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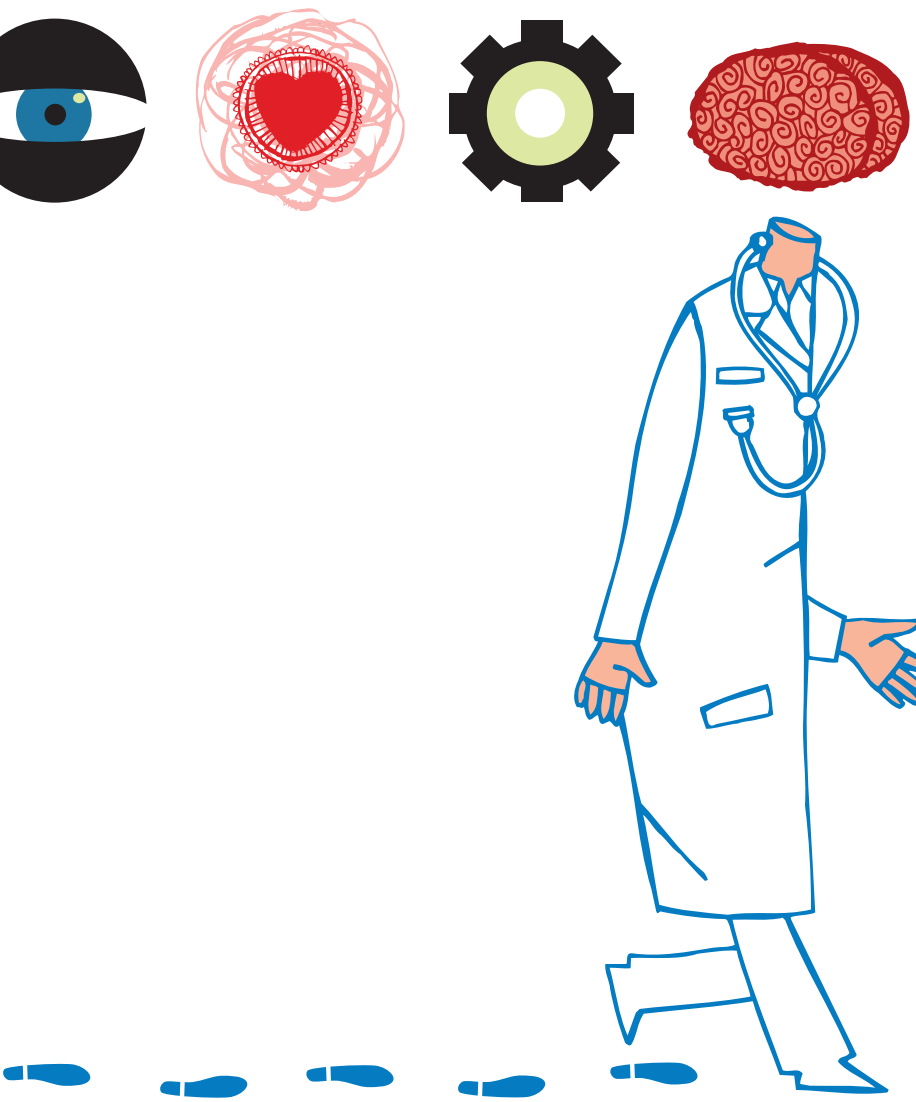
MEDICAL SCIENCE & PRACTICE

NEW REPORTS SBU Results in Brief |16–22



Kenneth Andersson

Time for a New Approach?

Health care should be based on scientific evidence and time-tested experience. Nevertheless, treatments other than those that have proven to be most effective are often used.

A treatment that has proven to be ineffective, or even harmful, should be eliminated from the healthcare repertoire as soon as possible. But there is often a good deal more interest in adopting new approaches than weeding out old ones.

– The healthcare profession needs a better system for getting rid of ineffective treatments, says SBU Director Nina Rehnqvist. Such treatments are still in use here and there even though they produce poor results and siphon off

Never Get too Cozy With the King

There has always been a certain amount of tension between medical practitioners and the powers-that-be. Every time Frederick II of Prussia (1712–1786) saw his personal physician, he reportedly started their conversation by smirking, "Well, Doctor, how many cemeteries have you filled since we last met?" His physician, who must have been a brave man, allegedly replied, "Considerably fewer than Your Majesty, and with far less glory."

This kind of tension is not necessarily a bad thing. We would have reason to be far more worried if scientists always defended those in power. The real difficulties arise when scientists sell out their integrity to serve ideological ends, dressing up political agendas as scientific problems.

A thought-proviking article in the Journal of Medical Ethics expresses concern that evidence-based guidelines may actually be "politics disguised as science." Their main argument is that making recommendations requires judgment and that "being transparent and democratic on these points will allow us to use EBM better for both the good of individual patients and for rationing purposes."

That is an important point. We must keep in mind that practice guidelines, even if they are evidence-based, never deal with purely scientific matters. Translating knowledge into practice (or even into practice guidelines) also requires judgment. Without judgment, you are in no position to make sound decisions. When scientific evidence encounters the real world and becomes the basis for clinical decision-making and healthcare policies, we must accept that facts begin to interact with the opinions of policymakers, professionals and patients.

However, discriminating between fact and opinion is a hallmark of evidence-based healthcare, so the process of developing guidelines must always be transparent. Those who read the guidelines must be able to distinguish fact from opinion.

As an independent assessment body, SBU does not issue guidelines. Our evidence helps decision makers, but we don't tell them what to do. We give them the map, and they do the driving. Hopefully our approach clarifies the distinction between fact and opinion.

Users of assessment reports sometimes have very different views on how to apply the same piece of evidence. That's probably the way it should be. Balancing the various aims and goals of health care – cure, caregiving, security and fairness – requires political decisions. No matter how evidence-based our healthcare system becomes, it will always involve judgment. The role of science is not to justify health policy decisions, but to inform them.

RAGNAR LEVI, EDITOR

Robert Nyberg

resources from methods that are indisputably worthwhile.

– Just as clinical studies must test new treatments in order to assess their efficacy and costs, the worst clinical practices need to be discarded in as orderly a manner as possible.

NOT UNCOMMON

As opposed to what many people may believe, outdated treatments are not at all uncommon.

Heparin treatment during the acute stage following stroke serves as a useful illustration. We have scientific evidence that the treatment does no good under such circumstances. Not only that, but it can cause serious bleeding. But data compiled by the Swedish National Board of Health and Welfare indicates that some of the country's hospitals still administer heparin to 20–25 percent of patients with acute stroke.

And even though special stroke units have proven to be most effective, some counties handle almost half of their stroke patients differently.

Similarly, data culled from national quality records suggest that the long-term outcome of inguinal hernia surgery varies considerably. Certain surgical procedures entail less risk of recurrence than others. Nevertheless, the medical profession again employs different types of surgery in nearly half the cases.

One argument put forth in favor of long-term estrogen therapy for healthy, postmenopausal women was that it would prevent dementia and cardiovascular disease.

– But when I was involved in trying to obtain funding for a randomized trial on the efficacy of the treatment, we encountered a general lack of interest, and even active resistance, recalls Rehnqvist.

CONVINCED

– Many people, including doctors, were thoroughly convinced of its benefits. Hardly anyone was bothered by the absence of evidence.

When a study was finally carried out, the treatment turned out to do more harm than good, increasing the risk of breast cancer, stroke and myocardial infarction.

Mats Eliasson is an associate professor of medicine and a member of the SBU Scientific Advisory Committee.

– Unfortunately, it comes as no surprise that some clinical practices still rely on weak or non-existent research findings, he says.

So how can we promote evidence-based health care? According to Eliasson, encouraging a genuinely scientific attitude means allowing plenty of room for skepticism.

ALARM CLOCK

– We must always have the courage to demand proof for any assertions that are made, even by an authority in the field, continues Eliasson.

– An alarm clock should go off in our heads whenever a colleague is hopeful or fearful about a particular therapy while exhibiting a lack of interest in the scientific evidence, or even arguing that it is not amenable to empirical testing.

– By the same token, healthcare policymakers have to stop relying on unconfirmed discoveries. A single research finding uncorroborated by additional trials is rarely sufficient reason to adopt new treatments.

Limiting yourself to isolated case histories won't lead to sound clinical practices either.

– The selection may not be representative, while the treatment itself hasn't always been administered in a controlled manner or systematically compared with an alternative, says Eliasson.

– If we're serious about evidence-based health care, we must be willing to re-examine our attitude toward empirical evidence that differs from what we had expected to find.

– I can't take for granted that my particular opinion is correct if well-designed studies suggest otherwise.

PSEUDOSCIENCE

Both the healthcare profession and the research community offer countless examples of both pseudoscience and unwarranted faith in authority, says Sven Ove Hansson, professor of philosophy at the Royal Institute of Technology in Stockholm.

