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Colofon

Erasmus Journal of Medicine is a scientific magazine by and for students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the medical students' organization of Erasmus MC). The journal appears twice a year. It will be published on paper (2000 copies) and on the EJM website.

The journal contains papers describing original research (Full articles), systematic reviews (Reviews), summaries of recently conducted studies (Extended abstracts), short descriptions of research projects looking for students to participate (Research News), opinion papers written by students (Opinions), editorial comments and letters to the editor.

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Research code

In my foreword for the previous issue of Erasmus Journal of Medicine, I praised the system of peer reviewed publishing as a method of quality review for scientific articles and as a motivating factor for researchers. I am convinced that the substantive quality of a researcher's work can be best, if not exclusively, assessed by his or her colleagues. This is assuming, of course, that researchers acted in good faith in carrying out their research and in their reporting of research results to editors of scientific journals.

This seems inevitable. Maybe even so self-evident, that we have long considered the academic world to be the conscience of scientific research. It is here, after all, where research is carried out independently and to a large extent assessed by bodies comprised of leading scientists, our scientific role models. Therefore, the moral standards for our work can also best be laid down here. In administrative terms this is called self-regulation of the field.
In the meantime, it has become painfully evident that damage to scientific integrity can also occur in the academic setting. It even became clear that this not only occurs elsewhere, but even within Erasmus MC.

As such, Erasmus MC was well prepared for this situation. The availability of an Integrity Counselor and guidelines for scientific misconduct were put into force years ago. We published 'Research Codes' in March 2011. This publication, aimed at our own researchers, once more outlines the main principles of honest and meticulous scientific research. These principles also apply to academic integrity, intellectual property and dealing with patient data and biological material. We did not actually develop the written guidelines ourselves; they were based on national and international legislation and codes of conduct, such as the Dutch Code of Conduct for Scientific Practice of the Association of Universities in the Netherlands (VSNU).

It is vital that researchers are aware of these codes of conduct and of the resulting individual responsibility of every researcher to guarantee the quality and credibility of scientific research. The development towards more transparent reporting, also in scientific research, by making research data available online, for example, will hopefully help ensure that every researcher remains aware of this at every point in his or her career and under all circumstances.

Some people link scientific misconduct to the high pressure put on researchers to publish. Unfortunately, this may indeed occasionally result in the psychological pressure on researchers causing boundaries to become blurred. I truly hope that everyone can avoid this dangerous pitfall. Not only you will be fooling others, but most of all you will be fooling yourself.

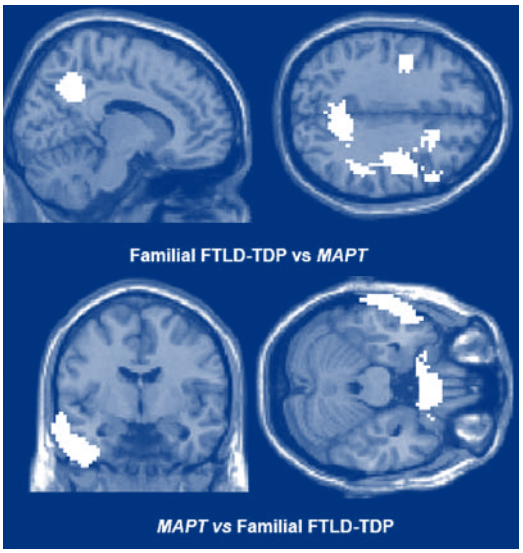
Huibert Pols, Dean and Vice Chairman of the Executive Board of Erasmus MC

The Erasmus Journal of Medicine: a first step into the "real-world" of biomedical publication

The primary purpose of the Erasmus Journal of Medicine (EJM) is to give students at the Medical Faculty of Erasmus University experience in critically reading and effectively writing research articles. Our medical curriculum prepares students to become research-oriented doctors, and the EJM plays a role in this.
A secondary purpose is to communicate the results of student-driven research to a wider readership.

By giving medical students an opportunity to publish their work, the EJM encourages them to take a first step into the "real world" of biomedical communication. Writing for an international biomedical journal is a challenge, and getting a paper published is a true achievement. The EJM provides a learning environment for students to gain experience in writing, peer-reviewing, and publishing biomedical research.

Erasmus Journal Of Medicine



Perfusion pattern of familial FTLD-TDP compared to MAPT. p 41.

"A single lie destroys a whole reputation of integrity."

In the past year academic integrity has made the headlines of the newspapers, regrettably not in a positive way. These incidents have rocked the academic community, and the results of conducted and ongoing research were questioned, PhD candidates were left in uncertainty with regard to their promotion programme and the reputation of the scientific community as a whole has been tainted.

There is no doubt about it, the pressure on academic writers is quite high. Making deadlines in the small hours of the night, skipping social activities just to get those few extra hours of work in, all for the greater good of science. The temptation to cut a few corners along the way is hard to resist. However, no concessions should be made when it comes to academic integrity.

As a junior member of a research group it is difficult to point out misconduct of your seniors. After all, they have granted you the opportunity to make exciting discoveries, make a contribution to science and last, but not least, to further your own academic career. Not to mention the personal bond you have developed with your supervisors. When you raise your concerns, they might be easily dismissed by arguments backed up by their seniority.

The above being said, you still have a responsibility towards your patients, your colleagues and your institution to report violations of academic integrity. These groups grant you and your fellow researchers their trust, hard work and funds to further medical knowledge. It is not only your right, it is your duty, to report academic misconduct.

To empower young researchers in raising the matter of academic misconduct of their supervisors the Erasmus University Medical Centre has appointed a confidential counsellor to handle the reports. This ensures anonymity of the whistleblower, and impartial evaluation of the report. It was through this way that a PhD candidate revealed academic misconduct to the executive board, who could then take appropriate action.

This case illustrates that, even as a young researcher, you can make a difference in ensuring the integrity of the scientific community, and specifically the Erasmus Medical Centre.

On behalf of the student board of the EJM,

Erik Dieters, medical student, Erasmus MC University Medical Center Rotterdam, the Netherlands

The future of Erasmus Journal of Medicine

The release of the fourth issue of the Erasmus Journal of Medicine, volume 2 issue 2 shows that we are able to produce the journal at regular intervals, and with stable quality.

The journal is intended as platform for students who set their first steps on the rough and windy road of scientific research. We want Erasmus MC students to read papers written by Erasmus MC students and we want them to experience that tinge of pride, jealousy and admiration for their fellows that will prompt them to start writing a paper themselves. And that is also the purpose of the journal, to make students acquainted with a professional review process, either as an author, as a member of the editorial board or as external reviewer. Most of the papers in the journal were written as part of an assignment, and many have scientific limitations. The editorial board recognizes this, but we feel this should not pose a problem, as long as these limitations are properly addressed in the discussion.

We have made a major change to the organization of our review process. More than 20 student- and staff members have volunteered to act as independent reviewer for the journal. From now on, papers can be submitted to one of the members of the editorial board or to the journal's office. The review process will be coordinated by a staff- and a student editor. They will assign reviewers and will make editorial decisions based on the reviewers' comments, the author's response and the reviewers' recommendations. Difficult decisions will be forwarded to the editorial board. Our editorial assistant will keep track of this process. We expect that we can speed up the review process and maintain, or even increase its quality. An additional advantage of this change is that now we can handle more papers at the same time.

As always, we want to thank everyone who has contributed to the journal, authors, reviewers, editors, and publisher. We hope that the Erasmus Journal of Medicine will continue to contribute to the outstanding learning environment of Erasmus MC.

Diederik Dippel
Co-editor in chief

Vaccination of health care workers; a matter of debate

In this issue of the journal van der Veen pleads for mandatory influenza vaccination of health care workers, stating that hospitalization and death can thereby be prevented among elderly and chronically ill.

Caplan from the center for Bioethics in Pennsylvania is clear in his statement in this years issue of the Lancet: "Vaccination is a duty that one assumes in becoming a health-care provider. Mandating vaccination is consistent with professional ethics, benefits many, including some of whom must rely on health-care workers to protect them, maintains a stable workforce, and sets an example that permits honest engagement with others working in hospital settings and with the general public in educating them to do the right thing about vaccination. The fact that vaccination against influenza works is important in discussing mandates. The moral case for mandates when integrated with this fact can command the support of health-care workers. It is time to acknowledge professional duty and make influenza vaccination of health-care workers a mandatory obligation."

But, apart from juridical implications (e.g. for religious reasons people may choose not to be vaccinated), what is the scientific evidence? This is a matter of debate also in the lay press. Sure, there are studies that demonstrate a reduction in the number of influenza cases after vaccination.
But a recent publication of a meta analysis also states that influenza vaccination only provides a moderate protection against virologically confirmed influenza, which is greatly reduced or absent in some seasons. Furthermore evidence for protection in adults aged 65 years or older is lacking. The optimum efficacy of influenza vaccine is dependent on matching between vaccine strains and circulating strains. Lack of such matching might explain why a systematic review by Thomas et al found no significant effect of the vaccine given to health-care workers on laboratory-confirmed influenza and pneumonia-associated mortality in elderly patients.

Unlike most other vaccines compulsory for health-care workers (e.g. hepatitis B), the effectiveness of influenza vaccine is less certain, so mandating influenza vaccination is harder to justify as a measure proportional to the strength of evidence of its efficacy in improving outcomes for patients.

Although mandatory influenza vaccination at first appears to be appealing, for now I would advocate a voluntary approach.

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The right to refuse

Can a medical doctor refuse to apply a treatment even when there is no other treatment option for a disabling disease with very poor prognosis?

Jessica Willems discusses in the present issue of the *Erasmus Journal of Medicine* the pros and cons of the so-called liberation-treatment as a new innovative treatment modality for patients suffering from Multiple Sclerosis. The author highlights the actual criticism regarding the underlying hypothesis and the efficacy of this as yet not approved vascular intervention.

The "Liberation treatment", first described by a vascular surgeon and professor at the University of Ferrara in Italy, is a controversial therapy for multiple sclerosis based on the dissolvement of occlusions in the jugular and azygos veins. While the hypothesis of occlusions in the jugular and/or azygos vein causing reflux of blood and waste products is not scientifically proven, Zamboni and his advocates made steps forwards and applied balloon catheterization to resolve this so-called phenomenon of Chronic Cerebro-Spinal Venous Insufficiency.

After comprehensive review of medical literature it can be concluded that the existing data cannot provide us with compelling evidence for or against the Zamboni's theory as they all studied different patient- and control-groups, and applied different methodology, not mentioning the fact that most of these studies were not randomized, and not blinded in interpretation of obtained results. The author states that the 'evidence' is insufficient and further research and randomized placebo controlled trials in homogenous patient and control groups with longer follow-up are urgently needed.

The wish to treat should be seen in the light of *primum non nocere*. According to the author, the patients should be protected by the physician against potentially harmful treatments. A doctor's job is to remain objective and makes sure the patient stays well-informed. A doctor should not respond with sniggering or rejection when a patient refers to the possibility of a new emerging treatment, but should take the patient seriously and enter the dialogue!

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What data sofar can(not) tell about the place of delivery

In this issue of the Erasmus Journal of Medicine, the article of Maarten Meijer addresses some important issues in relation to the place of delivery and of home birth in particular. Two questions should be addressed separately in the case of home birth: (1) can the home birth option be responsible for the poor performance of the Dutch perinatal system in terms of perinatal mortality? (2) what are the pros and cons of home birth, relative to other options of midwife-led care?

The first answer is clear since the absolute perinatal mortality rate of home birth in the Netherlands is low (about 1.5 per 1000, excluding stillborns), as well as the share of home births in relation the total of deliveries (about 20%). So even in the case of significant perinatal mortality disadvantage this will not translate into notaceable excess mortality at large [1-3]. While critized at onset, Evers' study appeared valid after re-appraisal [4].

The second question is more difficult to address. Judging the evidence first requires some decisions on the data available in published studies.

Differences in inclusion of study populations
The first choice regards the population to be compared. In the Netherlands, as a consequence of suboptimal risk selection prior to delivery, a group of women starts their delivery under the supervision of a midwife, who better could have given birth under supervision of the obstetrician (e.g. premature birth, missed congenital anomalies) [5]. Part of this group is refered during delivery. The paper of Evers et al. sheds light on the higher than expected risk level of this group [3,4]. Others chose to exclude home births from analysis that did not fully comply with the guidelines or represented an increased risk in hindsight [6]. This approach can be challenged as guidelines departures and emerging unexpected complications are part of the system.

Alternative settings
A second difficulty regards the alternative options to compare home birth with. The dominant alternative for home birth in the Netherlands sofar has been midwife-led care in the hospital ('poliklinisch'). In the Netherlands, more recently birth centres adjacent to hospital and independent, free birth practices ('kraamhotels', 'kraamsuites') and fully integrated birth centres in hospitals were introduced. The comparison with obstetrician-led care is difficult, as low risk women (given the guidelines) are not supposed to deliver this way.

Different groups
A third difficulty refers to the availability of observational rather than experimental RCT data on delivery outcome in different delivery settings. The main problem is the difficulty to adjust for incomparable groups (casemix), since women giving birth through home birth are in general at lower risk (more of Dutch origin, higher educated, self confident) than women giving birth through midwife-led care in hospital [7].
Researchers in this field used statistical methods (casemix adjustment by regression analysis) to make groups comparable [1,5,6,7]. However, these predicting factors are limited to maternal factors (e.g. age, parity, ethnicity) and do not include all risk factors known for perinatal mortality. Supposed equality of the groups after can therefore be challenged.
With the limitations of casemix control of results in mind, we will now summarize the evidence.

Mortality and Morbidiy
Absolute mortality in low risk women is low regardless the place of birth and is therefore not an explanation of the poor performance of the Dutch perinatal system. Home birth in the United Kingdom most likely increases perinatal mortality to some degree [1]. In the Netherlands however, home birth under routine conditions, is generally not associated with an higher perinatal death, yet in subgroups additional risks cannot be excluded. Excess mortality arises from unexpected high risk cases. Following UK evidence some safety disadvantage may be primarily restricted to nulliparous women. In combination with the observation that referral rate during labour in nulliparous women both in the UK and the Netherlands is 45%, this raises the question whether home birth should be restricted to low risk multiparous women only. [1,5]

Costs
A detailed Dutch cost study showed a small advantage for home birth [8]. Most likely the difference becomes even smaller if additional casemix adjustment is applied [6]. Even if average costs are slightly higher, it is difficult to project cost differences on the individual level into cost impact or savings on the macro level. The so-called 24/7 availability costs of the hospital (in particular reflected by the overhead costs in hospital cost per delivery) are not saved, if more births take place outside the hospital and cannot be saved with such a shift [8].
Focussing on direct care costs setting, differences are rather trivial. Home birth costs may even become more expensive if monitoring demands during parturition are intensified, with birthcentres attached to the hospital showing efficency advantages above homebirths (data presented by the Birthplace project team London, 25 Nov 2011). Taken together, a clear cut economic preference for homebirth seems unjustified.

