase of prescriptions in many countries[23–25,30] and there is a heightening debate about abuse, criminal drug trafficking, effects on quality of life and overdosing.[24,26,27,30–32]

3. Development of guidelines

Many arguments have been based on traditions, expert opinions, practical experience and uncontrolled anecdotal observations. More recently, guidelines based on randomized controlled trials (RCTs) of adequate methodological quality have strived for evidence-based treatment recommendations. One such guideline was commissioned by the German Society for the Study of Pain (DGSS). The DGSS convened a panel of 35 clinicians and scientists representing 16 German medical and scientific societies concerned with CNCP (www.uni-duesseldorf.de/AWMF/ll/041-003m.pdf). According to the criteria of the Scottish intercollegiate guidelines network (SIGN) (www.sign.ac.uk/) each member had to declare actual or potential conflicts of interest (e.g. consultancies, employment, expert testimony, honoraria, speakers bureaus, retainers, stock options, ownership). The panel developed a guideline and treatment recommendations termed “long-term use of opioids in non-tumour pain” (LONTS; www.uni-duesseldorf.de/AWMF/ll/041-003.pdf) based on meta-analyses of published data (sample sizes, means, variances).

4. Meta-analyses

Four investigators independently and in duplicate screened over 3600 publications on CNCP including RCTs, meta-analyses, narrative reviews and clinical practice guidelines concerning the use of analgesic drugs or non-pharmacological treatments. Data sources included seven electronic databases (1990–2009), grey literature and personal inventories, without language restrictions. Using the PRISMA guideline[33] and the World Health Organization (WHO) classification, five independent, methodologically unified meta-analyses of studies on WHO-III (strong opioid), WHO-II (weak opioid) and WHO-I (non-opioid) analgesics compared with placebo, and on physiotherapy and psychotherapy compared with active or waiting-list controls were conducted. Only high-quality published RCTs (according to the SIGN criteria) were included to avoid flaws from merging data of high-quality with those of low-quality trials.[34–36] Studies were included if treatment duration was at least three weeks and data were sufficient for meta-analysis. Data on patient and study characteristics, pain scores, physical functioning, quality of life, adverse effects, and dropout rates were extracted. Effect size estimates (standardized and weighted mean differences) were derived from studies whenever the reported data permitted.

4.1. Magnitude and duration of analgesic effects

A total of 46 studies (over 10,700 patients) were included. The eligible RCTs were conducted over periods of up to 3 months. Weighted mean differences between pain intensities were calculated and pooled to conduct separate meta-analyses for each of the five treatment categories. At the end of treatment the weighted mean differences for pain reduction (on a 100 point scale) was about 12 for strong opioids, 11 for weak opioids, 8 for non-opioids (each versus placebo), 5 for psychotherapy, and 5 for physiotherapy (each versus active controls). Placebo treatment produced average pain reductions of 15 in non-opioid studies and 18 in opioid studies. There were no statistical differences in efficacies between the five interventions. Extending opioid treatment beyond 6 weeks did not result in increasing but rather in diminishing pain relief. Uncontrolled observational studies in more than 2400 patients indicated that continuing opioid treatment beyond 3 months did not significantly reduce pain.

4.2. Adverse side effects, functioning and quality of life

About 33% of patients treated with opioids and 25% of patients treated with non-opioids terminated RCTs prematurely due to lack of effectiveness or adverse effects. Strong opioids produced more nausea, constipation, sedation, pruritus, vomiting and fatigue than weak opioids, but discontinuation rates due to side effects were similar (about 22%). Data on functioning and quality of life were suitable for descriptive analyses only. Overall quality of life was not improved by opioid treatment. Opioids slightly enhanced physical functioning in arthritis, neuropathic and back pain, and improved quality of sleep.

Following this meta-analysis, treatment recommendations were developed in a Delphi consensus process among the panel members (www.uni-duesseldorf.de/AWMF/ll/041-003.pdf).

5. Discussion

5.1. Effectiveness, side effects, bias

The most prominent result of the LONTS meta-analysis was that during long-term application neither opioids nor non-opioids produce significant analgesic effects, and that opioids are not more effective than non-opioids. Dropout rates due to side effects were high in pharmacological studies.

At the outset it must be noted that more than 60% of the relevant RCTs were published with incomplete results. This is in line with the extensively debated issue of reporting bias and the resultant data transparency movement.[9,37–39] From statistical studies comparing a large number of meta-analyses, it is known that effect sizes of unpublished RCTs are generally lower than those of published RCTs.[40] None of the published RCTs in the present meta-analyses provided any efficacy data of patients who aborted the studies (about 33% in opioid and 25% in non-opioid trials). Usually RCTs are performed in carefully selected patients with pain syndromes presumed to be responsive to analgesics since sponsors and authors are generally interested in finding “positive” results. In addition, none of the known problems of meta-analyses (publication bias, reporting bias, optimistic bias) produces an underestimation of effects. Therefore, the effect sizes found in the LONTS analysis likely represent the maximum achievable reductions of pain scores.

5.2. Clinical importance

Therapeutic decisions are usually based on an evaluation of outcome differences in terms of clinical importance. In the LONTS meta-analysis the question arises as to the clinical importance of a maximum pain reduction of 12 units (by interventions) or 15–18 units (by placebo) on a 100 point scale. For several types of CNCP a 30% reduction of pain scores, corresponding to a weighted mean difference of 20–22, is considered a minimal important change.[41–46] Thus, in LONTS the average reductions of pain scores