– We start running into difficulties whenever we grow so convinced that fashionable experts are capable of telling us what is true and false that we uncritically accept their assertions, says Hansson. All of a sudden we forget to ask for the evidence.

– Not even academia, which is supposed to be a bastion of knowledge, is untouched by pseudoscience, Hansson continues. A professor of medicine recently asserted that anorexia nervosa and sudden infant death syndrome are caused by lack of love and that schizophrenia can be treated by past life regression.

– A pseudoscientific approach doesn't necessarily involve ignoring all research. Maybe you accept only whatever can corroborate your particular hypothesis. Whenever a contradictory finding comes along, you dismiss it out of hand or explain it away.

Rehnqvist argues that the healthcare profession is in want of a consistent method for weeding out the treatments that have proven to be least effective so as to free up more resources for those that provide documented benefits.

– We need a variety of treatments to choose from, she says.

– But if we're going to let a thousand flowers bloom, we have no choice but to weed our garden.

SOME QUESTIONABLE OR INEFFECTIVE TREATMENTS

PSYCHIATRY

- Non-specific counseling for substance abuse (no proven benefits – other more effective treatments are available)
- Neuroleptics for anxiety without psychosis in the elderly (does more harm than good)

SURGERY

- Sympathectomy for lower limb ischemia (no evidence)
- Removal of the first rib for nerve impingement in thoracic outlet syndrome (no evidence)
- Gastric pacing for obesity (no well-designed studies on the benefits)

MEDICINE

- Dietary treatment for gastric ulcers (no evidence)
- Albumin drip instead of saline solution for intensive care patients with heavy blood loss (not proven to be any better)
- Unfractionated heparin for deep vein thrombosis (low-molecular-weight heparin is often better and simpler to administer)
- Air filters for asthma (studies have not demonstrated any benefits)

TESTING

- Early X-ray for acute back pain in the absence of another suspected disease or trauma (does not provide any useful data)
- Routine lung X-ray or ECG prior to scheduled surgery (no proven benefit for healthy patients with no past medical history)
- Bone density screening of people with risk factors for fracture (has proven to be a poor predictor of hip fracture)

Sources: Assoc. Prof. Jörgen Malmquist, Prof. David Bergqvist, Prof. Jan Palmblad, Prof. Lars Werkö

image 100/Matton

How to Put New Drugs to the Test

According to the Swedish Medical Products Agency, few new medications translate into improved patient health. Only a small percentage have been shown to be more effective than existing options – nor have their potential side-effects been adequately documented. In other words, the advertising notion that "if it's new, it's got to be better" should be seriously challenged by healthcare professionals.

"Every now and then, drug companies bring an innovative drug to the market, but mainly they turn out a seemingly inexhaustible supply of leftovers – 'me-too' drugs that are versions of drugs in the distant past," writes Dr. Marcia Angell, former editor-in-chief of the prestigious *New England Journal of Medicine* in her exposé *The Truth About the Drug Companies*.

Professor Björn Beermann of the Swedish Medical Products Agency and member of the SBU Scientific Advisory Committee agrees.

COSTS LESS

– Of course, developing new versions of old drugs is the cheaper way to go, Beermann explains.

– And even if the "me-too" versions are neither less expensive at the pharmacy counter nor more effective, intensive promotion can ensure them a significant share of the market for the most widespread diseases.

– In other words, investing

DOES A NEW DRUG LIVE UP TO THE MANUFACTURER'S PROMISES?

BENEFITS
Has the new medication been compared with previous treatments? If so, which ones? What comparisons are missing? What dosages and treatment periods are involved? Are the studies relevant to your particular patients? How much variation was there among the different test subjects?

PHARMACODYNAMICS AND PHARMACOKINETICS
What is the significance of claims that a drug is most selective, most potent, x percent bioavailable (as opposed to y percent for a competitor), etc.? Do such putative characteristics really make a difference when it comes to patient health?

SURROGATE MEASURES
What are the study's key questions and outcome measures? Is the alleged effect based on a surrogate measure – an outcome measure that replaces a gauge of the therapy's true intended purpose? A surrogate measure is not necessarily an accurate reflection of mortality, morbidity or quality of life.

NUMERICAL DATA
Watch out for treatment outcomes reported as percentages only. Demand to see the actual numbers. Don't settle for data about relative risk and risk reduction – ask for the absolute figures. Request the number needed to treat (NNT) and the confidence interval.

NUMBER OF TEST SUBJECTS
Did the initial phase of the study involve a power calculation of the number of subjects needed in order to demonstrate a particular difference in efficacy? Information about such a calculation is often lacking.

STATISTICS
Data that are not normally distributed (such as rating scales) are often erroneously presented by means of parametric methods (arithmetic mean, standard deviation, Student's t-test, etc.). The greater the number of statistical comparisons, the larger the risk of significant results that appear simply by chance. Has a correction been made for such an eventuality?

SIDE-EFFECTS
What do expressions like "placebo-level side-effects" really mean? The potential side-effects of a new drug cannot be fully known – the rare ones are detected much later on. If only a few people have been exposed to the drug, the absence of serious incidents cannot prove the absence of severe side-effects. How long is clinical follow-up?

CHARTS AND GRAPHS
Beware of axes that don't start at 0. Are there correct measures of dispersion – such as standard deviation, percentiles and confidence intervals – that show the degree of variation? If the standard error of the mean (SEM) is used, the confidence interval should be specified as well. Does the graph include significance data?

POPULARITY
Judge for yourself instead of relying on claims like, "Dr. X or Clinic Y uses this drug and regards it as a useful alternative."

UNPUBLISHED DATA
Studies that have not been published in peer-reviewed journals, or that have not been scrutinized systematically, are incomplete. Don't trust data on file, preliminary findings or articles in the supplements of well-known journals unless the results have been subject to external scrutiny.

For additional information in Swedish, see Läkemedelsboken 2005/2006.

in similar versions of a particular medication may turn out to be a profitable venture for the drug companies.

What value does the fifth or eighth version of a particular drug hold out for patients? Minor differences, such as metabolic factors or potential side-effects, can be meaningful. But according to the 1987–2000 assessments issued by the Swedish Medical Products Agency, 6 out of 10 new drugs offer absolutely no clinical benefits.

"ME-TOO" DRUGS

Of the 415 new medications approved by FDA in 1998–2002, 77 percent were classified as "me-too" drugs that had proven to be no more effective than existing preparations for the same condition.

– Modified copies of existing drugs are frequently approved without any evidence that they provide additional benefits, says Beermann.

– They might even turn out to be less effective. The only criterion for approval is that they outperform placebo.

The most important question – which drug is best for patients – usually remains unanswered.

CAN'T COMPARE

– The findings of different placebo studies on similar drugs can't be compared without further ado, continues Beermann. That's not a scientifically valid approach. While all the studies rely on placebo, they inevitably differ in a number of other ways – the kinds of test subjects who participate, the circumstances of treatment and the measurement procedures employed, just to name a few. So such comparisons leave huge gaps in our understanding of which drugs are most suitable.

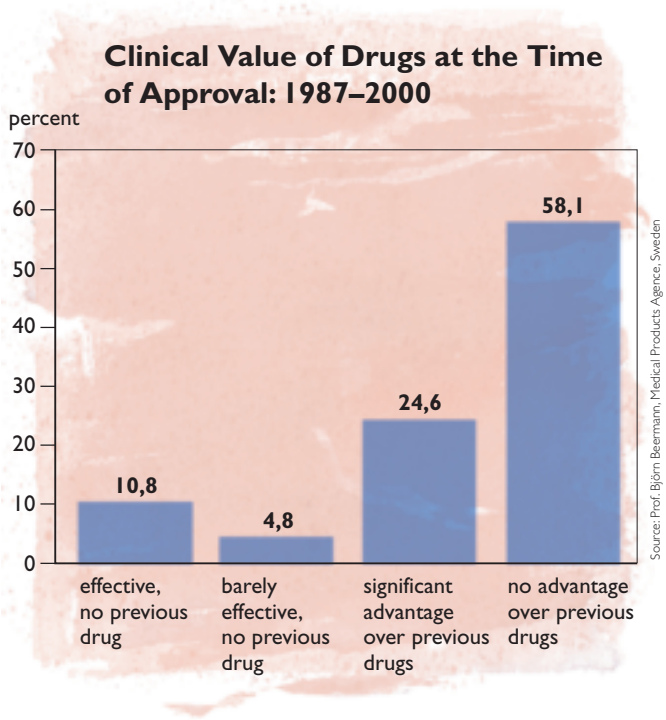
Angell regards that as a big problem. From her vantage point, the threshold for approval of new drugs – that they must simply be better than placebo – is much too low. That creates the mistaken impression that if it's new, it's got to be worth something.

TRULY BEST?

Rune Dahlqvist, professor of clinical pharmacology at Umeå University, would be thrilled to see the criteria for approval raised.