Choice
A last issue refers to choice. Choice is relevant to the extent that setting-related outcome differences are rather trivial and the patient can behave as a well-informed consumer.

Conclusion
Various reports on the Dutch Maternity reported some role for the Dutch system in general contributing to the perinatal mortality rates, where the mutual collaboration of midwives and gynaecologists was challenged. The home birth option is not pertinent to this problem. From available data, homebirth is a viable option, following UK data at least for low risk multiparous women. Time will show how informed consumers judge the emerging variety of midwife-led setting options, of which home birth is one.

It was a daring undertaking of Meijer et al. to address the scientific question on the safety of birth settings in a modern society, which apart from any political consideration, is a challenge. It is tempting to take position in the Netherlands where pregnant women and scientists alike are almost forced to show belief in one or the other position on home delivery - here the author was not always successful in presenting a balanced view. Actually, our own experience in research on the issue showed the real world is always more interesting than prior belief. The reward of discovery of the unknown is what makes being a scientist special.

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Comparing the cost effectiveness of nurse practitioners and physicians

A systematic review

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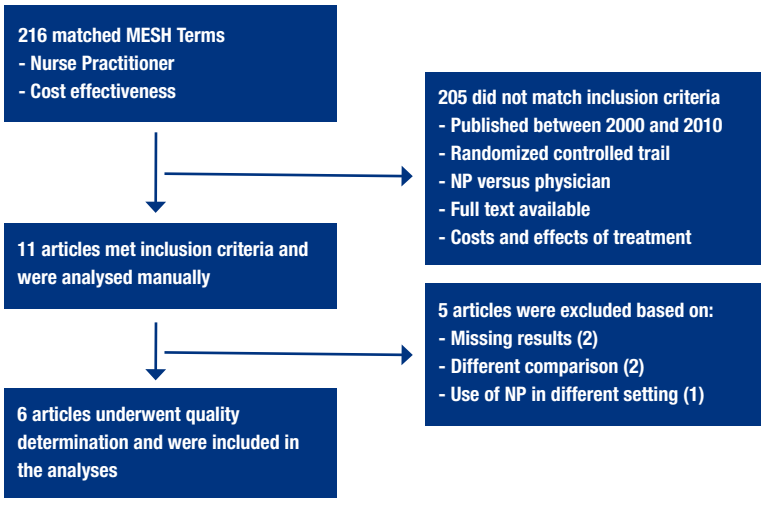
Introduction: **Due to the demand for efficient, cost effective and patient friendly health care, the role of nurse practitioners in Dutch hospitals is increasing. According to the available evidence, the service provided by nurse practitioners is equivalent to that provided by physicians. With the aim of reducing health costs, nurse practitioners can take over some tasks of physicians and facilitate communication between patients and physicians. However, there is no consensus on their cost effectiveness. The aim of this review was to determine whether nurse practitioners improve the cost effectiveness of health care services.**
Method: **We systematically reviewed randomized controlled trials that investigated the cost effectiveness of nurse practitioners in health care in comparison with physicians. We combined the MESH terms Nurse Practitioner and Cost Effectiveness, and included English articles published between 2000 and 2010. All articles had to show the health care costs and the effects of the treatment. Selection was not based on specific patient characteristics, on the specialty of the nurse practitioner and the physician, or on the type of effectiveness outcome.**
Results: **We included six randomized controlled trials in our review. Two of these indicated that nurse practitioners resulted in lower health care costs during the trial and two showed no difference in costs. The remaining two did not statistically analyze their results, so no conclusion could be drawn from them.**
Conclusion: **Although the results from the reviewed studies were not unequivocal, over the long term nurse practitioners may improve the cost effectiveness of health care services.**

Introduction

Modern health care should be efficient, cost effective and above all patient friendly. This has led to an expansion of the role of nurses who take over some of the tasks of physicians.

Nurse practitioners (NPs) are advanced-level clinical nurses who have received additional education and training. NPs are able to practice autonomously, make clinical decisions and instigate treatment. Consequently they are fully accountable for their own practice [1].

Figure 1 - Flowchart



The aim of this review was to determine whether NPs improve the cost effectiveness of health care services.

Previous studies have unanimously shown positive results about patient satisfaction and the role of NPs [2-5]. Moreover, we could not find a single study indicating that NPs provide inferior service, so clinical quality does not appear to be an issue either. NPs can safely provide care management of patients equal to that provided by physicians [6]. However, there is no consensus about the cost effectiveness of NPs. Some studies have shown similar or even higher health care costs compared to physicians [4]. Other studies have shown lower health care costs and improved cost effectiveness of NPs [7].

We systematically reviewed the literature using PubMed to determine the cost effectiveness of NPs. We addressed the following research question: are NPs cost effective compared to physicians?

Method

To determine whether nurse practitioners are cost effective compared to physicians, we used PubMed to search for randomized controlled trials comparing nurse practitioners to physicians. Our search criteria were the following: literature in English published between 2000 and 2010 combining the MESH terms Nurse Practitioner and Cost Effectiveness. To prevent older studies from influencing the results, we included only the most recent publications. Inclusion criteria: full texts had to be available for all articles and the results had to show the costs and the effects of the treatment. Exclusion criteria: articles were excluded when they used physicians assistants instead of physicians. Selection was not based on specific patient characteristics, on the specialty of the nurse practitioner and the physician or on the type of effectiveness outcome.

Table 2 - Study specifications

Study	Setting	QD[a]	Population	Conditions	Follow-up	Measured unit	Results NP vs. GP (SD)	P-value	Study limitations
Chan et al. 2009 [9]	University Hospital. GNP vs. GP.	7.	Adult men and women. n = 175	Dyspepsia-patients who underwent gastroscopy	6 months.	Anti-ulcer drug cost.	£35.5 (48.8) vs. £71.7 (63.1)	<0.001	Single centre. Only medicine costs.
						Gladys score.	4.9 (2.9) vs. 7.2 (3.9)	<0.001	
Dierick-van Daele et al. 2009 [11]	Primary care. NP vs. GP.	5.	Men and women. > 16 year n = 1397	Common conditions	2 weeks.	Direct cost per consult.	€31.94 (36.29) vs. €40.15 (49.94)	<0.001	No cost-effectiveness was calculated. No adverse events and related costs.
Paez et al. 2006 [12]	University Hospital or Primary care. Usual care +NP vs. usual care + GP or cardiologist	6.	Adult men and women. N = 228	Patients with hypercholesterol-emia and coronary heart disease who underwent coronary revascularization.	12 months.	Total cost per patient per year.	$1573.31 vs. $1182.82	Not estimated	Drug compliance was not considered in the calculation of cost effectiveness. The drugs only were identified at 6- and 12 months, not previously. Short-term outcome.
						LDL-c reduction (mmol/L).	1.5.8 vs. 1.1.8	0.001	
Williams et al. 2005 [13]	Primary care. Continence NP vs. standard care.	6.	Men and women > 40 years. n = 3746	Urinary inconti-nence and storage symptoms.	6 months.	Cost per patient.	£252 vs. £73	Not estimated	All of the data at baseline, after 3 month and after 6 months were obtained by interviewing.
						Relieve of one or more symptoms.	62% vs. 52%	<0.001	
						Cost per hospital stay.			
Harris et al. 2005 [14]	General Hospital. NLIUb vs. acute wards.	7.	Adult men and women. n = 175	Post acute recovering patients, medically stable and with no change in medical manage-ment.	Length of stay in the NLIU[b] or in the acute ward. Total follow-up 20 months.	Patient independen-ce improvement.	£5144 vs. £4100	0.159	Short-term outcome.
						Cost of initial consult.	3.6 vs. 2.6	Not significant	Single centre. Less experience with staff cooperation in the NLIU[b].
Venning et al. 2000 [16]	Primary care. NP vs. GP.	6.	Adult men and women and accom-panied children. n = 1316	Common conditions	2 weeks.	Total cost per patient.	£11.71 (25.23) vs. £14.14 (29.62)	0.204	This study only eva-luated NPs who work alongside GPs.
							£18.11 (33.43) vs. £20.70 (33.43)	0.247	Return consults were not timed.

[a] Quality determination

[b] Nurse-led inpatient unit

We found 216 articles of which 11 met the inclusion criteria. These eleven studies were read and evaluated manually. Subsequently, 5 more articles were excluded based on missing results, different comparisons or the use of a nurse practitioner in a different setting. This is shown in Figure 1.

The remaining 6 articles underwent a systemic quality check using a 7-point system, which is shown in Table 1. This system was based on the Delphi list [8]. An article had to have at least a score of 4 out of 7 to be included in the study. The results of this quality determination are shown in Table 2, together with the other aspects of the included studies.

Table 1 - Quality determination

1. Was a method of randomization performed?	Yes/No
2. Was the treatment allocation concealed?[a]	Yes/No
3. Were the groups similar at baseline?	Yes/No
4. Were point estimates and measures of variability presented for the primary outcome measures?	Yes/No
5. Was there a description of withdrawals and dropouts?	Yes/No
6. Did the analysis include an intention-to-treat analysis?	Yes/No
7. Are the groups, apart from the intervention, treated equally?	Yes/No

[a] *A concealed treatment allocation means that a random assignment sequence is generated by an independent person not responsible for determining eligibility of the patients. This person has no information about the patients included in the trial and has no influence on the assignment sequence or the decision about eligibility of the patients.*

Results

The main results of each study are shown in Table 2. Chan et al. demonstrated that over a follow-up period of six months the costs of anti-ulcer drugs were significantly lower in the patient group treated by gastro-intestinal nurse practitioners (GNPs) than in the group treated by general practitioners (GPs) [9]. The symptom improvement in the GNP group, measured with the Gladys score, was also significantly better. The Gladys score is a self-reported questionnaire about disease burden and symptoms [10]. Furthermore, patients reported that the GNPs helped them to improve their lifestyle better than the GPs did.

In the study, Chan et al. assessed only the costs of medication, not the total costs of the treatment using GNPs. Dierick-Van Daele et al. evaluated these total costs [11]. They observed that the costs of an NP consult was significantly lower than the costs of a GP consult. This difference was caused mainly by a difference in salary. An assessment of the effectiveness was not conducted.

Both Paez et al. [12] and Williams et al. [13] concluded that care provided by NPs was more effective than standard care. Paez et al. found that care provided by NPs resulted in a significantly greater reduction in LDL cholesterol compared to GPs or cardiologists. The nurse reported that they spent the largest percentage of their time on counseling lifestyle changes. Williams et al. showed that 62% of the participants randomized to the NP continence service were relieved of one or more urinary symptoms, compared to 52% in the standard care group. This difference was shown to be significant. However, neither study provided statistical analysis of the differences in costs between the intervention and the control group. In both studies the NPs appeared to have higher costs in absolute terms relative to standard care. However, due to the absence of p-values, no conclusions can be drawn from these results.

Harris et al. showed that there was no significant difference in costs between the nurse-led inpatient unit (NLIU) and the acute wards [14]. The patients nursed in the NLIU showed a greater, although not significant, improvement in functional independence in comparison to the acute ward. The Barthel index was used to assess functional independence [15]. In addition, there were no differences in mortality and readmission between the treatment-group and control group.

When comparing the NP consult to the GP consult, Venning et al. found no significant difference in costs per patient or costs per initial consult [16]. The patients were significantly more satisfied with the treatment given by the nurse practitioner. The NP consultations were significantly longer than the GP consultations. The authors therefore adjusted the outcomes for length of consultation. After this adjustment, the difference in satisfaction remained significant, in favor of the NP.

Discussion and conclusion

In this review we evaluated the cost effectiveness of nurse practitioners in comparison to physicians. The quality of the reviewed studies was ascertained with the systemic quality check. All 6 studies subjected to the test, scored at least 4 out of the 7 points.

Of the 6 randomized controlled trials included in our review, 2 indicated that total health care costs of the NPs were lower during the trial [9,11] and 2 showed no difference in costs [14,16]. The remaining 2 studies did not present a statistical analysis, so no conclusion could be drawn from them [12,13].

Our review and the included articles had a few limitations. All six RCTs defined health care costs differently, making it difficult to compare the trials. Per study, however, the same definition applied to nurse practitioners and physicians. Therefore it was still possible to compare the results.

Not all studies included the effect of the treatment, which made the evaluation of the cost effectiveness less accurate.

Venning et al. evaluated NPs who worked alongside GPs; this is not the same as our definition of a nurse practitioner [16]. Moreover, these NPs were required to have prescriptions signed by a GP, so they did not work autonomously, which also differs from our definition. The time for each consult included the time which was needed by the NPs to get a signature. On average, this took three minutes per consult. If this approval time was eliminated – assuming full autonomy – the average time for each NP consult would be reduced. As a result, the NPs could have significantly lower health care costs than GPs.

Harris et al. reported higher treatment costs in a nurse-led acute ward (nurse-led-inpatient unit – NLIU) than comparable physician-led wards [14]. However, the staff on the physician-led acute wards had more experience working together than the staff on the NLIU. If adjusted for this factor, the health care costs in the NLIU could be lower than reported.

When calculating costs Peaz et al.[12] did not consider drug compliance. Because the compliance in the NP group was significantly higher than in the standard care group, which included treatment by a cardiologist or GP, the reported costs could actually be lower.

The study conducted by Williams et al. concerned a continence service provided by NPs, that delivered evidence-based interventions using pre-determined care pathways [13]. This treatment was compared with existing primary care including GP and continence advisory services located near patients. The focus of the study was more on the evidence-based interventions than on the added value of the NPs.

All of the studies that we included examined the effect of NPs on health costs in the short term. If the comparatively more positive effects of treatment by NPs on lifestyle [12], compliance [12] and independence [14] were to persist, the long-term costs could decrease. We recommend a longer follow-up period to ascertain this possible decrease in costs.

Although we found no significant difference in cost benefits when comparing NPs to physicians across all the studies in our review, NPs could still be cost effective, especially over the long term if the following aspects will be taken into consideration.

Firstly, cost effectiveness might be achieved when NPs autonomously operate alongside physicians. The physicians can then focus on the more challenging patients and the NPs treat the common conditions. Using this approach, more effective treatment could be offered to patients which could ultimately reduce costs. This approach can apply not only to primary care, but also to hospital settings such as a polyclinic.

Secondly, cost reductions could become apparent over the long term due to improving effectiveness of NPs. As the NPs become more experienced, their effectiveness should improve. Among other things, this would result in fewer return consults and briefer consultations [16]. Consequently, the long-term costs could be lower.

Thirdly, therapy compliance is better with NPs compared to physicians [9]. This could also improve the effectiveness of health care and thereby reduce costs.

Fourtly, patients report that NPs spend more time on lifestyle changes and risk prevention than physicians [9,12]. These changes could reduce both medicine consumption and disease incidence. This could reduce health care related costs in society.

Finally, research shows that NPs perform better than physicians when it comes to patient satisfaction [2-5]. They also provide equal o[illegible]rior health care service and safe care management. [6]

When taking all these points into consideration, an NP program may be cost effective over the long term.

Although our review did not definitively show that NPs are more cost effective than physicians, we can conclude that NP programs are certainly effective in other ways. Moreover, it is likely that NP programs will become more cost effective over long term. Therefore, we recommend that investments in new programs should not be postponed, and we advise the hospitals to continue the existing NP programs.

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Osteonecrosis in patients infected with HIV

A systematic review of the risk factors

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Objective: **The prevalence of osteonecrosis is higher in HIV infected patients than in the healthy population. As a result of osteonecrosis, patients must undergo total hip arthroplasty surgery every 10 to 15 years. If we want to reduce the prevalence of osteonecrosis, especially in HIV infected patients, it is important to understand the HIV infection-specific risk factors for osteonecrosis.**
Methods: **We searched Pubmed for publications useful for our review. To be included in our review, the publications had to be written in English. We excluded review articles and articles that were not available for Erasmus MC online.**
Results: **After applying our exclusion criteria to the search, we ended up with 6 studies. Frequently recurring predisposing factors for osteonecrosis in HIV-positive patients are alcohol abuse, steroid use and hyperlipidemia. The studies we found through our Pubmed search investigated additional factors related to HIV infection.**
Conclusions: **Alcohol abuse, steroid use and low CD4+ cell count are risk factors for the development of osteonecrosis in HIV infected patients.**

Introduction

Since HAART (Highly Active Anti-Retroviral Therapy) was introduced in 1996, the rates of mortality and severe morbidity related to HIV infection have been drastically reduced. HAART results in a longer life expectancy for HIV infected patients. Due to this longer survival, complications and comorbidities of HIV infection, such as osteonecrosis, have become increasingly prevalent. The pathogenesis of osteonecrosis is complicated and poorly understood. In patients with this disease, cell death in various bone components is caused by a lack of blood supply. Preliminary research has indicated a relationship between HIV infection and osteonecrosis.

The prevalence of osteonecrosis is higher in HIV infected patients than in the healthy population. Osteonecrosis is a serious complication of HIV infection and affects relatively young patients, mostly under the age of 50. Osteonecrosis induces progressive arthrosis; if this affects the hip, this ultimately requires total hip arthroplasty (THA) surgery every 10 to 15 years. This means that young people affected by osteonecrosis are subject to major surgery several times in a lifetime.

Table 1 - Found cases of osteonecrosis and associated risk factors in HIV+ patients

	Morse et al.(1) (n = 339)	Yombi et al.(2) (n = 815)	Scribner et al.(3) (n = 2673)	Lawson-Ayayi et al.(4) (n = 12)	Glesby et al.(5) (n = 17)	Larrañaga et al.(6) (n = 19)
Cases of osteonecrosis	5.6%	0.74%	0.37%	N/A	N/A	N/A
Risk factor						
Protease inhibitors	N/A	N/A	N/A	-	-	N/A
NNRTI	N/A	N/A	N/A	-	N/A	N/A
Alcohol	N/A	N/A	-	+	-	-
Steroid use	N/A	N/A	-	+	+	+
Hyperlipidemia	N/A	N/A	-	-	-	N/A
Low CD4+ nadir	N/A	N/A	N/A	-	-	+

Note N/A = Not applicable (the factor was not studied); n = study population; + = The factor was found to be significant: - = The factor was nog found to be significant: NNRTI = Non-nucleoside reverse transcriptase inhibitors

It is therefore important to recognize the risk factors for osteonecrosis. For this purpose we searched the literature to address the following questions: (1) What is the prevalence of osteonecrosis in the HIV-positive population? (2) What are the predisposing risk factors for osteonecrosis in HIV-positive patients?"

Methods

On January 14, 2010 we searched Pubmed for publications useful for our review. We used the following MeSH terms, specifically combined with AND, OR and round brackets, to optimize our results: "HIV Infections"[Mesh] AND "Osteonecrosis"[Mesh]) AND "Risk"[Mesh] AND ("clinical trial"[ptyp] OR "epidemiologic studies"[Mesh]). To be included in our review, the publications had to be written in English. The remaining articles were screened with our exclusion criteria: we excluded review articles and articles that were not available for Erasmus MC online.

Results

Our Pubmed search produced 11 publications. After screening with our criteria, 6 studies remained. These studies indicated that osteonecrosis occurs up to 100 times [1] more frequently HIV patients than in HIV-negative subjects. Yombi et al. [2] reported that 0.74% of the HIV-infected patients had osteonecrosis; Scribner et al. reported a frequency of 0.37% [3] and Morse et al. reported a frequency of 5.6% [1] [Table 1].

Predisposing factors for developing osteonecrosis in HIV infected patients were found to be the same as in HIV-negative subjects: alcohol, steroid use and hyperlipidemia [3-6]. In addition, HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI), and nadir CD4+ cell count (low CD4+ cell count) were identified as HIV-specific risk factors [Table 1]. The only factors that remained significantly relevant after statistical correction were alcohol use[4], a history of steroid use[4-6] and a low nadir CD4+ cell count (<60 cells/μL)[6] [Table 2].

Some publications reported conflicting results. Scribner et al.[3], Glesby et al. [5] and Larrañaga et al. [6] found that alcohol was not a significant risk factor [Table 2]. Steroid use was not found to be a significant risk factor in Scribner et al. [3] [Table 2], and a low nadir CD4+ cell count was not found to be associated with osteonecrosis by Lawson-Ayayi et al.[4] and Glesby et al.[5] [Table 2].

Discussion

1) Prevalence of osteonecrosis

Three articles stated the prevalence of osteonecrosis in HIV infected patients[1-3]. Two of which we used solely to illustrate the prevalence of osteonecrosis in HIV infected patients. We did not use these articles to study the possible risk factors for the development of osteonecrosis in HIV infect patients [1,2]. The much higher percentage of osteonecrosis in HIV infected patients found by Morse et al. can be explained by the fact that they screened all their 339 subjects for osteonecrosis; consequently, they also diagnosed asymptomatic patients [1]. In the other studies, only symptomatic patients were diagnosed [2,3]. Most cases of osteonecrosis remain asymptomatic for a long time.

Table 2 - Odds ratio, 95% CI and p-values for risk factors from Table 1

Risk factor Publication	OR	95% CI	*p*-value
NNRTI			
Scribner et al.(3)	N/A	N/A	N/A
Lawson-Ayayi et al.(4)	1.03	0.98-1.10	0.25
Glesby et al.(5)	N/A	N/A	N/A
Larrañaga et al.(6)	N/A	N/A	N/A
Protease inhibitors			
Scribner et al.(3)	N/A	N/A	N/A
Lawson-Ayayi et al.(4)	1.03	0.99-1.08	0.18
Glesby et al.(5)	3.7	0.68-20	0.13
Larrañaga et al.(6)	N/A	N/A	N/A
Alcohol			
Scribner et al.(3)	1.56	0.51-4.74	0.56
Lawson-Ayayi et al.(4)	**20.48**	**1.83-229.72**	**0.01**
Glesby et al.(5)	1.2	0.30-4.6	0.82
Larrañaga et al.(6)	0.72	0.23-2.23	0.570
Steroid use			
Scribner et al.(3)	6.68	0.66-67.88	0.58
Lawson-Ayayi et al.(4)	**16.96**	**1.20-239.12**	**0.04**
Glesby et al.(5)	**13.1**	**1.6-106**	**0.016**
Larrañaga et al.(6)	**4.27**	**1.25-14.57**	**0.020**
Hyperlipidemia			
Scribner et al.(3)	1.49	0.52-4.31	0.58
Lawson-Ayayi et al.(4)	22.67	0.69-745.95	0.08
Glesby et al.(5)	3.2	0.58-18	0.18
Larrañaga et al.(6)	N/A	N/A	N/A
Low CD4+ nadir			
Scribner et al.(3)	N/A	N/A	N/A
Lawson-Ayayi et al.(4)	6.46	0.68-61.37	0.10
Glesby et al.(5)	7.2	0.81-64	0.077
Larrañaga et al.(6)	**5.15**	**1.44-18.49**	**0.012**

Note The studies by Lawson-Ayayi et al.[4], Glesby et al.[5], and Larrañaga et al.[6] defined different CD4+ levels as a low nadir, respectively <100 cells/mL, <0.050 cells x 109/L and <60 cells/L. N/A = Not applicable (the factor was not studied); NNRTI = Non-nucleoside reverse transcriptase inhibitors; OR = Odds ratio; CI = Confidence interval; Significant p-values are written in **bold**

It can therefore be concluded that the actual prevalence of osteonecrosis is much higher than normally assumed. Osteonecrosis is a rare disorder in the HIV-negative population [7], but the prevalence of osteonecrosis in HIV-infected patients is much higher. A reliable picture of the prevalence of osteonecrosis in HIV-infected patients requires a larger study population than those in the reviewed studies.

2) Risk factors

The conflicting results about risk factors in the various cohorts may have several explanations.

First, all studies reported low numbers of cases of osteonecrosis in HIV-infected patients. Therefore, statistical significance was problematic. Moreover, not all articles studied the same risk factors, possibly resulting in a biased comparison of risk factors. It is known that HIV infection on its own is a risk factor for osteonecrosis. Together with other risk factors, such as coagulation disorders, this effect can be even stronger. We have found no large studies that have investigated osteonecrosis in relation to HIV infection. Secondly, the studies we reviewed used different methods for diagnosing osteonecrosis. Scribner et al. described their method as follows: "Inclusion as a case of osteonecrosis required evidence of both a clinical and radiographic diagnosis of osteonecrosis alone or with a pathologic diagnosis of osteonecrosis". The diagnosis was made by plain radiography in 20 patients and by MRI in 4 patients [3]. Lawson et al. detected symptomatic cases of osteonecrosis on the basis of clinical symptoms and confirmed the diagnosis of osteonecrosis by using radiological or scintigraphical imaging [4]. Glesby et al. identified osteonecrosis on the basis of radiologic evidence of osteonecrosis at any stage and a compatible clinical history [5]. Larrañaga et al. recruited all consecutive HIV infected patients with suspected hip osteonecrosis; the diagnosis was confirmed by magnetic resonance imaging [6].

Thirdly, different definitions for low CD4+ cell count, hyperlipidemia, level of alcohol consumption and steroid use were used. Scribner et al. classified patients as having a history of alcohol abuse if concern about this condition was noted by the patient's clinician [3]. Lawson et al. defined alcohol consumption as regular or heavy alcohol use, according to physicians' reports [4]. Glesby et al. and Larrañaga et al. used alcohol abuse as risk factor, but they did not report a cutoff value or definition for alcohol abuse [5]. The studies by Lawson-Ayayi et al., Glesby et al. and Larrañaga et al. defined different CD4+ levels as low: <100 cells/mL, <0.050cells 10^9/L and <60 cells/µL [4-6]. Scribner et al. had no cut off value for CD4+ count; they only reported the median CD4+ cell count [3]. Steroid use was defined differently in the studies by Scribner et al., and Lawson et al. [3,4]. Scribner et al. considered corticosteroid use as a risk factor if the patient was taking prednisone ≥30mg/day, or an equivalent steroid dose, for at least 1 month before onset of symptoms [3]. Lawson et al. defined steroid use as receiving at least 1 intravenous or oral course of steroid treatment [4]. Larrañaga et al. and Glesby et al. only reported history of steroid use and did not specify the duration of use and dosage [5,6]. For hyperlipidemia, different cut-off values were used in the studies as well [3-5]. Scribner et al. classified patients as having hyperlipidemia as a risk factor if they had a serum triglyceride level >400 mg/dl or serum total cholesterol >250 mg/dl [3]. Lawson et al. defined their cutoff value as a total cholesterol level of ≥6.2 mmol/L or triglyceride level of ≥4.5 mmol/L [4].

Conclusions

Although further research is required, alcohol abuse and steroid use appear to be important risk factors for the development of osteonecrosis. Therefore, clinicians should be cautious with the prescription of steroids in HIV infected patients and should inform them about the risks of alcohol abuse. Knowledge about the risk factors could also advance the development of medication and help reduce the high cost of medical care related to osteonecrosis. In any case, HIV-positive patients with symptoms in their joints should see a doctor and ask for an MRI to screen for symptoms of osteonecrosis. With earlier diagnosis, prophylactic measures can be taken and severe effects can be prevented.

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Do adults with congenital heart disease have a good quality of life?

A systematic review

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Objective: **Most children with congenital heart disease now survive into adulthood. Our research question was therefore the following: Is the quality of life – both health-related and general – of adults with congenital heart disease comparable with the healthy population?**
Design: **We included articles that studied patients between 17-66 years with only a congenital heart defect and no other syndromes. These studies also had to compare the patients' quality of life to the healthy population. We excluded review articles, comment articles, articles about quality of life questionnaires and articles not digitally available at Erasmus MC. The quality of each article was scored according to the Gill and Feinstein criteria from 0 to 100%.**
Results: **The summary scores for individual articles ranged from 0% to 89% with a mean of 45.1 %. Patients with congenital heart disease had significantly worse physical health and significantly more social support. Other domains showed no significantly results. Patients with congenital heart disease often had a better overall score on quality of life compared to the healthy population.**
Conclusion: **The quality of life is equal for patients and controls, except for physical health, social support and the overall score.**

Introduction

Advances in surgery have increased the life expectancy of children with congenital heart disease [1]. Consequently, most children with congenital heart disease now survive into adulthood, creating a new patient population. Due to this longer lifespan, the long-term results of surgery should be ascertained in young adulthood. If we can determine the quality of life of these patients compared to healthy controls, then healthcare professionals will have more insight into the consequences of their heart defects. This can help healthcare professionals design new programmes that aim to improve the patients' quality of life.

The World Health Organization recently defined health as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity"[2]. Our measurement outcomes were defined with the help of this definition.

The aim of this review was to identify the quality of life in adults with congenital heart disease without distinguishing between the underlying cardiac diagnoses. Our research question was the following: Is the quality of life – both health-related and general – of adults with a congenital heart disease comparable with the healthy population?

Methods

On the 21st of January 2011 we searched the PubMed database for English language articles published between January 2001 and January 2011 using the following Mesh-terms in the search strategy: ("Quality of Life"[Majr] AND "Heart Defects, Congenital"[Mesh]) NOT "parents"[Mesh] NOT "child"[Mesh]. We searched for articles published during the past 10 years because we wanted to keep factors like social contacts through the internet comparable between studies.

Two independent reviewers identified potentially eligible studies according to the predefined inclusion and exclusion criteria. The inclusion criteria were: (1) articles in which all the patients were between 17 and 66 years of age; (2) patients with only a congenital heart defect and without other syndromes; (3) the quality of life of the patients was compared to the healthy population. The exclusion criteria were: (1) a review or comment article; (2) a study about quality-of-life questionnaires; (3) not digitally available in the electronic library of Erasmus MC. Differences of opinion regarding selection of studies were resolved between the two reviewers through discussion and consensus.

The ten criteria previously developed by Gill and Feinstein [13] were used to score the quality of the studies individually (Table 1). To indicate how well individual studies performed, a summary score was calculated by adding the number of criteria a study fulfilled and dividing this sum by the number of criteria for which the study was eligible to be evaluated. The resulting value was then multiplied by 100. Summary scores ranged from 0 for studies complying with none of the criteria, to 100 for studies complying with all of the criteria. The quality of the studies is addressed in the Discussion.