– The key challenge for both doctors and patients is

"We must have the guts to question new products"



to identify the most effective treatment, he says. We can't begin addressing that question until new drugs are compared head to head with existing ones. Requiring that such studies be conducted would be a big step in the right direction.

Another option mentioned by Dahlqvist is to record and monitor the treatment outcomes for all Swedish patients who are taking a particular drug.

Other countries keep such data. But partly due to privacy concerns, Sweden has been reluctant to start down that path.

– What we need to keep in mind is that new drugs are often launched in the absence of sufficient data about rare and perhaps serious side-effects, not to mention comparisons with other medications, says Dahlqvist.

GUTS TO QUESTION

– We must have the guts to question new products, Dahlqvist asserts. Do they make good on their promises?

What kind of misleading advertising do drug companies engage in? According to associate professor Göran Wennersten, the Swedish pharmaceutical industry's information examiner, overblown and unqualified claims about drug characteristics and efficacy are far too common.

Moreover, price comparisons may be misleading, particularly when normal doses in accordance with the Swedish pharmacopeia (FASS) or equivalent indications are missing.

But drug companies most often receive official reprimands for exaggerations or lack of reliability. For instance, an ad might promote dosages, indications or uses other than those for which the medication has been approved.

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– New drugs are often launched in the absence of sufficient data about rare and perhaps serious side effects, not to mention comparisons with other medications, says Rune Dahlqvist, professor of clinical pharmacology.

Johan Gunéus

Does Research Present a Slanted View?

Reports of scientific findings are often much less rigorous than they appear. In fact, many studies are structured and reported so as to present a distorted view of reality. Readers need to stay on their toes.

KEEP FINDINGS AND INTERPRETATION APART

Reporting research findings is one thing, interpreting them is another. Research reports generally contain both results and interpretations, and the trick is to keep them apart.

For instance, researchers tend to conclude scientific articles with a section in which they discuss their findings. Not uncommonly, they exaggerate both the importance of their own work and the potential of future research. They may also be overly optimistic about the prospect that the results will lead to better health care.

Critics have pointed out that reports of clinical research can easily be slanted in favor of special interests, such as the sponsor of the study. Drug testing is a case in point. The odds that a study will recommend an experimental treatment are five times as great if the sponsor stands to gain financially.

Discriminating readers concentrate on the Methods and Results sections while looking at the Discussion section with a wary eye.

SEEK DIFFERENT INTERPRETATIONS

Normally performed by at least two independent referees, systematic reviews of the literature follow predefined criteria. That approach minimizes the risk of bias.

Only by systematically searching for and compiling all the available research on a particular topic, and not simply relying on the findings of a single study by one group of researchers, can the referees take the various possible explanations for a conclusion into consideration.

Similarly, certain medical journals specialize in assigning experts the task of reviewing, commenting on and summarizing the findings of other researchers.

Among such publications are ACP Journal Club, Evidence-Based Medicine and Evidence-Based Mental Health. They all make an extra effort to ensure that special interests don't influence the interpretation of research findings.

CONSIDER THE CONTROL GROUP

Treatment studies, such as clinical drug trials, tend to focus on how much the treated subjects improved. But examining what happened to the control group is equally vital to a proper interpretation of the results. A treatment that is alleged to have proven efficacious should always raise one fundamental question – "compared to what?"

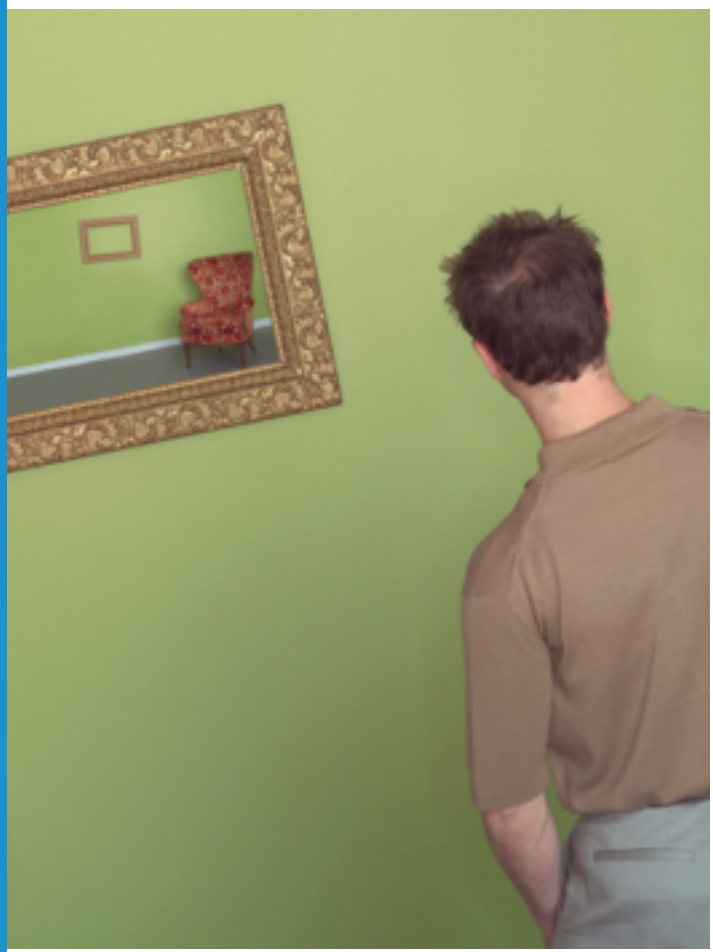
Studies that randomize test subjects to a treatment and a control group base their conclusions on a possible divergence between the two. Thus, many such studies are structured so as to make sure that the difference is as big and unequivocal as possible. For instance, researchers fre-

Simon Watson/Stone+

quently compare the new drug with placebo instead of with the most effective existing treatment – which is the issue of greatest clinical relevance. But it goes without saying that both caregivers and patients want to know how well the new therapy stacks up against what they are already familiar with, not sugar pills.

Another way of overstating the difference is to go ahead and treat the control group according to the best conceivable alternative but not with the optimal dosage or form.

A number of systematic overviews have demonstrated that studies funded by the pharmaceutical industry tend to claim greater efficacy than those whose sponsors have nothing to gain financially. The approach to treating the control group may be the culprit.



BEWARE OF AGGREGATE OUTCOME MEASURES

In order to facilitate statistical analysis, researchers occasionally develop aggregate outcome measures. While covering widely divergent aspects of the test subjects' health, such measures have not necessarily won general acceptance. For instance, a study might report that 65 percent of the treated patients experienced "improved cardiac health" in terms of reduced mortality, lower risk of myocardial infarction or more favorable laboratory values.

But since those three scenarios are miles apart as far as patients are concerned, it's hard to make much sense out of such a statistic. Mortality and myocardial infarction are obviously of direct concern to the patient, albeit for different reasons, but laboratory values may be totally irrelevant to their health status.

What's more, an aggregate outcome measure is misleading if at least one of its components is much more common than the others. In the above illustration, more favorable laboratory values might show up a lot oftener than the other two benefits. So it would be easy to get the impression that "cardiac health" had improved more than it actually did.

DON'T CONFUSE STATISTICAL AND CLINICAL SIGNIFICANCE

If a study is big enough and includes a large number of test subjects, it can always ferret out modest differences between the treatment and control group. The evidence of even small differences will be statistically reliable. But statistical significance does not automatically translate into clinical significance, ie, benefits for the patient.

BE CAREFUL WITH SUBGROUPS

If the researchers retrospectively broke the study down into a large number of subgroups, you might want to take a step back. There are lots of ways to design such a breakdown. The greater the number of subgroup analyses, the larger the risk of statistically significant results that appear merely by chance.

A rule of thumb is to exercise restraint in analyzing subgroups and not make all too much of the findings.