We divided the results of our studies into two main groups: studies that measured health-related quality of life and studies that measured general quality of life. The difference between these groups is that the health-related quality of life only measures the health-related factors, such as physical, functional, and mental well-being. In contrast, the overall quality of life not only includes health-related factors, but also non-health-related elements such as job, family, friends and other life circumstances or elements. By focusing only on health-related quality of life, investigators could potentially overestimate the impact of health-related factors and therefore underestimate the impact of non-medical factors.

The domains of one study were compared with the same domains in other studies. A domain was considered significant if more than 50% of the studies showed that same significant result. Studies with quality scores over 50% according to the Gill and Feinstein criteria were also reviewed individually.

Some domains were named differently between studies. We therefore classified the terms physical health, physical functioning, physical domain and physical activity as part of the physical health domain.

We also classified the terms mental health, psychological domain, psychosocial domain and emotional behaviour as part of the mental health domain.

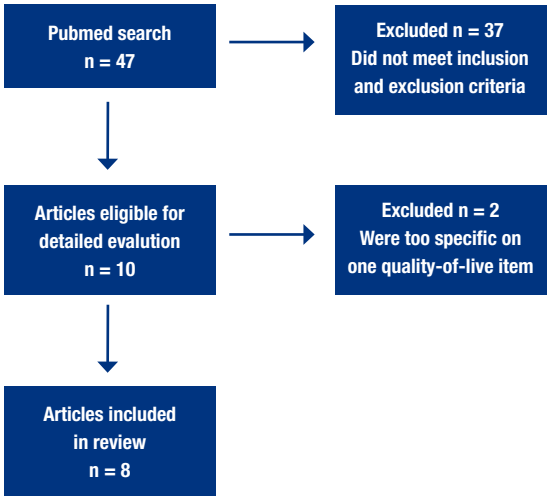
Results

Studies reviewed

Our PubMed search yielded 47 studies. Figure 1 shows the flowchart of the studies included in this review. Of these 47 studies, 10 met the inclusion and exclusion criteria [3-12].

After we identified the eligible studies, we began our detailed evaluation. Of the ten eligible studies, two [6,12] addressed only a too specific quality-of-life domain. One of these addressed only the results of styles of coping [12] and the other addressed only stress-induced heart symptoms [6]. These studies were also eliminated.

Figure 1 -
Flow of studies through the review.



Quality of the studies

All eight selected studies [3-5,7-11] were evaluated with the ten criteria developed by Gill and Feinstein[13]. The criteria are summarized in Table 1. Note that criteria 8 to 10 are conditional on the preceding criterion. The scores on the criteria ranged from 0 for studies complying with none of the criteria to 100 for studies complying with all of the criteria.

Table 1 - The 10 criteria developed by Gill and Feinstein.

1	Did the investigators conceptually identify what they meant by quality of life?
2	Did they state the domains they wanted to measure as components of quality of life?
3	Did the investigators give reasons for choosing the instruments they used?
4	Did the investigators aggregate the results from multiple items, domains, or instruments into a single composite score for quality of life?
	Instrument-specific criteria
5	Were patients asked to give their own global rating for quality of life?
6	Was overall quality of life distinguished from health-related quality of life?
7	Were patients invited to supplement the items listed in the instruments offered by the investigators?
8	If so, were these supplemental items incorporated into the final rating?
9	Were patients asked to indicate which items (either specified by the investigator or added by the patients) were personally important to them?
10	If so, were these importance ratings incorporated into the final rating?

Table 2 shows the scores of the studies on the ten criteria. Three of the studies [7,8,11] defined quality of life. Five studies [4,5,7,9,11] explicitly defined the quality of life domains. Five studies [4,5,7-9] also explained why the specific instrument was chosen. Three studies [7,8,11] assessed quality of life with a single-item instrument or with a composite score of multiple-item tools that provided one overall score. Two studies [7,9] allowed the patients to self-rate their perceived quality of life. Five studies [3-5,7,8] explicitly distinguished between overall quality of life and health-related quality of life. All eight studies [3-5,7-11] used multiple-item instruments, where one study [8] provided a way for the respondents to select items they found important.
Three studies [5,7,8] used an instrument that allowed respondents to rate the importance of respective items in the instrument. The selected items and the importance rating were incorporated into the overall score. Summary scores for individual articles ranged from 0% to 89%, with a mean of 45.1 %. Three studies [5,7,8] scored above 50%.

General health-related quality of life

The different domains used are listed in Table 3. Domains of general health-related quality of life were measured in four studies [3,5,8,11]. The conclusion of the first study [8] was that there is no significant difference in the general quality of life between adults with congenital heart disease and the healthy population. Daily activity was measured in two studies [3,5], but they found no significant difference with the healthy population. Finally, one study [11] that measured general quality of life concluded that the quality of jobs, leisure time and nourishment was significantly higher in adults with congenital heart disease. It found no significant difference in the number of children conceived or having a partner, husband or wife.

Health-related quality of life

Domains of health-related quality of life were measured in six studies [3-5,9-11]. Five studies [4, 5,9-11] measured physical health. Four studies [4,5,9,11] reported significantly poorer physical health in patients with congenital heart disease ($p<0.001$ [5,9,11], $p=0.003$ [4]). In the study by Raap et al. [3], the results were not significant. Mental health was measured in five studies [4,5,9-11]. One study [9] reported significantly poorer mental health in patients with congenital heart disease ($p<0.001$). One study [11] measured a significantly better mental health in patients with congenital heart disease ($p<0.001$). In the other three [4,5,10] studies the results were not significant. Social support was measured in one study [9] and was found to be significantly higher in patients with congenital heart disease ($p<0.001$). General health was measured in three studies [4,5,10]. One study [5] reported significantly poorer general health ($p<0.001$). In the other two studies [4,10] the results were not significant. Perceived health, self-esteem and anxiety were measured in one study [10], but none of these domains yielded significant results. Depression was measured in four studies [3,5,9,10]. One study [9] reported a significantly higher depression rate in patients with congenital heart disease ($p<0.001$). The other three studies [3,5,10] found no significant results. Pain was measured in four studies [3-5,10], none of which showed significant results. Disability was measured in one study [10], but the results were not significant.

Overall quality-of-life score

The overall quality-of-life score was measured in three studies [7,9,11]. One study [7] reported a significantly higher overall score for the patients with congenital heart disease ($p<0.01$). Another study [11] also reported significantly higher overall score ($p=0.001$). The third study [9] showed a significantly lower quality of life for the patients with congenital heart disease ($p<0.001$).

Table 2 - The score of the studies individually by the ten criteria developed by Gill and Feinstein. NA: Not Available

	Conceptual definition of QoL	Domains of QoL defined	Reason for choosing measure-ment	Score aggregated into a sigle index	Patient's rating on overall QoL	Distinction between overall and health-related QoL	Patient could supplement items	These items were incor-porated in final rating	Patients could rate personal importance of items	Importance rate was incor-porated into final rating	Summary score
L. Daliento et al. 2005[4]	-	+	+	-	-	+	-	NA	-	NA	38%
M. Kamphuis et al. 2002[5]	-	+	+	-	-	+	-	NA	+	+	56%
P. Moons et al. 2005[8]	+	NA	+	+	-	+	+	+	+	+	89%
P. Moons et al. 2006[7]	+	+	+	+	+	+	-	NA	+	+	89%
G. Raap et al. 2007[3]	-	-	-	-	-	+	-	NA	-	NA	13%
M. Rose et al. 2005[9]	-	+	+	-	+	-	-	NA	-	NA	38%
Z. Saliba et al. 2001[10]	-	-	-	-	-	-	-	NA	-	NA	0%
L. Simko et al. 2003[11]	+	+	-	+	-	-	-	NA	-	NA	38%
Summary of data	3	5	5	3	2	5	1	1	3	3	Mean 45,1%

Separate analysis of studies with quality scores over 50%
Three studies [5,7,8] had scores over 50% according to the Gill and Feinstein criteria. The results of these studies mostly corresponded with the results of the other studies, except for the domains job/education, leisure time, nourishment and general health. Moons [8] found that job/education, leisure and nourishment time were not significantly different between patients and controls. According to another study [11], these domains were significantly better in the patient group. For the " general" domain, the study by Kamphuis et al. [5] showed significantly lower scores ($p<0.001$). This is different from the other two studies [4,10], which showed no significant result.

Discussion

Regarding their health-related quality of life, patients with congenital heart disease have significantly poorer physical health and significantly better social support compared to the healthy population. The overall score on the quality of life differs between studies, but patients with congenital heart disease often had a higher overall score on quality of life compared to the healthy population.

The other domains of the health-related of life showed no significant results. Multiple studies concluded that general health is not significantly different. Moreover, the study by Kamphuis et al. [5] is given extra weight because it had a quality rating over 50%.

We found that the domains influencing the general quality of life in patients with congenital heart disease are not significantly different compared with healthy counterparts. Moons et al. [8] scores better on the criteria than the study from L.Simko et al. [11]. Therefore the results of Moons et al. [8] were considered more reliable for the domains job/education, leisure time and nourishment.

An explanation for a higher quality of life can be that the patients adapt to their disease. By accepting their disabilities and recalibrating their personal expectations, they can normalize their functioning in everyday life. Poorer physical health can be explained by the limitations patients have as a result of congenital heart disease. Some patients have poorer physical health because of their heart defect. The significantly better social support is possibly because close family or relatives believe that they have to support patients more than they would otherwise.

Regarding the quality of the studies, two of the eight studies [7,8] had a high score of 89%. Both articles had the same lead author (Moons). One article scored 56% [5]. All the other studies [3,4,9-11] scored below 50%. The criteria were developed by Gill and Feinstein in 1994, before any of the articles were written. We therefore expected higher quality scores in the included studies.

The countries where the studies were performed is a notable aspect. The included studies were performed in six different countries. Therefore, our results can be generalized for multiple countries.

Study limitations

The differences between the eight published studies may be due to differences in quality of life conceptualization and instruments. Seven different instruments were used in the eight studies. Also, some definitions used in the various studies differed from each other.

Another limitation could be that all the studies used an instrument with a questionnaire. Patients who are unable to fill in such a questionnaire are automatically excluded. Therefore, the scores on quality of life can be overestimated.

Because we did not distinguish between the various cardiac malformations, we cannot make any conclusions about a specific congenital heart disease.

Table 3 - The different domains measured by the studies. NS: Not Significant *: Overall significant difference between groups

	P. Moons et al. 2005[8]	P.Moons et al. 2006[7]	M. Kamphuis et al. 2002[5]	L. Daliento et al. 2005[4]	M. Rose et al. 2005[9]	L.Simko et al. 2003[11]	G. Raap et al. 2007[3]	Z. Saliba et al. 2001[10]
General quality of life								
Family status	NS							
Job/education	NS					Sig. higher		
						p<0.001		
Friends	NS							
Leisure time	NS					Sig. higher		
						p<0.001		
Children	NS					NS		
Married/partner	NS					NS		
Financial means and material well-being	NS							
Perception of future	NS							
Pets	NS							
Environment	NS							
Nourishment	NS					Sig. higher		
						p=0.001		
Daily activities			NS				NS	
Health-related quality of life								
Physical health*			Sig. lower	Sig. lower	Sig. lower	Sig. lower		NS
			p<0.001	p=0.003	p<0.001	p<0.001		
Mental health			NS	NS	Sig. lower	Sig. higher		NS
					p<0.001	p<0.001		
Social support*					Sig. higher			
					p<0.001			
General health			Sig. lower	NS				NS
			p<0.001					
Perceived health								NS
Self esteem								NS
Anxiety								NS
Depression			NS		Sig. higher		NS	NS
					p<0.001			
Pain			NS	NS			NS	NS
Disability								
Happiness			NS				NS	NS
Overall score		Sig. higher			Sig. Lower	Sig. higher		
		p<0.01			P<0.001	p=0.001		

Conclusion

We aimed to identify the quality of life in adults with congenital heart disease in comparison with healthy counterparts. We have taken a step toward identifying the problems in quality of life that patients with congenital heart diseases can experience. This provides crucial information that will give healthcare professionals better insight into the consequences of heart defects on patients' quality of life. This review can help the healthcare professionals design new programmes that aim to improve patients' quality of life.

We recommend further research into the quality of life related to specific congenital heart diseases. Studies that focus on a single congenital heart disease can give more information about that specific patient group. In addition, we recommend research into programmes that are based on the information in our review.

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Review

Comparison of Fesoterodine, Tolterodine, Oxybutynin and Solifenacin in patients with overactive bladder

A systematic review

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Objective: **For the treatment of overactive bladder (OAB), tolterodine, solifenacin, fesoterodine, darifenacin and oxybutynin are the most frequently prescribed drugs. The aim of this review was to compare these five antimuscarinic agents in order to recommend a therapy for overactive bladder.**
Methods: **We performed a systematic review using PubMed search. We searched on January 11th, 2011. Six studies were included. Our inclusion criterion was: comparison of two antimuscarinic agents.**
Results: **Solifenacin and tolterodine were equally effective as treatments for OAB. Solifenacin and oxybutynin showed improved efficacy, but more adverse effects were also reported. Dry mouth was reported in 35% of the subjects taking solifenacin vs. 83% of the subjects taking oxybutynin (p< 0, 0001). Fesoterodine was significantly better than tolterodine regarding urge urinary incontinence UUI episodes (p< 0.001), mean voided volume (MVV) (p< 0.001) and number of continent days per week (p<0.05).**
Conclusion: **After studying the adverse effects and efficacy for treating symptoms of overactive bladder, we recommend fesoterodine.**

Introduction

In the Netherlands, five antimuscarinic drugs can be prescribed for the treatment of overactive bladder (OAB): tolterodine, solifenacin, fesoterodine, oxybutynin and darifenacine [1]. This drugs work by blocking the M3 muscarinic acetylcholine receptor, which is responsible for bladder muscle contraction.

Overactive bladder is an idiopathic symptom complex suggestive of detrusor overactivity. OAB is characterized by urge urinary incontinence (UUI), usually with urinary frequency and nocturia [2,3]. The prevalence of OAB among adults in the USA and Europe has recently been estimated at 16-17% [4], which means that as many as 34 million people are affected in the USA alone [5]. OAB with urge incontinence is more likely to occur in women than in men (9.3 and 2.6% respectively) and it increases with age in both sexes [4].

OAB is under-treated by clinicians, despite clear evidence that antimuscarinics reduce OAB symptoms [3]. By blocking the muscarinic receptors, antimuscarinic agents inhibit the abnormal bladder contractions (detrusor overactivity) and reduce OAB symptoms. However, they also act on muscarinic receptors in other parts of the body, causing adverse effects such as dry mouth and constipation, which limits their use [6].

In recent decades, several new compounds have been developed that have fewer adverse effects than the oldest of the currently available antimuscarinic drugs, oxybutynin. Tolterodine was the first agent introduced for this purpose. This medicine is bladder-selective and has been shown in animal studies to have a greater affinity for the bladder than for other organs [7]. Clinically, tolterodine has been shown to have fewer side effects than other antimuscarinic agents [8].

Another antimuscarinic agent is solifenacin, which has also proven to be bladder-selective. Clinical trials demonstrated that solifenacin is effective in the treatment of OAB and is generally well tolerated [9].

Fesoterodine is a more recently introduced antimuscarinic agent. It acts functionally as a prodrug and is rapidly and extensively converted by nonspecific esterases to its primary active metabolite, 5-hydroxymethyl tolterodine (5-HMT). Fesoterodine is not detectable in plasma after oral dosing. 5-HMT is also the major active metabolite of tolterodine, but is formed from tolterodine via cytochrome P450 2D6-mediated oxidation in the liver [10].

Oxybutynin is another antimuscarinic treatment; it relaxes the smooth muscle of the bladder.

Darifenacin is the fifth antimuscarinic agent addressed in the present study. Similar to the other antimuscarinic agents, it works by blocking the M3 muscarinic acetylcholine receptor.

Although several studies compared two of these medications, to the best of our knowledge no comparison of all five of these medications has been reported. The aim of our study was to determine the best medication for patients with overactive bladder. In this systematic review, we addressed the following research questions. (1) Which medication shows the best decrease in UUI episodes, total voids, nocturnal voids urgency episodes and the best increase in MVV/void? (2) Which medication has the fewest adverse effects? (3) Which medication is associated with the best patient perception of bladder condition and has the highest score on the OAB questionaire? The answers to these three questions will be used to recommend a therapy for OAB.

Methods

We searched the National Library of Medicine's PubMed database on January 11th, 2011. The MeSH terms used were oxybutynin [Substance] or darifenacin [Substance] or quinuclidin-3'-yl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate [Substance] (solifenacin) or fesoterodine [Substance] or tolterodine [Substance] and urinary bladder, overactive/drug therapy [Major Heading]. Our limits were humans, randomized controlled trial and English as language.

Our inclusion criterion was that the article compared at least two drugs. Exclusion criteria were: neurogenic overactivity, cost-utility analysis, studies in which one group used two different antimuscarinics, pharmacokinetic profile and the involvement of non-antimuscarinic drugs. We applied these criteria to the titles of the articles. The primary efficacy parameters we used in this study were: urge urinary incontinence (UUI), total voids, nocturnal voids, urgency episodes and the maximum voided volume (MVV). The primary tolerability parameters we used in this study were PPBC (patient perception of bladder condition) and adverse effects.

Results

Our literature search on PubMed resulted in 461 studies about overactive bladder. After applying our inclusion and exclusion criteria, six studies remained: four randomized controlled trials and two randomized post-hoc analysis studies. These six studies were used for our review.

Five of these studies were multicentric. One study was conducted in Taiwan, two in Europe and three in Canada and the USA. More than 80% of these patients were women, and the mean age was approximately 60 years.

Efficacy

In these studies, a total of four antimuscarinic agents were compared. Some studies used a placebo as well. The four agents were solifenacin, tolterodine, oxybutynin and fesoterodine. No studies on darifenacin were found. Four of these studies lasted 12 weeks, one study 8 weeks and one study 4 weeks. The data on UUI episodes, total voids, nocturnal voids, urgency episodes and MVV were collected.

Table 1 shows study details and efficacy of these agents.

Ho et al. (2010) and Chapple et al. (2007) [6,11] compared solifenacin 5 mg to tolterodine 4 mg. In both studies at week 12, the mean changes from baseline in number of micturition per 24 hours were not significantly different between the solifenacin ($p = 0.58$) and tolterodine groups [6,11]. In both studies, the two groups both showed significant improvements in reducing urgency episodes per 24 hours. At the endpoint of both studies, the mean changes from baseline were not significantly different for urgency episodes between the solifenacin ($p = 0.37$) and tolterodine groups (p = ns) [6,11]. However, these two studies reported contradictory results in mean voided volume per micturition. In one study, mean voided volume per micturition increased significantly relative to baseline in the solifenacin group, but not in the tolterodine group [6], while the other study reported no difference between these two drugs relative to baseline (Table 1) [11].

In two other studies, Herschorn et al. (2009) and Chapple et al. (2008), fesoterodine 8 mg was compared to tolterodine 4 mg, and both drugs were compared to a placebo. In both studies fesoterodine significantly improved UUI episodes at week 12 compared with tolterodine extended release (ER) (in one study, $p = 0.017$ [12] and in the other, $p< 0.001$ [10]). In both of these studies fesoterodine was associated with significantly greater improvements in MVV than tolterodine ER (in one study, $p = 0.005$ and in the other $p < 0.05$ [10,12]). In one of these studies, tolterodine compared with placebo showed significant improvement in UUI episodes, total voids/24 h and urgency episodes/24 h, but not in MVV [12], while in the other tolterodine compared with placebo showed a significant improvement in MVV and urgency episodes, but not in UUI [10]. No significant improvement in nocturnal voids/24 h was found between fesoterodine and placebo and tolterodine and placebo ($p = 0.506$) (Table 1) [12].

Anderson et al. (2005) compared extended-release oxybutynin 10 mg to extended-release tolterodine 4 mg. The mean weekly UUI episodes (SD) decreased from 37.5 (14.0) recorded at baseline to 10.2 (13.7) for the ER oxybutynin treatment group, and from 36.2 (13.9) to 9.3 (13.3) for the ER tolterodine group.

Table 1 - Study details, tolerability and efficacy: summary of the clinical data

Variables Article	Duration (weeks)	Dose	No. of patiens	Completed the study (%)	UUI episodes/24 h	Total voids/ 24 h	Nocturnal voids/24 h	Urgency episodes/24 h	MVV/void (mL)
Ho	12	Solifenacin 5 mg	39	38 (97)	-2.79 ±3.31	-2.56	/	-1.70 ±3.07	27.61 ±51.74 ‡
et al. 2010		Tolterodine 4 mg	36	35 (97)	-4.67 ±4.56	-2.44	/	-1.15 ±2.68	10.60
		No placebo							
Herschorn	8	Solifenacin OD 5 mg	68	52 (76)	/	/	/	/	/
et al. 2010		Oxybutynin TID 5 mg	64	40 (63)	/	/	/	/	/
		No placebo							
Herschorn	12	Fesoterodine 8 mg	679	598 (88)	-1.72 * #	-2.2 *	-0.6	-3.5 *	32.9 * #
et al. 2009		Tolterodine ER 4 mg	684	629 (92)	-1.61 *	-2.1 *	-0.6	-3.1 *	23.5
		Placebo	334	304 (91)	-1.46	-1.5	-0.5	-2.0	16.8
Chapple	12	Fesoterodine 8 mg	287	272 (95)	-85 % * ^	/	/	-20 % †	36 † #
et al. 2008		Tolterodine 4 mg	290	281 (97)	-70 %	/	/	-16 %*	24 *
		Placebo	283	277 (98)	-50 %	/	/	-14 %	11
Chapple	4	Solifenacin 5 mg	593	575 (97)	-1.22 ‡	-1.71*	-0.51	-1.96	28.51
et al. 2007		Tolterodine 4 mg	607	590 (98)	-0.91 ‡	-1.47*	-0.44	-1.67	24.29
		No placebo							
Anderson	12	Oxybutynin ER 10 mg	381	52 (14)	-27.3 ±13.7	-31.7 ±22.0 #	/	/	/
et al. 2005		Tolterodine ER 4 mg	399	42 (11)	-26.9 ±13.3	-28.5± 21.3	/	/	/
		No placebo							

Mean change from baseline to week 12 in UUI episodes/24 h, MVV/void, total voids/24 h, nocturnal voids/24 h and urgency episodes/24 h. Data represent the full analysis set for patients reporting symptoms at baseline * $p< 0.05$ drug vs. placebo; # $p< 0.05$ drug 1 vs. drug 2; † $p< 0.001$ vs. placebo; ^ $p<0.001$ drug 1 vs. drug 2; ‡ $p< 0,05$ vs. baseline; OD= once daily; TID= 3 times daily; ± = standard deviation. In Anderson et al. (2005) the variables were measured weekly.

Table 1 a – continued

Variables Article	Dry mouth (no.(%))	Adverse effects Constipation (no.(%))	Withdrawal (%)
Ho	7 (18.0)	5 (12.8)	1 (2.6)
et al. 2010	3 (8.3)	1 (2.8)	1 (2.8)
Herschorn	24 (35)	9 (13)	16 (23.5)
et al. 2010	53 (83)	/	24 (37.5)
Herschorn	189 (27.8)	37 (5.4)	42 (6.2)
et al. 2009	112 (16.4)	28 (4.1)	28 (4.1)
	20 (6.0)	10 (3.0)	6 (1.8)
Chapple	97 (33.8)	13 (4.5)	15 (5)
et al. 2008	48 (16.9)	8 (2.8)	9 (3)
	20 (7.1)	4 (1.4)	6 (2)
Chapple	108 (18.2)	18 (3.0)	19 (3.2)
et al. 2007	91 (15)	7 (1.2)	16 (2.6)
Anderson et al.	107 (27.5)	20 (5.2)	20 (5.1)
2005	100 (25.2)	41 (10.2)	19 (4.8)

For the ER oxybutynin group, the mean weekly micturition frequency (SD)
decreased from 96.5 (27.1) voids recorded at baseline to 64.8 (22.0) at last observation, compared with a decrease from 97.9 (24.2) to 69.4 (21.3) for the ER tolterodine group. The difference between the groups was significant (p=0.035) (Table 1) [13].

Safety and tolerability

Several adverse effects were associated with antimuscarinic drug use. The most common were dry mouth and constipation, but diarrhea, headache, urinary tract infection and dizziness were also frequently reported. Generally, side effects were mild and occurred only in a minority of patients. Table 1a shows an overview of the tolerability and the safety of several drugs (some compared to placebo).

Ho et al. (2010) and Chapple et al. (2007) [6,11] compared the tolerability of solifenacin 5 mg and tolterodine 4 mg. In the solifenacin group, 38.5% of patients suffered from at least one adverse effect, compared to 25.0% in the tolterodine group. However the percentages did not significantly differ between the two groups
(p = 0.23) [6]. The reported adverse effects included dry mouth, constipation, hiccups, palpitations and dizziness, with the most common being dry mouth (p = 0.31) and constipation (p = 0.20) [6]. These percentages were consistent with the other study [11]. In the two groups the incidence of each adverse effect was similar (Table 1 a) [11].

In these two studies, there were a few patients who dropped out of the study because of adverse events. One patient in the solifenacin group dropped out because of dizziness, and another in the tolterodine group dropped out because of palpitations [6]. However, in Chapple et al. (2007) 35 patients dropped out because of adverse events. The primary reason was dry mouth, which was given as reason by 6 patients in the solifenacin group and 6 in the tolterodine group. Four patients in the solifenacin 5 mg group dropped out, giving constipation as the primary reason. The rest of the patients dropped out for several other reasons (Table 1a) [11].

Herschorn et al. (2010) compared solifenacin to oxybutynin [14]. In this study, significantly fewer patients on solifenacin reported dry mouth compared to the oxybutynin IR (immediate-release) group (95% CI 33–62, p <0.0001). In those reporting dry mouth, solifenacin was associated with significantly lower severity of this adverse effect than oxybutynin IR (p = 0.001) [14]. Excluding dry mouth, the overall incidence of other adverse events was 59% in the solifenacin group and 70% in the oxybutynin IR group (p = 0.17). After dry mouth, the most commonly reported adverse events in the oxybutynin IR group were nasal dryness in 14% of patients, dizziness in 9% and fatigue in 9%. In contrast, the most commonly reported adverse event in the solifenacin group was constipation in 13% of patients [14]. Oxybutynin was associated with higher rates of adverse events. Similar results were found by Anderson et al. (2005) when comparing oxybutynin to tolterodine [13]. Dry mouth was the most commonly reported adverse event in each group. Dry mouth was more common in the extended release (ER) oxybutynin group compared to the ER tolterodine-treated group (p = 0.004). The majority of dry mouth events were mild in severity [13]. While the overall dropout rate did not differ significantly between the solifenacin and oxybutynin IR groups (p = 0.081), significantly fewer solifenacin patients dropped out due to dry mouth compared to the oxybutynin IR treated group (3% vs. 19%, p = 0.003) [14]. Similar results were found in the study with oxybutynin and tolterodine. However, the overall dropout rate in this study did not differ significantly between the tolterodine and oxybutynin IR groups (Table 1a) [13].

Compared to solifenacin, tolterodine was associated with fewer adverse events [6,11]. In two studies, tolterodine 4 mg was also compared with fesoterodine 8 mg [10,12]. The most frequently reported adverse events in the fesoterodine group were dry mouth, headache and constipation. These were also the most frequently reported adverse events in the tolterodine ER group and in the placebo group. Fesoterodine was associated with more adverse events than tolterodine [12]. In another study, fesoterodine was also associated with more adverse events than tolterodine. [13]. The most common adverse events reported in this study were dry mouth and constipation (Table 1a).

In all treatment groups studied by Herschorn et al., the majority of adverse events, including dry mouth, were mild or moderate [12]. Overall, 3.2% of patients dropped out of this study because of an adverse event. The reasons included urinary retention, which occurred in 1% of patients in the fesoterodine 8 mg group, and which required catheterization in one patient. However no patients receiving tolterodine ER or placebo dropped out due to urinary retention, and none required catheterization. Only one patient (<1%) in either group dropped out because of dry mouth. One patient (0.3%) in the fesoterodine 8 mg group dropped out because of constipation; no patients in the tolterodine ER or placebo groups dropped out because of constipation (Table 1a) [10].

Patient Perception of Bladder Condition and OAB-q

Besides considering the effects on the bladder and the adverse effects, quality of life was estimated as well. The instruments for estimating quality of life differed per study. The instruments used most often were the Patient Perception of Bladder Condition (PPBC) and the OAB Questionaire (OAB-q).

Patients completed the Patient Perception of Bladder Condition (PPBC) [6,12,14] and OAB Questionnaire (OAB-q) at baseline and at week 12 [10,12,14]. The PPBC is a validated single-item questionnaire that asks patients to rate their overall bladder condition; lower scores indicate less-severe bladder-related problems [15]. The validated OAB-q includes an eight-item Symptom Bother scale and a 25-item HRQL scale [16]. Symptom Bother items address the level of bother associated with the patients bladder condition; lower scores indicate less symptom bother.

The categorical change in PPBC score from baseline to week 12 was significantly improved in the solifenacin and tolterodine groups. At week 12, the mean changes (SD) from baseline in PPBC

were −1.40 (1.40) in the solifenacin group and −1.40 (1.60) in the tolterodine group; the two groups did not differ significantly ($p = 0.72$) [6].