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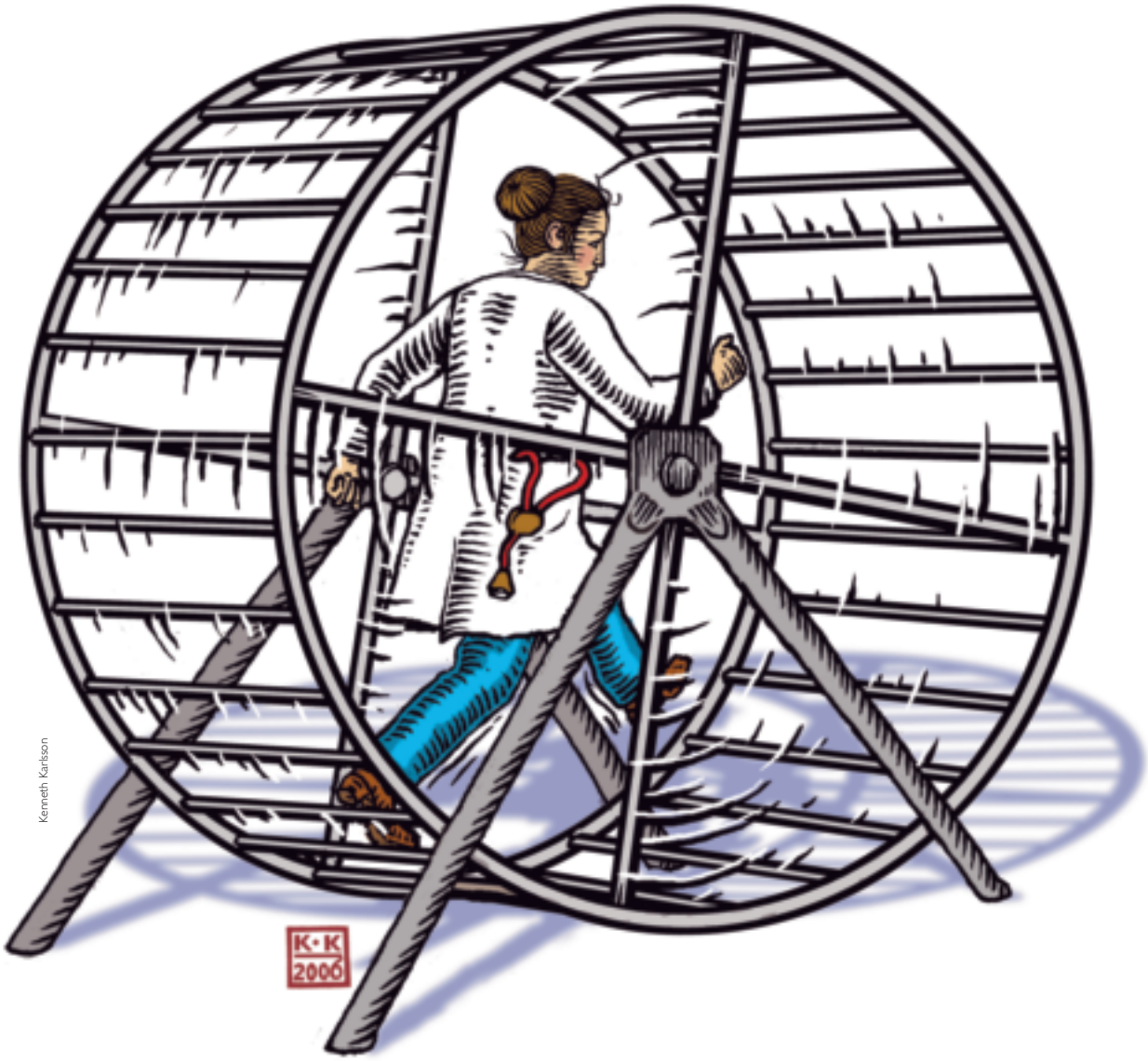

Kenneth Karlsson

End Useless Treatment

– We healthcare professionals are more inclined to start on a treatment than to end it, says Kurt Boman, professor of medicine at Umeå University and former member of the SBU Scientific Advisry Group. But both issues are just as important when weighing the interests of the patient.

– If we stopped all unnecessary treatment, our patients would do better and our costs would decline dramatically, Kurt Boman maintains.

YEAR AFTER YEAR

The way things are now, treatment that is ineffective or no longer useful can go on year after year. Despite the high costs and potential damage to the patient's health, nobody assumes responsibility for reconsidering what is actually called for.

– One reason may be insufficient coordination among the various caregivers, continues Boman.

A doctor who would like to terminate a particular treatment might not know enough about the patient's medical history. Why was the treatment ordered in the first place? Was the diagnosis correct?

The case notes may lack information about how long the treatment is supposed to go on.

– There's an unfortunate tendency to reconsider a particular medication only when palpable side-effects or clear contraindications show up, says Dr. Kurt Boman, professor of medicine at Umeå University.

– Once a newly prescribed medication has been tried for a certain amount of time and the hoped-for effect has failed to materialize, the treatment should be discontinued, says Boman. But unless that time limit shows up in black and white in the case notes, the next caregiver who comes along is prone to renew the prescription without giving it a second thought.

Boman argues that the healthcare system is derelict when it comes to both continuity and information sharing.

– If I'm going to make a wise decision about discontinuing or going ahead with treatment that was ordered by another caregiver, I need access to certain basic facts – otherwise I'm out in the dark when it comes to weighing the benefits against the risks.

– But communication among various healthcare professionals often breaks down.

RELUCTANCE TO STOP

Boman points out that when a patient has a number of different caregivers, the responsibility of reconsidering treatment easily falls between the cracks. A general practitioner might be reluctant to discontinue treatment ordered by an internist, and vice versa.

– In a worst case scenario, it's like an orchestra of soloists without a director to pull it all together, says Boman. All you hear is cacophony of specialists each doing their own thing.

Many caregivers are understandably hesitant to re-examine an approach that holds out the potential of helping the patient.

– Of course, ordering a particular treatment is accompanied by a generous portion of hope, says Boman. The doctor has got to believe that the patient truly stands to benefit.

A RISKY ENDEAVOR

– So it's perfectly logical that discontinuing such treatment may appear to be a risky endeavor. Charging ahead is the path of least resistance.

– There's an unfortunate tendency to reconsider a particular medication only when palpable side-effects or clear contraindications show up. Sometimes a caregiver is scared away by the time and effort required to discontinue treatment.

– For instance, the patient or family may object, says Boman. In that case, you've got no choice but to sit down and talk it over with them.

– Once treatment ends, the placebo effect is gone as well. A patient who improved in the initial stages may expect a deterioration at this point.

– And that can become a self-fulfilling prophecy.

Patrick Degerman

PHASE IT OUT

Some medications need to be phased out according to a special timetable. The patient may experience a rebound effect, the return of the symptom being treated when the dosage is decreased, particularly if suddenly discontinued. That poses a challenge to both doctor and patient – as well as their ability to communicate with each other.

Faced with such obstacles, treatment may be extended even though it is doing more harm than good, not to mention squandering valuable resources.

– All treatment should be reconsidered at least once a year, concludes Boman. One of the doctor's responsibilities is to make it clear in the case notes just how long the treatment is supposed to last and who is to keep track of its effectiveness.

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Dividing Up Findings Can Mislead

Study findings may become unreliable if researchers divide up the test subjects into subgroups and compare them retrospectively. The greater the number of subgroups, the larger the risk of statistically significant differences that are due to chance only.

Research findings are often broken down according to subgroups of test subjects. Sometimes that's done retrospectively in order to determine whether any particular category of patients responded differently than the others.

Age and gender are just two of the many criteria that, in varying combinations, may form the basis of such a breakdown.

But as the number of subgroup analyses increases, so does the risk of statistically significant results that are purely random in origin. For instance, more than 30 such analyses of the same evidence raises the probability to over 80 percent that at least one of them will show a statistically significant difference ($p<0.05$).

Small subgroups give rise to another problem. Researchers calculate the requirements for a study to have sufficient statistical power before it starts. They figure out how many subjects

Corbis

are needed in order to demonstrate a difference of a particular magnitude among the experimental groups with a certain statistical power and at a certain level of statistical significance.

RELEVANT TO PROVE

In addition to the specified power, the input to the calculation includes the desired level of statistical significance, the presumed variability of the findings and the expected difference – or the smallest difference deemed relevant to prove – among the groups. The bottom line is the number of participants required to ensure that those criteria are met.

If the power calculation concerns the study as a whole, analyses of smaller subgroups have insufficient statistical power. Two difficulties emerge as a result. First, genuine differences among the subgroups cannot be corroborated statistically. Second, statistically significant differences that stem wholly from chance may arise.

If the researchers feel that differences among subgroups are worth examining, the power calculation must be based on the size of these subgroups. More subjects must participate in the study than would otherwise be the case.

EXERCISE RESTRAINT

A rule of thumb is to exercise restraint in analyzing subgroups and not make all too much of the findings. The examples of misleading conclusions as a result of such analyses are legion.

In discussing this very problem, Assmann et al reported that 35 of 50 articles presenting clinical research findings from the summer of 1997 included a subgroup analysis. A difference among subgroups appeared in 21 of them, while 13 brought that fact up in their abstract or conclusions. Most of the articles assigned unwarranted importance to the results of subgroup analyses.

STRIKING ILLUSTRATION

The subgroup analyses that were performed following the ISIS-2 study provide a striking illustration of differences that can arise by chance. The study concerned the efficacy of aspirin after acute myocardial infarction.

When the subjects were divided up according to their astrological birth signs, aspirin turned out to improve survival rates for everyone except Libras and Geminis. No great stretch of the imagination is required to see the hand of chance here. If the categories had had a real medical basis, pinning down

HOW STUDIES CAN USE AND INTERPRET SUBGROUPS

- Generally speaking, subgroup analyses should be performed only if they were designed before data compilation began. Any such analyses performed retrospectively should be clearly identified.
- The power calculation should consider all the subgroups on which the researchers plan to report separately. Shooting for so many subjects that even weak correlations among the subgroups can be demonstrated is not a realistic approach.
- Subgroup analyses performed retrospectively on selected results are singularly inappropriate. Such analyses must always be based on a statistical test of the interaction between the findings and a group. If the outcome of the test is positive, there is good reason to examine the differences among the groups in greater detail.
- Don't exaggerate the importance of findings about subgroups. Even when the conclusions are strongly corroborated, viewing the results as the basis for new hypotheses is the better part of wisdom. Be especially on your guard when results suggest that the treatment works for one subgroup only.

Freely adapted from Brookes ST, et al. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technology Assessment. 2001;5(33).

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the unreliability of the results would have been much harder. The article to the right offers more examples of erroneous conclusions.

The National Coordinating Centre for Health Technology Assessment in the UK published a report on subgroup analyses in randomized trials. The report indicated that any subgroup analyses should be planned when designing the study so that the number of test subjects may be adjusted accordingly. Such analyses can often form the basis of hypotheses that are testable by subsequent studies. Even so, all conclusions must be drawn with a great deal of caution.

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Divided Data Yielded Misleading Results

Dividing up a study population into subgroups can lead to misleading results. But it can't always be avoided.

Healthcare practitioners and theoreticians often have a different take on things. For instance, they may not see eye to eye when it comes to assessing a study's findings with respect to various subgroups of test subjects. While statisticians are concerned about the risk of spurious conclusions, clinicians are anxious to pinpoint the influence of age and other factors.

A recent article in The Lancet argues that both approaches make sense. Peter Rothwell, the author, stresses the importance of applying such analyses sparingly. Nevertheless, they are particularly useful when significant differences among the subgroups are likely, practical issues involving indications are at stake or the value of the treatment for a specific group has been called into question.

Rothwell proposes a series of rules for planning, implementing and reporting on subgroup analyses. The examples in the box below make it clear that the results must be interpreted with care.

EXAMPLES OF ERRONEOUS CONCLUSIONS

- Aspirin is an ineffective way of preventing stroke recurrence in women.
- Blood pressure treatment does not provide primary prevention in women.
- Blood pressure treatment is ineffective or harmful in the elderly.
- ACE inhibitors do not reduce mortality or hospitalization in heart failure patients who are taking aspirin.
- Beta blockers are ineffective following myocardial infarction in the elderly and patients with inferior infarction.
- Thrombolysis becomes ineffective six months after acute myocardial infarction.
- Thrombolysis for acute myocardial infarction is ineffective or harmful in patients with previous infarction.
- Tamoxifen is ineffective for breast cancer in women under 50.
- Due to the greater risks involved, the benefit of carotid surgery for symptomatic stenosis is less with patients who take aspirin in low doses only.
- Amlodipine reduces mortality in patients with chronic heart failure due to nonischemic cardiomyopathy but not in patients with ischemic cardiomyopathy.

Based on Rothwell PM. The Lancet 2005; 365: 176-86.

Anders Norderman

Health Technology from an Ethical Viewpoint

All health care, not only controversial measures like euthanasia and genetic screening, is value-laden. That's why ethical analysis should be an integral part of health technology assessment, says moral philosopher Björn Hofmann.

Björn Hofmann describes medicine as Janus-faced. An issue that appears at first glance to be strictly medical may call for profound moral reflection about what constitutes the good life and the role of health care in promoting it.

A researcher at the Oslo University Center for Medical Ethics, Hofmann argues that the prevailing view of medical technology as value neutral is oversimplified.

– New diagnostic and treatment procedures are changing our attitudes about what constitutes disease, what diagnoses should be sought and what should be treated, Hoffman says. Technological advances are constantly reshaping our values and expectations.

The orthodontic concept of an "ideal bite" illustrates this dynamic. The mere existence of various methods for straightening crooked teeth has sent many patients and dental professionals scurrying for a way of correcting imperfect alignment even when the bite is unaffected.

According to Hofmann, the fact that all treatment aims to help people automatically raises moral issues.

– The values on which a particular medical procedure is based aren't necessarily controversial, he says. But unless we are up front about what they are, it's impossible to take an informed position.

– That's exactly why an ethical assessment is needed. Once we have identified the principles that are at stake, we can make more prudent decisions.

MORE THAN EFFICIENCY

– The adoption of new technologies entails more than just efficiency, Hofmann points out. And their consequences extend beyond the health arena. An ethical frame of mind can bring out the different considerations involved.

The moral philosophers who appear in the media love to debate spectacular treatments – everything from fetal surgery to genetic engineering – that beg for ethical stances.

But Hofmann maintains that even more modest innovations can shake up our notions of what is desirable. For instance, the various options for treating high blood pressure have changed our view of what constitutes a healthy level.

– In addition, both diagnosis and treatment often occupy the gray area between health and sickness, says Hofmann. That in itself opens an ethical can of worms.

Hofmann is critical of the tendency to regard medical ethics as a peripheral or academic exercise. Frequently it's just the opposite.

– Of course, it's always possible to take health technologies so much for granted that you overlook the judgments on which they are based, Hofmann points out. Nevertheless, value neutral health care is nothing but a myth.

ETHICAL CHALLENGE

– Actually, every decision to start on a particular treatment or refrain from doing so has ethical repercussions, says Hofmann. The issues extend from practical considerations, such as autonomy and the allocation of resources, to the larger questions of good and bad, as well the degree of trust that the public places in the healthcare system. Our concept of health and illness, including the measures we choose for promoting wellness and warding off disease, involves a distinction between good and bad states. And the fact that many of those treatments have not yet been assessed poses its own ethical challenge.

TENDS TO EXCLUDE

Hofmann readily concedes that the vocabulary of ethicists occasionally tends to exclude rather than speak to the people who are directly affected.

– On the contrary, medical ethics address everyday problems that demand concrete answers, he says. Such problems concern not only caregivers, but policymakers and each of us who some day will be a patient or deal with a loved one confronted by difficult healthcare choices.

Pressens Bild

KEY ETHICAL ISSUES

PROBABILITIES
What are the potential risks, opportunities, effects and side-effects of a particular treatment? What is the likelihood that the patient's health and quality of life will improve? How does the patient feel about it? For instance, the percentage of false positive and false negative results might be a moral consideration due to the nature of the diagnostic method. How does the patient weigh the various risks against each other?

HUMAN RIGHTS
Does a treatment infringe on the patient's ability to make their own decisions? Is their privacy or dignity at stake? Does going through with the treatment necessitate sidestepping basic human rights?

EXPECTATIONS
Will use of the treatment spawn greater expectations? Can they be met? For instance, a new diagnostic method may make the patient more hopeful that a truly effective remedy can be found.

SOCIAL STATUS
Will the treatment influence society's view of a particular disease? How about the patient's reputation, social status or self-image? Does the treatment have any positive or negative symbolic significance?

OUTLOOK ON LIFE
Does the treatment conflict with any religious, political or cultural values? For instance, a particular type of contraception may be unacceptable to certain religious denominations.

LEGAL CONSIDERATIONS
Does the treatment violate the law in some way? Is a legislative change required? For instance, recently discovered procedures for fetal diagnosis and stem cell therapy have led many countries to pass new laws.

RESPONSIBILITIES
Does a treatment alter the relative responsibility of the patient and the healthcare system? What is the impact on the indications for treatment? How about the doctor–patient relationship? For instance, a simple and inexpensive new method may heighten the risk of medicalization, overdiagnosis and overtreatment.

RESOURCE ALLOCATION
Will a treatment affect the general public's access to medical care or the allocation of healthcare resources? Who stands to gain or lose? Is that consistent with generally accepted standards for a just distribution of wealth?

PROFESSIONAL ETHICS
What impact does the treatment have on the caregiver's options and ability to perform their duties in accordance with prevailing professional ethics? Does it make any difference in terms of how they view their professional identity?

THIRD PARTIES
What is the effect on third parties, such as donors, family members, other relatives (when diagnosing hereditary conditions) and surrogate parents?

SPECIAL INTERESTS
Would the use or assessment of the treatment serve the special interests of researchers, policymakers, innovators or manufacturers?

Freely adapted from Hofmann B. Toward a treatment for integrating moral issues in health technology assessment. Int. J Technol Assess Health Care 2005; 21: 312–8.

Recent SBU Findings

Dementia

According to SBU's systematic review of various measures for diagnosing and treating dementia, diagnosis can be structured more effectively by means of standardized interviews with family members and similar approaches.

Current treatment is primarily an attempt to suppress development of symptoms. None of the present methods are able to cure dementia disorders. The SBU report shows that drugs offer some benefits for people with mild or moderate Alzheimer's disease, but their effectiveness must be monitored and reviewed for each individual patient.