However, in the other study PPBC was significantly more favorable in the fesoterodine group than in patients on placebo ($p < 0.001$) and tolterodine ER ($p < 0.001$) [12]. Changes in the tolterodine ER group were also significantly more favorable than in the placebo group ($p < 0.001$). Consistent with this finding, the proportion of patients reporting 'some minor problems' or better on the PPBC at week 12 was higher in the fesoterodine group (55%) than in the tolterodine ER (45%, $p < 0.001$) and placebo (33%, $p < 0.001$) groups. The difference between the tolterodine ER and placebo groups was also statistically significant ($p < 0.001$) [12].

According to the OAB-q scores, fesoterodine was also more favorable compared to tolterodine and placebo. Improvements in OAB-q scores from baseline to week 12 were significantly greater in the fesoterodine than the placebo group on the Symptom Bother scale, total HRQL scale and all four HRQL domains (all $p < 0.001$) [12].

Discussion

Based on our findings, we recommend fesoterodine. This drug has shown the best decrease in UUI episodes, total voids, nocturnal voids urgency episodes and the best increase in MVV/void. Although oxybutynin improves the UUI episodes and total voids more than fesoterodine (Table 2), the adverse effects must be considered as well. The most prevalent adverse effects were dry mouth and constipation. Studies on oxybutynin [14] and fesoterodine [10,12] reported more cases of dry mouth than studies on the other antimuscarinics. The drug most associated with constipation was solifenacin [6,14]. The other adverse effects that were measured were reported by only a small percentage of the patients. Most adverse effects did not bother patients enough to discontinue the treatment. Dropout rate was low, except in the study comparing oxybutynin and solifenacin (Table 1 a) [14]. We therefore conclude that fesoterodine is the best medication for overactive bladder. It is effective and has fewer adverse effects than oxybutynin.

This conclusion is subject to a number of limitations. First, no studies on darifenacin were found, so we cannot draw any conclusions about the advantages or disadvantages of this drug. Second the patient populations for the other four medications differed. In total, 1973 patients took tolterodine, but only 455 patients were placed in the oxybutynin group. Third, fesoterodine was compared only to tolterodine, not to any other drugs. Fourth, the patients did not live in the same area of the world. One study was done in Taiwan, while the others were done in Europe, Canada or the USA. Differences between the populations, such as lifestyle, could have affected the efficacy of the drugs.

Another limitation concerns the inclusion and exclusion criteria. The inclusion criteria were generally the same, but the exclusion criteria differed. Some studies excluded patients with specific diseases, while others did not. It is possible these diseases affected the results, but we have no evidence about this.

An evidence-based recommendation is difficult to make due to the different or unclear parameters used in the studies. For example, Herschorn et al. (2010) did not discuss the parameters used (Table 1). Those researcher primarily investigated the adverse effects, but they did state a p-value or confidence interval to support their assertion that PPBC improved significantly [14]. The parameters for the quality of life were especially different between the studies. Different quality of life questionnaires are difficult to compare. Therefore we were unable to answer the third research question. For future studies, we recommend that researchers use common parameters.

Other limitations of the various studies should be mentioned. Anderson et al. (2005) distinguished between patients who used antimuscarinics prior to the study and those who did not. We used only the results from the second group, because the other studies in our review excluded patients who used antimuscarinics during a short period prior to the study.

In Chapple et al. (2007) the patients were randomized for the two drugs at baseline. After week 4 they looked at the results, and requests for increased dosage from patients in the solifenacin group were approved. However, the subsequent results showed that the number of patients in tolterodine changed as well. Because there was no explanation for that change, we used only the results after week 4.

In Chapple et al. (2008) the decrease of UUI and urgency episodes were given in percentages instead of numerical changes.

Some of the studies did not discuss the results compared to baseline. Therefore we could not conclude that the drugs improved bladder condition significantly. However, we assume that all these types of antimuscarinics significantly improve the OAB symptoms, otherwise they would not be used at all.

Two major adverse effects were reported: dry mouth and constipation. One of the studies primarily investigated the adverse effects, in particular dry mouth. In that study, dry mouth was reported much more often than in the other studies. When we compared medications, we found major differences between the oxybutynin group in Herschorn et al. (2010) and the oxybutynin group in Anderson et al. We suspect that the high prevalence of dry mouth Herschorn et al. (2010) was influenced by the fact that the primary aim of this study was to determine the effect of the medications on dry mouth.

At present, we conclude that fesoterodine should be recommended as therapy for overactive bladder. However, we recommend that future studies should compare the five drugs to each other using the same parameters and equal populations of patients.

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Table 2 - Summary of the efficacy data

Variables Medication	UUI episodes/ 24 h	Total voids/ 24 h	Nocturnal voids/ 24 h	Urgency episodes/ 24 h	MVV/void (mL)
Solifenacin	-1.22 to -2.79	-1.71 to -2.56	-0.51	-1.70 to -1.98	27.61 to 28.51
Tolterodine	-0.91 to -4.67	-1.47 to -4.01	-0.44 to -0.6	-1.15 to -3.1	10.60 to 24.29
Oxybutynin	-3.9	-4.53			
Fesoterodine	-1.72 to 85%*	-2.2	-0.6	-3.5 to 20%*	32.9 to 36

This numbers are ranges of different drugs in different studies. * Mean percent reduction from baseline. In the article of Anderson et al. 2005 the variables were measured weekly, so the numbers in table 1 are divided by 7.

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Does pharmacologic treatment prevent children from emergence agitation after sevoflurane anesthesia?

A systematic review

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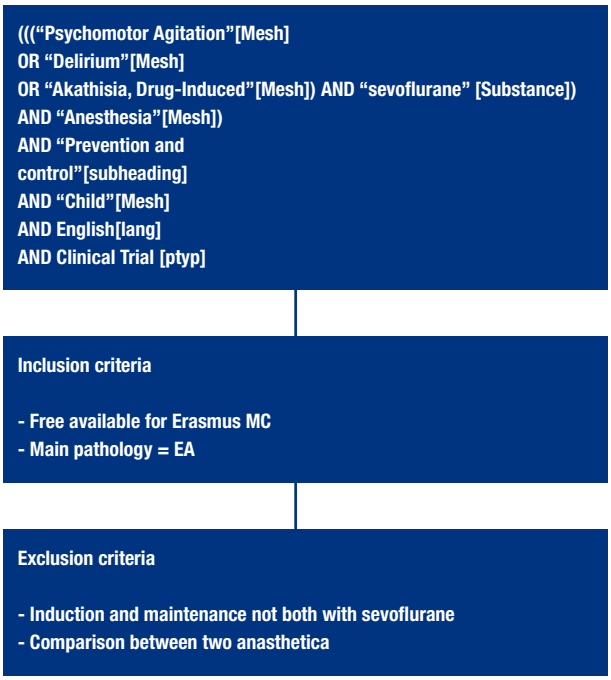
Objective: **To determine whether pharmacologic treatment is likely to decrease the incidence of Emergence Agitation (EA) in children after sevoflurane anesthesia.**
Methods: **We performed a Medline search using the MeSH terms sevoflurane, emergence agitation, child, anesthesia and prevention. We included prospective clinical trials written in English.**
Results: **During anesthesia for nonsurgical diagnostic procedures, propofol, dexmedetomidine and fentanyl all caused a significant decrease in the incidence of EA. In surgical patients, ketamine (in combination with midazolam), a caudal block (in combination with midazolam), dexmedetomidine and tropisetron all significantly decreased the incidence of EA, whereas midazolam and clonidine did not.**
Conclusions: **For pain-free diagnostic procedures, we recommend the use of propofol to decrease the incidence of EA. In surgical patients, ketamine (with midazolam) and tropisetron may be promising options.**

Introduction

Emergence agitation (EA) is very common in children who receive sevoflurane anesthesia. One out of many definitions of EA is "a disturbance in a child's awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post anesthesia period (within the first 30 minutes of emergence from anesthesia)" [1].

Depending on the definition used, the age of the children and other factors, the incidence of EA can range from 10% to as high as 80% [1]. EA is a more frequent side effect in preschool children than in older children [2].

Figure 1 -
Search strategy and study selection



EA creates a challenging situation for post-anesthesia care providers. Moreover, it may lead to higher complication rates: increased bleeding from operative sites, pulling out surgical drains or IV catheters, pulling surgical dressings, unhappy parents and disturbances to the other recovering patients [3].

The etiology of EA is not well understood. There are several factors that probably contribute to EA: rapid emergence, intrinsic characteristics of the anesthesia, postoperative pain, surgery type, age, preoperative anxiety, child temperament and adjunct medication [1].

Compared to halothane and propofol anesthesia, EA occurs more often after sevoflurane anesthesia [4,5]. However, sevoflurane is the most frequently and widely used anesthetic in children. The reasons for the widespread use of sevoflurane are several substance-specific properties such as “fast and well tolerated induction, low hepatotoxicity, hemodynamic stability, and rapid emergence from anesthesia”[6]. Because of these beneficial effects of sevoflurane compared to propofol and halothane, it is important to improve the emergence status of children when sevoflurane is used.

No golden standard for treating EA after sevoflurane anesthesia is currently available. The main question is, can pharmacologic treatment be used for this purpose? Our aim was to answer this question by systematically reviewing the published research on the recommended pharmacological treatments of EA in children after sevoflurane anesthesia.

Methods

Search strategy

We performed a Medline search (January 10, 2011) for publications written in English with the following MeSH-terms defining EA: “psychomotor agitation” OR “delirium” OR “akathisia, drug-induced”. To add sevoflurane to our search we used the term “sevoflurane” as a substance and added the MeSH-term “anesthesia”. Sevoflurane and anesthesia were both added with the AND option to the MeSH-terms for EA. Because our research question concerned medical treatment for decreasing the incidence of EA in children after sevoflurane anesthesia, we added the MeSH-term “child” and the subheading “prevention and control” to our search. Finally, we limited our search to clinical trials. Figure 1 shows this search strategy together with the inclusion and exclusion criteria, which are discussed in the next paragraph.

Study selection and data extraction

Studies were selected by reading the titles and abstracts using the following inclusion and exclusion criteria.

The inclusion criteria were that the full text articles were available online for free at the Erasmus MC and that the study focused on EA as the main pathology. Publications were excluded when the induction and maintenance of anesthesia were not both performed with sevoflurane. Studies that compared two anesthetics were also excluded.

Processing the results

While processing the results, we distinguished between pain-free and non pain-free interventions. Because pain probably is one of the main contributing factors in the etiology of EA [1], this could be a confounder in the non pain-free study results.

Results

A total of 9 articles met the criteria of our Medline search. Three of them describe pain-free procedures and six describe non pain-free procedures.

Pain-free procedures

Abu-Shawan conducted a trial in 83 children aged 2-7 years undergoing magnetic resonance imaging (MRI) [7]. Children in the intervention group were given 1 mg/kg of propofol (≤ 30 mg) (n=42), while children in the placebo group were given saline as a control (n=41). No other sedative medication was given to any of the children. In the recovery room, EA was evaluated using the pediatric anesthesia emergence delirium scale (PAED, Table 1). Patients were considered agitated if they had a score of 16/20 or higher at any time interval during the first 30 minutes after surgery. EA was observed in 11 (26.8%) children in the control group and two (4.8%) children in the propofol group ($p<0.05$).

Isik et al. randomly assigned 42 children, aged 18 months to 10 years, to receive either dexmedetomidine 1 mg/kg IV (n=21) or placebo (n=21) after induction of anesthesia for an MRI scan [8]. Patients were not premedicated. EA was assessed with a 5-point scale (1=Sleeping; 2=Awake and calm; 3=Irritable and crying; 4=Inconsolable crying; 5=Severe restlessness and disorientation) and recorded every 5 minutes from discontinuation of sevoflurane until the patients were awake, alert, calm and responsive to their parents. EA was defined as an agitation score of ≥4 for ≥5 minutes duration. The incidence of agitation was 47.6% in the placebo group and 4.8% in the dexmedetomidine group ($p<0.05$).

Table 1 - PAED scale

	Score
The child makes eye contact with the caregiver	4 = not at all
The child actions are purposeful	3 = just a little
The child is aware of the surroundings	2 = quite a bit
	1 = very much
	0 = extremely
The child is restless	0 = not at all
The child is inconsolable	1 = just a little
	2 = quite a bit
	3 = very much
	4 = extremely

Table 2 - Results pain-free procedures

Source	No.	Study Design	Drug (Patients, No.)	Control (Patients, No.)	Non-painful procedure	Results (percent with agitation)	Age children	premedication	Used agitation scale
Abu-Shawan[7]	85(83)	RCT	Propofol	Placebo	MRI	Propofol 4.8%	2-7 years	None	PAED
			1 mg/kg (n=42)	(saline) (n=41)		Placebo 26.8%			
Isik et al.[8]	42	RCT	Dexmedetomidine	Placebo	MRI	Dexmedetomidine 4.8%	18 months -	None	Five-point scale
			1 µg/kg/h (n=21)	(n=21)		Placebo 47.6%	10 years		
Cravero et al.[9]	32	RCT	Fentanyl	Placebo (saline)	MRI	Fentanyl 12%	18 months -	None	Five-point scale
			1 µg/kg (n=16)	(n=16)		Placebo 56%	10 years		

RCT = randomized controlled trial. PAED = Pediatric Anesthesia Emergence Delirium Scale

Cravero et al. performed a trial in 32 pediatric outpatients receiving sevoflurane anesthesia for an MRI scan. Patients were randomly assigned to receive either placebo (saline, n=16) or 1 µg/kg Fentanyl (n=16) 10 minutes before discontinuation of their anesthetic [9]. No premedication was given. The level of agitation was recorded continuously beginning with discontinuation of sevoflurane application. The authors used an EA scale which rates agitation from 1 to 5. A score of 1 represents the obtunded patient with no response to stimulation, 2 designates asleep but responsiveness to movement or stimulation, 3 stands for awake and appropriately responsive, 4 crying and difficult to console, and 5 describes wild trashing behavior that requires restraint. EA was defined as an EA score of ≥4 for ≥5 minutes duration. The incidence of agitation in the placebo group was 56% and in the fentanyl group 12% (p=0.02). Table 2 contains a summary of the above results.

Non pain-free procedures

Abu-Shawan et al. published the results of a trial in 80 children aged 4-7 years undergoing dental repair [10]. All children were premedicated with acetaminophen (30 mg/kg) and midazolam (0.5 mg/kg). Ten minutes before end of surgery, the children were either given intravenous ketamine (0.25 mg/kg) (n=42) or placebo (saline, n=38). In the recovery room EA was evaluated using the PAED scale. Patients were considered agitated if they had a score of 16/20 or higher. The incidence of EA was significantly lower in children who received ketamine (16.6%) than in the placebo group (34.2%) (p<0.05).

Breschan et al. assessed the effects of rectal midazolam (1 mg/kg or 0.5 mg/kg) on EA in 115 children, aged 6 months to 5 years, undergoing minor surgery [11]. Midazolam was given rectally 10 to 15 minutes before surgery. Behavior at emergence from anesthesia was assessed on a three-point scale (1=Calm and cooperative; 2=Mildly anxious and agitated but consolable; 3=Severely agitated, totally out of control and inconsolable). Patients were considered agitated if they had a score of 3. The results of that study showed no evidence for a difference between the two treatments.

Two trials assessed the impact of dexmedetomidine on the incidence of EA. Ibacache et al. assessed dexmedetomidine (0.15 µg/kg (n=30) or 0.30 µg/kg (n=30) in 90 children, age 1-10 years, undergoing superficial lower abdominal and genital surgery [6]. After anesthetic induction and placement of the IV line, the children received either dexmedetomidine or placebo (saline, n=30). Behavior during the postoperative period was rated on a four-point scale (1=Calm; 2=Not calm but could be easily calmed; 3=Not easily calmed, moderately agitated or restless; and 4=Combative, excited or disoriented). Patients were considered agitated if they had a score of 3 or higher. The incidence of agitation was significantly lower (p=<0.05) in children who received dexmedetomidine 0.15 µg/kg (17%) or 0.30 µg/kg (10%) than in the placebo group (37%). Shukry et al. assessed dexmedetomidine (0.2 µg/kg/h) in 46 children, aged 1-10 years, undergoing elective outpatient surgical procedures [3]. Continuous infusion of dexmedetomidine (n=23) or placebo (saline, n=23) was started after securing the airway during induction of general anesthesia and was discontinued 15 minutes after admission to the post-anesthesia care unit (PACU). In the PACU, EA or delirium (ED) were assessed continuously and rated on the scale described by Watcha et al. (0=Child is asleep; 1=Calm; 2=Crying, but can be consoled; 3=Crying and cannot be consoled; 4=Agitated and thrashing around) [12]. On to this scale, patients had an ED episode if they had a score of 3 or higher. An episode was defined as 3 minutes of continuous ED. The incidence of ED was significantly lower in the dexmedetomidine group (26%) than in the placebo group (60.8%) (p=0.036). Also, the number of episodes of ED was significantly lower in the dexmedetomidine group (p<0.017).

Lankinen et al. randomly assigned 75 children aged 1-7 years, undergoing adenoidectomy, to receive either intravenous clonidine (n=24), tropisetron (n=25) or placebo (n=26)[13]. After anesthesia induction, an IV-cannula was established and the children received either clonidine (n=24), tropisetron (n=25) or placebo (n=26). In the recovery room a modified pain/discomfort scale (Crying: 0=Not crying; 1=Responding to comforting; 2=Not responding to comforting. Moving: 0=None; 1= Restless; 2=Thrashing. Agitation: 0=Asleep or calm; 1=Mild agitation; 2=Severe agitation/hysterical) was used to assess postoperative behavior. If the sum of the pain/discomfort scale exceeded 3 at any time, the child was considered as agitated. The incidence of postoperative agitation was significantly lower (32%) in the tropisetron group compared with placebo (62%) (p<0.05). Clonidine did not prevent agitation (54%) (p=0.60).

Aouad et al. applied either a preoperative caudal block (1 ml/kg plain racemic bupivacaine 0.25%) or fentanyl (1 µg/kg boluses) to 44 children, aged 2-6 years undergoing inguinal hernia repair[14]. All children were premedicated with oral midazolam (0.5 mg/kg) 20 minutes before induction of anesthesia. After induction of anesthesia, children assigned to receive caudal block (n=22) were positioned in the lateral position and injected with bupivacaine. Children assigned to the fentanyl group (n=22) received additional boluses of 1 µg/kg IV fentanyl if heart rate or systolic blood pressure increased by 25% from baseline during surgery. Agitation score was graded on a 4-point scale (1 if the child was calm; 2 if the child was not calm but could be easily consoled; 3 if the child was moderately agitated or restless and not easily calmed; and 4 if the child was combative, excited or disoriented, trashing around). Patients were considered agitated if they had a score of 3 or higher. The incidence of agitation was significantly lower in the caudal group (4.5%) than in the fentanyl group (59%) (p<0.001). Table 3 provides a summary of the above results.

Discussion

Various treatment options have been proposed to decrease the incidence of EA after sevoflurane anesthesia. We found evidence that some of these proposals may result in a lower incidence of EA.

Table 3 - Results non-pain-free procedures

Source	No.	Study Design	Drug (Patients, No.)	Control (Patients, No.)	Kind of surgery	Results (percent with agitation)	Age children	premedication	Used agitation scale
Abu-Shahwan et al.[10]	85(80)	RCT	Ketamine 0.25 mg/kg (n=42)	Placebo (saline) (n=38)	Dental repair	Ketamine 16.6% Placebo 34.2%	4-7 years	Acetaminophen 30 mg/kg Midazolam 0.5 mg/kg	PAED
Breschan et al.[11]	115	RCT	Midazolam 1 mg/kg (n=57), 0.5 mg/kg (n=58)	None	Minor surgery	Midazolam (1 mg) 42.1% Midazolam (0.5 mg) 36.2%	6 months – 5 years	None	Three point scale
Shukry et al.[3]	50(46)	RCT	Dexmedetomidine 0.2 µg/kg/h (n=23)	Placebo (saline) (n=23)	Elective outpatient surgical procedures	Dexmedetomidine 26% Placebo 60.8%	1-10 years	None	Watcha scale
Ibacache et al.[6]	90	RCT	Dexmedetomidine 0.15 µg/kg (n=30) 0.30 µg/kg (n=30)	Placebo (saline) (n=30)	Superficial lower abdominal and genital surgery	Dexmedetomidine (0.15 µg) 17% Dexmedetomidine (0.30 µg) 10% Placebo 37%	1-10 years	None	Four point scale
Aouad et al.[14]	48(44)	RCT	Bupivacaine 0.25%(caudal block) 1 ml/kg (n=22)	Fentanyl 1 µg/kg (boluses) (n=22)	Inguinal hernia repair	Bupivacaine 4.5% Fentanyl 59%	2-6 years	Midazolam 0.5 mg/kg	Four point scale
Lankinen et al.[13]	75	RCT	Clonidine 1.5 µg/kg (n=24) Tropisetron 0.1 mg/kg (n=25)	Placebo (n=26)	Adenoidectomy	Tropisetron 32% Clonidine 54% Placebo 62%	1-7 years	None	Modified pain/ discomfort scale

RCT = randomized controlled trial. PAED = Pediatric Anesthesia Emergence Delirium Scale

We performed a systematic literature review of currently recommended pharmacological treatments of EA in children after sevoflurane anesthesia. Our research question was whether pharmacologic treatment prevents emergence agitation after sevoflurane anesthesia in children. For most of the studies, in other words for the majority of the drugs currently used for the prevention of EA, there was little evidence that these drugs actually lowered the incidence of EA. In addition, only two of the studies were designed to compare different drugs in the same clinical scenario. Nevertheless, we can make some recommendations on drug therapy to reduce the incidence of EA.

Pain-free procedures

The first study with propofol by Abu-Shahwan showed that adding a subhypnotic dose of propofol at the end of sevoflurane-based general anesthesia for non-painful diagnostic imaging effectively decreased the incidence of EA without delaying recovery or discharge [7]. Propofol administration at the end of surgery under sevoflurane anesthesia resulted in smoother recovery than sevoflurane alone. However, propofol administered towards the end of general anesthesia resulted in delayed emergence. These results indicate that propofol administration at the end of surgery might be a promising option to prevent EA. Whether or not pre-emergence application of propofol is an option is highly dependent on the local setting. In busy ambulatory departments, any avoidable delay of patient flow through the MRI scanner or the operating room will certainly be regarded as unacceptable, whereas in other settings a brief delay may not be regarded as a significant issue as long as it benefits the patient. Compared to the other two pain-free procedure studies, this study had the largest research group and used the PEAD scale to score EA. Remarkably, the percentage of agitated children in the placebo group was much smaller than in the other two studies. This could result from using a different scale to score EA or from the different age of the research group.

The results of the study with dexmedetomidine from Isik et al. indicate that the administration of dexmedetomidine at a dose of 1 µg/kg, after anesthesia induction, reduces the incidence of EA following sevoflurane anesthesia in the MRI unit [8]. The low incidence of EA found in this study could be attributed to the dexmedetomidine dose given. But it is important to note that this study used a five-point scale to score EA. This means that a relatively small change in the behavior of a child could make a large difference in the agitation score; the difference between agitated or non-agitated could be very small. This makes it difficult to interpret the results of this study. The decrease in agitation score does not necessarily correspond with a clinically relevant decrease in the mental state of a child. The main problem with dexmedetomidine is that it is unavailable in most European Union countries, including the Netherlands. If it were available as post-anesthesia sedation, delayed recovery and the high costs might be an issue.

In their study with fentanyl, Cravero et al. found that the incidence and duration of EA in patients receiving sevoflurane without surgery was significantly decreased by the addition of 1 µg/kg fentanyl 10 minutes before the end of anesthesia [9]. Fentanyl could therefore be a promising treatment for EA. However, the study involved a relatively small number of patients, and they used the same five-point scale as Isik et al. Due to the abovementioned problems with the agitation scale, there is some doubt that the results of this study are clinically relevant. Moreover, fentanyl is an analgesic, which makes the corresponding decrease in agitation during a pain-free procedure remarkable. Finally, fentanyl-induced respiratory depression in young children might be an issue.

Non-pain-free procedures

Of the drugs studied by Breshan et al., midazolam did not show any benefits for treating EA [11]. Abu-Shahwan et al. found the incidence of EA in children premedicated with midazolam to be as high as 34.2%. This supports the assumption that midazolam has no effect on reducing the incidence of EA [10]. Therefore, midazolam treatment alone does not seem to be an option to prevent EA.

If ketamine is given in addition to midazolam [10], the incidence of EA is likely to be significantly reduced. This was shown bij Abu-Shahwan et al. in patients who were undergoing dental repair. However the possibility that analgesic properties of ketamine contributed to this positive effect can not be excluded.

Aouad et al. reported that a caudal block combined with midazolam during inguinal hernia repair had significantly better results than the use of fentanyl with midazolam [14]. Using a caudal block in combination with midazolam yielded the greatest reduction of EA. However, the caudal block is only functional for surgery below the umbilicus. Midazolam alone is not effective, but it can be used to reduce the incidence of EA when combined with either ketamine or a caudal block. The use of ketamine alone is not recommended. Further research is required determine if a caudal block alone also reduces EA.

Data on the possible role of α2-receptor agonists, like clonidine, studied by, Lankinen et al., and dexmedetomidine, studied by Shukry et al. and Ibacache et al., in reducing EA have been conflicting [13],[3]. Clonidine did not show any benefit on reducing EA, but dexmedetomidine did. Although different scales were used to measure EA in these studies, it would be interesting to investigate the mechanism of dexmedetomidine in reducing EA to understand why these results are conflicting. The main problem with dexmedetomidine, as mentioned above, is that it is unavailable in most European Union countries, including the Netherlands. In countries where it is available, the extremely high costs make it inappropriate as a first choice drug.

Lankinen et al. suggested the use of tropisetron for prevention of EA [13]. Tropisetron is mainly used as an antiemetic to treat nausea and vomiting. It is possible that tropisetron shows a positive effect on the prevention of EA because nausea and vomiting are common causes of EA. The surgery in this study was adenoidectomy, where swallowed blood can irritate the stomach, leading to nausea and vomiting. To determine whether reduced nausea actually reduces EA, tropisetron should be studied in a different clinical setting, where the surgical treatment does not lead to nausea.

Shortcomings

The reviewed studies were difficult to compare with each other primarily because they used different scales to define agitation; at least six different measurement tools were used. Two studies used the PAED scale, one study measured agitation with a three-point scale, two studies used a four-point scale and two studies a five-point scale. The other two studies used the Watcha-scale or the modified pain/discomfort scale. Although the PAED scale is the current golden standard, not all recent studies have used the PAED scale after it was developed in 2004 [15]. Most of the studies used self-developed scales, which are subject to the interpretation of PACU nurses. This could lead to misinterpretation about whether a child is agitated or not. Moreover, the various studies used different cut-off values for the definition of EA. The PAED scale is also subject to possible misinterpretation on two scale points, restlessness and inconsolability. In addition, it is difficult to distinguish between 'just a little' and 'quite a bit' in the scoring model of the scale. However, the other four points are more objective due to the more yes/no nature of the rating. Some other studies also have objective goals in their scale.

In any case the different scales lead to different incidences of EA. Therefore, we were unable to draw a conclusion about the most effective treatment for decreasing the incidence of EA. To overcome this effect, studies should compare more treatments in the same setting while using the same scale. This was done in only two of the reviewed studies.

Other possible confounders are the duration of surgery, the type of surgery and the pain that results from the different types of surgery. All of these probably are etiologic factors of EA. Therefore, to compare studies in an optimal manner, these factors should also be the same for all studies. Unfortunately, this was not possible for our review. There were too few studies on this topic to focus on only one type of surgery with exactly the same intrinsic anesthetic characteristics.

Future research

It is important to compare multiple drugs with each other in the same clinical setting. EA must be defined with only one scale in future research, otherwise comparison is difficult or impossible. Future research into the underlying cause of EA is also recommended.

Conclusion

Pain-free procedures

Analysis of the three pain-free trials included in our study showed that propofol, dexmedetomidine and fentanyl treatment all corresponded with decreased agitation after sevoflurane anesthesia. Considering the advantages and disadvantages of each sedative or analgesic, we recommend the use of propofol to decrease the incidence of EA. The sample size of the fentanyl study was relatively small and warranted by a post-hoc power analysis only. It might thus be advisable to repeat the study with a bigger sample size.

Non-pain-free procedures

Analysis of the six non-pain-free trials included in our study showed that ketamine (in combination with midazolam), a caudal block (in combination with midazolam) and, dexmedetomidine and tropisetron all showed a decrease in agitation after sevoflurane anesthesia, whereas midazolam and clonidine did not. Consequently, some evidence indicates that ketamine (combined with midazolam) and tropisetron may be promising options. However, further evaluation appears necessary.

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Neurofeedback: self-regulation of pain using real-time fMRI
A systematic review

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Objectives: **Chronic pain is a major cause of suffering for a large number of patients. The treatment of chronic pain is often not only difficult and inadequate, it is also expensive. A new approach to chronic pain control involves neurofeedback techniques based on real-time fMRI data. This makes it possible to train people to influence specific areas of their brain that are important in pain perception, such as the insula, the rostral anterior cingulate cortex (rACC) and the subgenual ACC (sACC). In this review we analyzed studies that used neurofeedback to reduce pain.**
Methods: **We retrieved and analyzed articles in PubMed with the MeSH terms 'Neurofeedback' and 'Brain/Physiology' and the terms 'Real-time fMRI', 'Self-regulation', 'Biofeedback', 'Neurofeedback' and 'Pain'. These articles were published from January 1, 1995 till January 16, 2011.**
Results: **We found 4 articles that reported a significant change in the activity of the insula, rACC or the sACC by using neurofeedback. One of these studies indicated that neurofeedback reduced the level of pain. No studies were found that examined long-term outcomes, comparisons with other treatments or cost effectiveness of neurofeedback treatment for pain.**
Conclusion: **Neurofeedback could be an effective option for patients with chronic pain. Further research needs to be done to determine long-term outcomes and cost effectiveness of neurofeedback as compared to approved standard treatment schemes.**

Introduction

Chronic pain is a primary reason for visiting a physician, a hospital or other healthcare resource. However, even after pursuing multiple treatment options, chronic pain patients often fail to find relief [1]. Moreover, in 2009 the cost of pain medication was estimated € 94.6 million in the Netherlands [2]. Therefore, chronic pain is considered as one of the most important clinical problems facing society.