The report also stresses that caregivers must receive better training if care and treatment of everyone with dementia is to work as it should. Municipalities are responsible for most dementia care in Sweden.

The foundation of satisfactory care is an ethical approach. For that to happen, family members and the municipality's caregivers need both support and sufficient knowledge about dementia disorders. For example, more training is required in how to handle people with severe dementia who have lost the ability to express themselves in a normal manner. One job of the caregiver is to understand and deal with that kind of situation. Not until people with dementia are treated as competent individuals will their remaining abilities be truly visible.

Ronnie Kaufman/Scanpix

No methods currently exist for detecting dementia disorders at an early stage. SBU's systematic review finds that the tests given today often lead to false alarms unless preceded by a clinical examination. Considering that treatment options are still very limited, there is no scientific basis for mass screening of the general population. For the time being, the best idea is to help patients and family members when they seek care.

Moderate scientific evidence exists for treating Alzheimer's patients with a class of drugs referred to as cholinesterase inhibitors. One-year studies have demonstrated that the drugs lead to some improvement of cognitive and physical functioning in people with mild to moderate Alzheimer's disease. But many of the patients suffer adverse effects such as nausea and dizziness. A drug called memantine has been shown to be similarly effective in patients with more severe Alzheimer's disease.

How the effectiveness of the various drugs stacks up against the associated costs cannot currently be assessed. The same is true with respect to individual treatment programs.

The report also emphasizes that certain drugs have been shown to be unsuitable for dementia disorders given that they disrupt cognitive functioning. Benzodiazepines, as well as older drugs for psychosis and depression, belong in that category.

Some evidence also exists that certain newer drugs for psychosis – referred to as atypical antipsychotics – that have been tried for behavioral symptoms in dementia patients may lead to increased mortality.

Some 140 000 Swedes currently have a dementia disorder, a figure that is expected to rise to 210 000 in 25 years. Dementia already costs Swedish society SEK 40 billion annually. The SBU

report points out that most of the costs are borne by the municipalities and that resources for dementia care should be allocated with that in mind. **JAN 2006**

Treatment of Chronic Pain

Pain is ordinarily referred to as chronic when it lasts for three months or longer. If there is a specific cause, it should be the focus of treatment. But particularly when the cause eludes treatment, approaches to relieving pain itself are often needed.

Treatment programs that combine several methods relieve pain and reduce sick leave more effectively than individual, less comprehensive approaches, concludes SBU's systematic review. Coordinated, interprofessional, intensive and active rehabilitation produces better results than isolated methods – such as medication – that do not call for the patient to play an active role.

The broad-based, coordinated treatment programs that have shown to be effective are referred to as multimodal rehabilitation. The programs may involve both psychological approaches – such as cognitive behavioral therapy or other treatment that alters behavior – and structured physical training or physical therapy. Patient education is included as well.

Patients with pain in their muscular and skeletal systems who are offered both psychological approaches and treatment that improves physical functioning have shorter periods of sick leave than those who receive one kind of treatment only. There is strong scientific evidence that multimodal rehabilitation is effective in many patients.

The SBU report also concludes that active, specific training led by a healthcare professional is more effective in relieving chronic pain as the result of tissue damage than treatments such as massage or ultrasound that do not actively involve the patient. Because improvement is short-term only, the training must proceed on a continual basis. Training is even more effective when combined with behavioral therapy.

The report also stresses that chronic pain is not the same as acute pain that lasts for an extended period of time. For instance, chronic pain changes the painful tissues, as well as the neural pathways that transmit pain impulses. It often gives rise to other symptoms, restrictions and difficulties in daily life as well. For that reason, chronic pain frequently necessitates the same kind of treatment regardless of cause.

The road to effective pain treatment is often a long one. Many patients try both active measures and medication. Chronic pain and unsuccessful attempts at treatment also have social and psychological consequences for the patient, including a sense of powerlessness and loss of dignity. Nevertheless, a diagnosis or explanation of the pain can make it easier to bear.

Many chronic pain patients are on sick leave. Chronic pain is estimated to cost Swedish society SEK 7.5 billion a year for direct care and SEK 80 billion for the indirect repercussions, primarily related to sick leave and loss of production. **MARCH 2006**

Robert Walker/Getty

Violence Risk Assessment in Psychiatry

Psychiatric risk assessment methods are more accurate than chance in predicting the propensity of male patients to commit future acts of violence in the community. Evidence is lacking that the methods provide reliable results for female patients.

The accuracy of risk assessments may be defined as the percentage of patients who are correctly identified as subsequently committing acts of violence. According to the best studies conducted thus far, the accuracy can be expected to be no higher than 70–75 percent.

Risk assessments can predict the propensity of relevant forensic and general psychiatric patients to commit acts of violence in the community for the next few years. However, there is insufficient scientific evidence to support more short-term risk assessments, ie, for the days and weeks

after a patient has left the clinic.

Both clinical evaluations and checklists of predefined instruments may be used in making risk assessments. The validity of the Violence Risk Appraisal Guide (VRAG) and the Historical Clinical and Risk Management Scheme (HCR-20), the two most widely used instruments, have not been shown to differ substantially. The uncertainty (inaccuracy) of forecasts based on instrumentalized assessments is at least 25–30 percent, ie, one out of every three or four patients is evaluated incorrectly. **OCT 2005**

Treatment of Anxiety Disorders

The assessment covers treatment of panic disorder, specific phobias, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD).

For each of these conditions, one or more treatments have proven to be effective. With the exception of specific phobias, both pharmacological treatment and psychotherapy are moderately effective. The symptoms are alleviated, but full remission is rarely achieved. With a few exceptions, the symptoms recur once treatment has been completed.

For adults, scientific evidence supports the use of paroxetine and sertraline for all syndromes except specific phobias. For the other SSRIs there is also evidence for the use of fluoxetine in OCD and PTSD, for fluvoxamine in social phobia and OCD, and for escitalopram in social phobia.

Other antidepressant drugs with strong scientific support are venlafaxine in social phobia and GAD, imipramine in panic syndrome and chlomipramine in panic syndrome and OCD.

Among psychological treatments, there is scientific evidence supporting cognitive behavior therapy for panic syndrome, specific phobias, social phobia, PTSD and GAD. Exposure, with or without other psychotherapeutic interventions, has scientific support for efficacy in panic disorder (in terms of the number of panic attacks and for agoraphobia), specific phobias, OCD and PTSD. Studies of psychodynamic therapies are almost totally lacking.

Use of eye movement desensitization and reprocessing (EMDR) has scientific support for the treatment of PTSD.

There is insufficient scientific evidence for comparing either the efficacy or cost effectiveness of different treatments. **SEPT 2005**

Dialectical Behavioral Therapy in Borderline Personality Disorder

Dialectical behavioral therapy (DBT) is an extensive and advanced form of cognitive behavioral therapy (CBT) that was developed specifically for chronically suicide-prone patients with borderline personality disorder. Borderline personality disorder is characterized by a consistent pattern of instability in controlling feelings, deficiency in controlling impulses, problems with relationships and poor self-esteem. In a clinical context, the disorder is expressed as difficulties in managing feelings, impulsive actions and aggressiveness, repeated episodes of self-inflicted injury and suicide attempts.

There is limited scientific evidence showing that Dialectical Behavioral Therapy (DBT) reduces self-injurious behavior and that the effect remains at 2-year followup. Treatment also appears to reduce the need for hospitalization and reduce drug use among people with addictions. Thus, DBT appears to be a promising form of treatment for patients with borderline personality disorder. However, it needs to be tested under Swedish conditions, and it is essential to conduct studies addressing the cost effectiveness of the method. **OCT 2005**

Björn Dawidsson/Bildhuset

Malocclusions and Orthodontic Treatment in a Health Perspective

One in four Swedish children and adolescents receive orthodontic treatment, a part of the general dental care for children and adolescent that is free of charge for patients up to 20 years of age. However, decisions regarding who should receive orthodontic treatment are not based on solid scientific evidence. There is insufficient evidence regarding the validity of morphological indices that are used for such treatment decisions.

Current evidence only partially clarifies the health benefits of orthodontic treatment. The prevalence of caries in people with occlusal deviations is the same as in those whose bite is normal. No correlation between moderate malocclusions and negative effects on the self-image of 11–14-year olds has been found. However, adults with untreated malocclusions express more dissatisfaction with the appearance of their bite than adults without malocclusions.

Scientific evidence is insufficient for conclusions on a correlation between specific untreated malocclusions and symptomatic temporomandibular joint disorders. Studies indicate that when the patient has a large overjet and the upper lip does not protect the front teeth, the incidence of trauma to the anterior teeth of the maxilla is higher. Also, if the maxillary canines are incorrectly positioned in the jaw bone before their eruption, there is an increased risk that they will damage the roots of the front teeth as they emerge.

Clinical practice and costs for orthodontic treatment vary considerably. Orthodontic treatment is initiated in most cases by the general dental practitioner. The appearance of the teeth is the patient's most important reason for seeking orthodontic treatment. Orthodontic treatment can also be performed on adults, but it is not free of charge. **OCT 2005**

Corbis

Therapeutic Hypothermia after Cardiac Arrest

Sudden cardiac arrest is not uncommon as a complication of coronary heart disease (ischemic heart disease). Most cases of cardiac arrest occur outside of the hospital. In Sweden, approximately 10 000 people per year experience cardiac arrest. Treatment outcomes among this patient group have not improved substantially in the past 20 years. Only 4 percent of those affected are discharged alive from the hospital following cardiopulmonary resuscitation and treatment. The outcome of treatment depends partly on the time that has elapsed between cardiac arrest and the reestablishment of stable circulation. Most patients who are resuscitated from cardiac arrest are unconscious and require care at an intensive care unit. Lowering the body temperature (induced hypothermia) after resuscitation from cardiac arrest is a treatment method intended to limit the damage, mainly to the brain, that occurs when blood circulation ceases. Body temperature is lowered to 89.6– 93.2 degrees, which usually requires sedation of the patient, administration of muscle relaxants, and the subsequent use of ventilator treatment.

In Sweden, an estimated 1 300 people per year are admitted to hospital alive following resuscitation from cardiac arrest. The potential target group for therapeutic hypothermia includes people who are unconscious after resuscitation from cardiac arrest and whose condition would suggest a risk for tissue damage due to oxygen deficiency. Most would be patients with coronary heart disease. Criteria have not been established for selecting patients for therapeutic hypothermia, so the size of the potential target group for this treatment method cannot be estimated.

SBU's assessment is based on a systematic literature review. The scientific evidence is insufficient to show that treatment with induced hypothermia after resuscitation from cardiac arrest improves survival or lowers the risk of permanent functional impairment. Although the scientific evidence is too weak to support reliable conclusions, the method appears to be promising and of potential clinical importance. However, it is essential to continue testing this method in Sweden under scientifically acceptable conditions so that


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its benefits, risks, and cost effectiveness can be assessed. Until adequate scientific evidence is available, therapeutic hypothermia should be used only within the framework of well-designed, prospective, and controlled trials, SBU concludes. **FEB 2006**

Scalp Cooling to Prevent Chemotherapy-Induced Hair Loss

Hair loss, a side effect of some types of chemotherapy, is a very negative experience for some patients. Scalp hypothermia (scalp cooling) is one approach used to prevent hair loss. The most common types of scalp hypothermia involve the use of either a pre-cooled cap or a cooling system that continuously cools a cap. Cooling must be started approximately 30 minutes prior to chemotherapy and must continue for 30 to 90 minutes after the conclusion of treatment. The target group for scalp hypothermia is estimated to be at least 2 000 patients per year, ie, patients with metastatic cancer who receive the types of chemotherapy associated with a high risk of hair loss.

According to SBU's systematic literature review, several studies, most of which included a very small number of patients, found that scalp hypothermia helped prevent chemotherapy-induced hair loss. Several different types of chemotherapy, in various combinations, were studied. Different degrees of hypothermia were used, and different assessment criteria were applied. The percentage of patients in the study group who were able to keep their hair ranged from 10 percent to 100 percent, while the corresponding figures in the control group ranged between 0 percent and 19 percent.

Apprehension about increased risk for scalp metastases has restricted the use of the method. This risk appears to be small, but the evidence is limited. Theoretically, the method could create a reservoir in the cooled scalp where circulating cancer cells might avoid the effects of chemotherapy. The magnitude of this risk is unknown since patients in the studies have not been followed up for a sufficient period to make this determination. Although the method causes some discomfort to the patient, most patients accept this in order to avoid hair loss.

The costs of scalp hypothermia are comprised of equipment costs, particularly devices for continuous hypothermia, and costs related to additional working hours and longer treatment sessions. No studies were identified that addressed the cost effectiveness of the method.

SBU concludes that there is moderately strong scientific evidence that scalp hypothermia reduces the extent of hair loss when treating solid tumors with various non-taxane chemotherapies alone or in combination. There is limited scientific evidence showing that the method also reduces the extent of hair loss in taxane or taxane-based combination chemotherapy. There is no scientific documentation on the cost effectiveness of the method. Further studies of patient benefit, risks, and cost effectiveness are needed. **JUNE 2005**

Elective Replacement of PIC to Prevent Thrombophlebitis

A peripheral intravenous catheter (PIC) is a thin tube that is inserted via a cannula into a vein, usually in the hand or arm. PIC insertion is a common procedure used in health care to administer fluids, nutrients, blood products, and medications to patients. A complication related to the use of PIC is the development of thrombophlebitis, ie, a concurrent inflammation and blood clot in a peripheral vein. A positive correlation has been found between the indwelling time of a catheter and the risk for developing thrombophlebitis. Hence, one hypothesis is that thrombophlebitis rates can be reduced if catheters are replaced at regular intervals. The target group for this method includes all patients in need of peripheral intravenous catheters.

According to SBU's review, findings from three randomized controlled trials suggest that elective replacement of peripheral intravenous catheters can reduce the risk and severity of thrombophlebitis.

Full Reports at www.sbu.se

The intervals between replacement of PICs vary between 12 and 48 hours. However, the trials are small and offer limited scientific evidence.

In Sweden, 5 million peripheral intravenous catheters are used annually at a cost of about SEK 50 million. The PIC replacement interval influences the number of PICs consumed, and thus the costs for this method. No studies were identified that thoroughly investigated the cost of elective replacement of peripheral intravenous catheters in relation to complications.

SBU concludes that there is limited scientific evidence that elective replacement of peripheral intravenous catheters reduces the incidence and the severity of thrombophlebitis. The appropriate intervals for PIC replacement have not been adequately assessed. No scientific studies have investigated the cost effectiveness of this method. **JUNE 2005**

Manual Lymph Drainage & Compression for Arm Lymphedema

Arm lymphedema is a common complication following breast cancer treatment. The condition increases arm volume, causes a sensation of heaviness and tightness, as well as pain and impaired mobility in some patients. Over time, the increase in fat volume results in tissue changes, making lymphedema increasingly difficult to treat. Treatment should be started during the phase when patients experience a sensation of tightness, increased tissue consistency and a minor increase in arm volume. The greatest risk for developing arm lymphedema (40–75 percent) is found in patients who have undergone procedures to remove lymph nodes in the armpit and have received radiation therapy in this area. It is primarily this group that should be followed up regularly for early detection of lymphedema. Compression has been found to yield good effects and comprises standard treatment for lymphedema. Compression can be achieved by using an elastic sleeve or by bandaging. To further enhance the effects of treatment, some attempts have been made to combine compression therapy with manual lymph drainage, ie, a type of gentle massage of the skin intended to stimulate lymph flow.

A rough estimate is that approximately 800 new cases of lymphedema following breast cancer treatment are detected annually in Sweden. Approximately 4 000 to 6 000 people in Sweden are estimated to have this diagnosis.

Three relatively small randomized controlled trials have studied manual lymph drainage combined with compression treatment for arm lymphedema. In each of these studies, edema volume and symptoms decreased in both the study and control groups. Two of the studies, in followup directly after they ended, showed statistically significant differences in the reduction of edema and symptoms that favored the group on combined treatment with manual lymph drainage. However, the third study did not show a statistically significant difference between the groups, in either reduced edema or reduced symptoms. Furthermore, the results of several case studies (including over 400 patients) clearly show that treatment with compression bandaging and manual lymph drainage had a volume-reducing effect. However, the design of these studies does not offer the opportunity to investigate the extent to which combined treatment with manual lymph drainage contributed to the reduction in lymphedema.

A few patients with various types of tissue-related pain may find it difficult to tolerate the discomfort associated with compression therapy. Combined treatment with manual lymph drainage has not been shown to cause additional complications.

The extra cost of adding manual lymph drainage is estimated at approximately SEK 4 000 per treatment cycle, ie, an average of 5–10 treatments for 1–2 weeks. No studies were identified that addressed the cost effectiveness of combined therapy for arm lymphedema.

According to the SBU review, evidence suggests that treatment involving a combination of compression therapy and manual lymph drainage yields reduced edema volume compared to compression therapy alone if volume is measured directly after the conclusion of manual lymph drainage. There is no evidence to show that this effect is permanent. Further randomized controlled trials of sufficient size should be conducted – where treatment effects could be studied more closely in both the short and long term – before a combination of compression therapy and manual lymph drainage can be recommended. Future studies should give particular consideration to the magnitude of lymphedema, given that some studies suggest that early treatment for minor lymphedema may have greater effects and permanent results. Furthermore, the costs for combined therapy should be calculated and studied in relation to the potential health benefits for patients. **MARCH 2005**

Dr P. Marazzi/Science Photo Library

Aromatase Inhibitors in Breast Cancer

Early stages of breast cancer are treated surgically. Various types of adjuvant therapy may also be prescribed, such as hormonal agents. Despite adjuvant hormonal therapy, approximately 13 percent of patients experience a relapse of breast cancer within 5 years. At recurrence, progress to advanced breast cancer, ie, metastasis beyond the mammary gland and regional lymph nodes, is most often the case.

To determine whether a patient can potentially benefit from hormonal therapy, an investigation is conducted to assess whether the tumors are receptor positive, ie, express estrogen and/or progesterone receptors. Approximately 70 percent of breast cancer tumors are receptor positive. Estrogen has the main stimulating effect on tumor growth. When hormone production in the ovaries ceases after menopause, estrogen is produced mainly through hormonal conversion in peripheral tissue exerted by the enzyme aromatase. The administration of drugs acting as inhibitors of this enzyme reduces estrogen production, resulting in lower estrogen levels.

Advanced disease: Three randomized studies, including slightly over 1 800 patients in total, have compared aromatase inhibitors as first-line therapy for advanced breast cancer versus antiestrogen therapy (tamoxifen). Results from two of the studies have shown that the time to disease progress was 3–5 months longer in the group treated with aromatase inhibitors. However, the third study reported no difference.

Adjuvant therapy: A randomized study of slightly more than 9 000 women, which compared aromatase inhibiting therapy (anastrozole) to tamoxifen therapy, showed after 68 months of followup that the group treated with anastrozole experienced 18.4 percent recurrence, compared to 20.9 percent recurrence in the group treated with tamoxifen. These results provided a basis for approving anastrozole for adjuvant therapy in postmenopausal women with estrogen-receptor-positive breast cancer. A study that compared the aromatase inhibitor exemestane against tamoxifen showed results favoring the study group after 3 years of followup. Furthermore, a study that randomized just over 5 000 patients, after 5 years of tamoxifen therapy, to treatment with the aromatase inhibitor letrozole versus placebo showed an improvement in disease-free survival for the aromatase inhibitor treatment group. It is too early to assess the effects on overall survival, given that these studies have not yet recorded a sufficient number of events (deaths).

The most common side effects associated with aromatase inhibitors are hot flushes, nausea, and genital dryness. Given the short followup times to date, fewer side effects have been reported with aromatase inhibitors than with tamoxifen, such as reduced risk of thromboembolic complications. However, adjuvant treatment with aromatase inhibitors affects bone mineral density and is associated with a higher incidence of fractures. Followup regarding long-term skeletal effects needs to be continued.

Image Source/Matton

The drug cost for aromatase inhibiting therapy is approximately SEK 14 000 annually, versus slightly over SEK 1 000 for tamoxifen. Shifting from tamoxifen to aromatase inhibitors would increase the annual cost in Sweden by approximately SEK 8 million for treating advanced disease and by slightly over SEK 100 million for adjuvant therapy.

Several cost effectiveness studies based on economic models have addressed the use of aromatase inhibiting drugs as first-line therapy in advanced breast cancer. Overall, they show that using aromatase inhibitors leads to a moderate increase in the cost per life-year gained compared with antiestrogen drugs. In one model study, the cost per life-year gained by adjuvant therapy with anastrozole was estimated at approximately SEK 300 000 based on calculations of 20 years and SEK 8.2 million based on calculations of 4 years. Little is known about the effects of treatment on future medical care consumption and survival, due to the short followup times in the studies from which the clinical data have been obtained. Thus, reliable conclusions cannot be drawn from these model analyses.

SBU concludes that in advanced disease, aromatase inhibitors as first-line therapy have been shown to extend the time to disease progression. Adjuvant therapy with aromatase inhibitors has been shown to reduce the risk of recurrence after followup of approximately 5 years. No scientific evidence is yet available on long-term effects concerning survival and side effects (beyond 5 years). Only limited evidence is available on the cost effectiveness of using aromatase inhibitors.

MARCH 2005

Creating New Patients

Disease mongering turns healthy people into patients, wastes precious resources, and causes iatrogenic harm, according to David Henry, professor of clinical pharmacology.

Photonica /Johnér

Three decades ago, Ivan Illich argued polemically that the medical establishment was "medicalizing" life itself, and in the 1990s, Lynn Payer described widening the boundaries of illness as "disease mongering".

In the following years, observers have described different forms of disease mongering: aspects of ordinary life, such as menopause, being medicalized; mild problems portrayed as serious illnesses, as has occurred in the drug company-sponsored promotion of irritable bowel syndrome, and risk factors, such as high cholesterol and osteoporosis, being framed as diseases.

INFORMAL ALLIANCES

Drug companies are by no means the only players in this drama. Through the work of investigative journalists, we have learned how informal alliances of pharmaceutical corporations, public relations companies, doctors' groups, and patient advocates promote these ideas to the public and policymakers – often using mass media to push a certain view of a particular health problem. While these different stakeholders may come to these alliances with different motives, there is often a confluence of interests – resulting in health problems routinely being framed as widespread, severe, and treatable with pills, as has happened recently with social anxiety disorder. These alliances are currently working with the media to popularize little-known conditions, such as restless legs syndrome and female sexual dysfunction, in each case lending credence to inflated prevalence estimates.

Many of the "disease-awareness" campaigns that inform our contemporary understanding of illness – whether as citizens, journalists, health professionals, industry leaders, academics, or policymakers – are now underwritten by the marketing departments of large drug companies rather than by organizations with a primary interest in public health.

PERCEIVED WEAKNESS

This is happening at a time when pharmaceutical companies perceive a need to build and maintain markets for their big-selling products and when pipelines for new and genuinely innovative medicines are perceived as being weak.

A number of individuals will benefit greatly from treatment and may be helped enormously by the publicity and marketing given to both the treatment and the disorder. The same marketing/awareness-raising campaign will be viewed very differently depending on the perspective of the observer: what an industry-linked professional group may consider to be legitimate public education about an underdiagnosed disease, an activist group free from industry sponsorship may regard as a crude attempt to build markets for potentially dangerous drugs.

GLOBAL CHALLENGE

Whatever perspective is taken, disease mongering poses a global challenge to those interested in public health, demanding in turn a global response. Until a rigorous research agenda is initiated, and the social renovations and policy reforms that research might inform are enacted and evaluated, our beliefs, like those advocating corporate-sponsored disease-awareness campaigns, will remain based more on opinion than evidence. It is time for further scientific exploration of disease mongering.

David Henry
Professor of clinical pharmacology, University of Newcastle, Australia

This article is based on Moynihan R, Henry D (2006). The Fight against Disease Mongering: Generating Knowledge for Action. PLoS Med 3(4): e191.

SOME CURRENT SBU PROJECTS

BENIGN PROSTATIC HYPERTROPHY
Contact: freyschuss@sbu.se
Expected publ: 2009

COMPUTER-ASSISTED EDUCATION & IMPAIRED MENTAL FUNCTION
Contact: tornqvist@sbu.se
Expected publ: Summer 2006

DENTAL CARIES
Contact: axelsson@sbu.se
Expected publ: Fall 2007

DYSPEPSIA (UPDATE)
Contact: norlund@sbu.se
Expected publ: Fall 2006

EARLY FETAL DIAGNOSIS
Contact: alton@sbu.se
Expected publ: Fall 2006

GLAUCOMA
Contact: eckerlund@sbu.se
Expected publ: Spring 2007

MEDICATION IN OLD AGE
Contact: sawe@sbu.se
Expected publ: Fall 2007

MILD HEAD INJURY
Contact: geijerstam@sbu.se
Expected publ: Fall 2006

MYRINGOTOMY FOR OTITIS MEDIA
Contact: pettersson@sbu.se
Expected publ: Fall 2007

NEW IMMUNOMODULATORY DRUGS FOR PSORIASIS
Contact: freyschuss@sbu.se
Expected publ: Summer 2006

NIDCAP FOR PRETERM INFANTS
Contact: tornqvist@sbu.se
Expected publ: Summer 2006

NITRIC OXIDE MONITORING IN ASTHMA MANAGEMENT
Contact: freyschuss@sbu.se
Expected publ: Fall 2006

PERCUTANEOUS VERTEBROPLASTY FOR BACK PAIN
Contact: freyschuss@sbu.se
Expected publ: Fall 2006

PERIPHERAL ARTERIAL DISEASE
Contact: sawe@sbu.se
Expected publ: Spring 2007

PROMOTION OF PHYSICAL ACTIVITY
Contact: eckerlund@sbu.se
Expected publ: Fall 2006

PROPHYLACTIC TREATMENT WITH ANTIBIOTICS
Contact: axelsson@sbu.se
Expected publ: Fall 2008

REFRACTIVE EYE SURGERY
Contact: eckerlund@sbu.se
Expected publ: Spring 2007

SLEEP APNEA
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