Much effort has been devoted to finding pain treatments that are more effective in terms of treatment outcome and costs [3]. A promising type of treatment that has emerged is neurofeedback training, also known as biofeedback or self-regulation. This technique uses biofeedback to train patients to influence specific areas of their brain [4]. The feedback provides real-time information about the level of activity in a particular part of the brain. The results of the patients' attempts to influence their brain activity are reflected in the feedback signal. These signals can be animated as graphs or in more figurative forms, such as the height of a beach bonfire, corresponding to changes in activation of a particular brain region [1,5]. The patients are instructed to alternately increase and decrease the activation level of a specific brain area.

Control over brain activation is a difficult issue. There are two types of control: implicit and explicit control [1]. Implicit control over brain activation is learned through normal development or as a skill; after the learning process the skill is often exerted automatically. Individuals exhibit implicit control over brain activation all the time. Explicit control over brain activation is learned wilfully; it allows a person to control his/her brain activity with deliberate cognitive choices that ultimately lead to a change in activation of a brain region [1].

One of the first neurofeedback studies measured brain activity with electroencephalography (EEG). It showed not only that humans are capable of gaining volitional control over regionally specific brain activity by using EEG signals as feedback, but also that controlling brain activation may be of therapeutic benefit [6]. More recently real-time functional MRI (rtfMRI) has been used, which allows for a more detailed mapping of brain activity in real time. This led deCharms RC et al. to state that [1]: "The ability to observe one's own brain as the mind processes unfold might allow us to become aware and learn to control some of the most important aspects of human life: conscious functions, and even the breakdown of these processes in disease." The new technique of rtfMRI extends the MRI process by taking advantage of the speed with which 3D MRI volumes can be collected. In rtfMRI the same volume is sampled repeatedly at short intervals (for example, once per second) using an MRI measurement that is sensitive to changes in blood iron concentration and oxygenation. Slight changes in the blood oxygenation level therefore result in corresponding changes in the fMRI signal. Since blood oxygenation levels are correlated with bloodflow and therefore with local neuronal activity, the changes in rtfMRI signals are an indicator for changes in brain activity. Blood Oxygen Level Dependent signal (BOLD) is currently the most used measurement of brain activity in fMRI studies [7]. Although the technique has drawbacks, such as lower resolution because of the increasing speed of imaging compared to a standard MRI and it has a low signal to noise ratio [1], it is presently the best method for measuring neuronal activity of well-localized individual brain regions in real time [1].

Several studies have demonstrated that people were capable of controlling activity in the brain, including the auditory cortex [8], sensorymotor cortex [9], insula [10] and dorsal/rostral Anterior Cingulate Cortex (ACC) [6]. It has also been used in diseases like autism [11], behavorial disorders [11] and sleep disorders [12]. In the Netherlands neurofeedback is being used successfully to treat ADHD, epilepsy and sleeping disorders [13].

Moreover, subregions of the rostral anterior cingulate cortex (rACC) and the anterior insular cortex have been shown to be involved in mediating conscious pain perception [5,10]. Despite evidence of its efficacy [1,5,6,14] for treating chronic pain, neurofeedback treatment is still not being used for this purpose in the clinic.

The most interesting regions for neurofeedback concern the gyrus cinguli, insula, rACC and somatosensory cortex, because these areas are believed to be important in processing and regulating pain [5,6,10,14,15].

In this systematic review, we addressed the following research questions: (1) Is it possible to change brain activity by using neurofeedback? (2) Can neurofeedback with rtfMRI be used as a treatment for chronic pain?

METHODS

Search strategy

The National Library of Medicine's PubMed database was searched from 1995 till 16 January 2011. Since neurofeedback is only one of the terms describing the subject we also used the other terms shown. The search, as seen in Figure 1, took place on 16 January 2011.

Figure 1

Search:
1. Real-time fMRI
2. self-regulation OR
Neurofeedback OR
neurofeedback* OR
Biofeedback
Pain AND Brain/Physiology+
3. #2 OR #3
4. #1 AND #4

* MeSH terms
\+ MeSH MaJR term

Study selection and data extraction

We used several inclusion and exclusion criteria. Because we found many articles with our search term (Figure 2), we first selected articles with inclusion criteria. The articles were hand-picked based on the titles, using our inclusion criteria: the use of rtfMRI to capture the activity of the gyrus cinguli, insula, rACC, somatosensory cortex and/or to regulate pain. We then excluded articles based on the abstract. The exclusion criteria were articles about regulating motorfunctions, behavior or syndromes that did not involve pain. We also excluded articles that were not available online or in the Erasmus MC library.

Figure 2

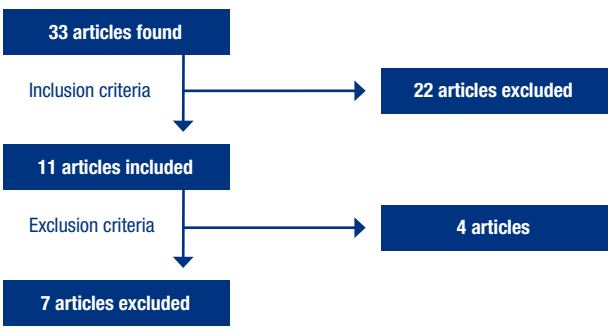


Table 1

Name	Author	Land	Study	Number of patients
Modulation of Subgenual Anterior Cingulate Cortex Activity With Real-Time Neurofeedback	Hamilton JP	USA	Controlled Clinical Trial	17
Regulation of anterior insular cortex activity using real-time fMRI	Caria A	Germany	Controlled Clinical Trial	15
Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): methodology and exemplary data	Weiskopf N	USA	Case Report	1
Control over brain activation and pain learned by using real-time functional MRI	deCharms RC	USA	Controlled Clinical Trial	48

RESULTS

By using the search method in Box 2 we found 33 articles. From the 33 articles we included 11 articles based upon our inclusion criteria. After applying exclusion criteria, 4 articles remained. These are listed in Table 1.

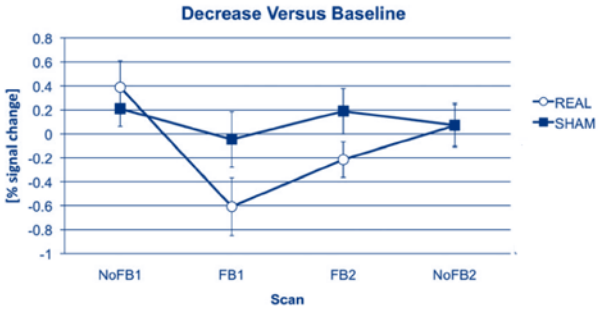
As described above the neurofeedback technique allows people to learn how to control the activity in certain areas of the brain. We limited our research to the results of neurofeedback on the sACC (Subgenual Anterior Cingulate Cortex) [6], insula [10] and rACC (rostral Anterior Cingulate Cortex) [5].

The effect of neurofeedback on the sACC was described by Hamilton et al. (2010). This nucleus is involved in generating affective states and in psychopathology and pain. In this study 17 participants were trained to decrease the sACC activity over time. They were told that they would see a neurofeedback signal from a brain structure involved in creating positive feelings (the red line on the screen) and a neurofeedback signal from the rest of the brain (the black line on the screen). Finally the participants were reminded that the neurofeedback signal in graphs was there to help train them, and that if one strategy did not produce the desired change in the neurofeedback signal, they should try another.

The participants were randomly divided in two groups: an experimental (n=8) and a sham group (n=9). The experimental group received real neurofeedback while the sham group received fake neurofeedback. Both groups were given four training runs, each lasting 5 m 20 s. During these sessions the experimental group received two sessions with real neurofeedback and two sessions without neurofeedback. The sham group received two sessions with fake neurofeedback and also two sessions without neurofeedback. All four scans were composed of five decrease blocks (each 32 s) interspersed with five baseline blocks (each 32 s). During the sessions with neurofeedback there was a significant difference ($p = 0.05$) in the signal change between the experimental group and the sham group (Figure 3). However without neurofeedback there was no significant difference.

Based on the finding that the sACC BOLD signal was decreased during presentation of sACC neurofeedback in the real but not in the sham group, the researchers concluded that sACC activity can be down regulated with the aid of a neurofeedback signal.

Figure 3

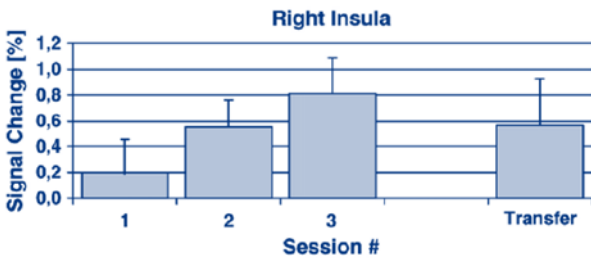


Caria A., et al. (2007) studied neurofeedback training in the right anterior insular cortex, another brain region that is involved in pain perception. The participants were naive to neurofeedback and fMRI experiments. Out of 15 participants in total, 9 were trained to voluntarily control the local BOLD signal of the right anterior insular cortex using the rtfMRI information. The remaining 6 subjects participated in two different control conditions. These control experiments were conducted to verify that the effects of the self-regulation of the insular activity were due to rtfMRI feedback.

The training of the first 9 subjects consisted of four feedback sessions, followed by a transfer run. One feedback session consisted of four regulation blocks (22.5 s each) during which the participants were asked to increase insula activity, alternating with five baseline blocks (22.5 s each) during which they were asked to decrease the activity to baseline level. During the transfer run, participants were instructed to perform the same task as during feedback, but fMRI information was not provided. The transfer session was performed to verify the efficacy of the feedback and to check whether training effects might persist beyond the experimental situation.

The first control group (3 participants) performed three sessions of the same experimental paradigm, but received sham feedback. This sham feedback was not specific to any particular brain area but consisted of information from a large background region of interest from the same subjects not encompassing the anterior insula. The second control group (3 participants) was provided with the same instructions and same strategies as the experimental group, but no rtfMRI information was available. They performed three consecutive sessions during which they were asked to recall and evoke memories and imagery of personally relevant affective events. Figure 4 shows the signal change in the insula of the experimental group during the various sessions. This change is calculated by averaging the difference between task and rest obtained for each of the participants. During the first three sessions, participants were able to significantly increase the activity of their right insula ($p = 0.001$). Furthermore a small, but significant increase was found between the third and first sessions ($p = 0.019$). However, the transfer session did not show a significant increase.

Figure 4

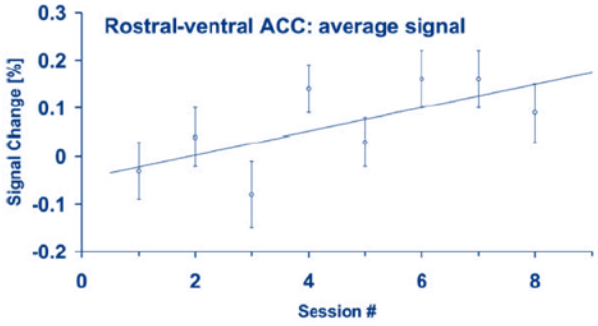


This study showed that the BOLD signal in the right anterior insular cortex increased in proportion to the number of feedback sessions, indicating training effects and learning. The researchers concluded that a specific modulation of the right anterior insula is possible with rtfMRI feedback.

Weiskopf N., et al. (2003) investigated the possibility of self-regulation of activity in the rACC. This study involved only a single participant, who underwent eight training sessions to regulate the activity of his rACC. In each training session the rACC activity was shown to the subject using the rtfMRI-signal. The subject had to control his activity under two different conditions. During the activation blocks, he had to increase the activity in the rACC, and during the baseline blocks he had to decrease the activity back to the pretask level. Each activation block was followed by a baseline block. Each block took 60 seconds, and one run consisted of four pairs of activation and baseline blocks.

The average signal change of activity of the rACC is shown in Figure 5. The participant was able to increase the activity in his rACC during the activation blocks of the training sessions. Furthermore, the signal change kept increasing during the eight sessions, as shown in Figure 5. The researchers concluded that training can be used to increase the activity of the rACC.

Figure 5



The rACC is involved in pain perception and regulation [6]. As seen in the previous study it is possible to self-regulate the activity of the rACC. DeCharms RC., et al. (2005) examined the correlation between the self-regulation of rACC activity and pain. This study involved 48 participants: 36 healthy volunteers and 12 chronic pain patients from the Stanford University Pain Management Service.

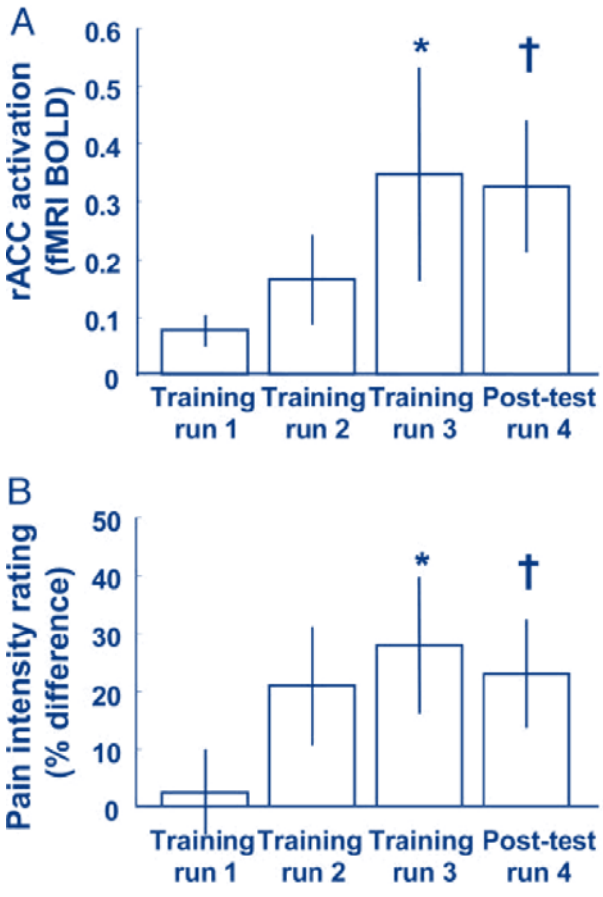
Of this group 8 healthy volunteers and 4 chronic pain patients underwent a series of training runs inside the scanner while receiving rtfMRI information about their rACC. Healthy volunteers, but not pain patients, were presented with nociceptive stimuli for 30s using a Pelthier thermode on the subject's left palm during each training block. Each training run took 13 minutes and consisted of five increase and decrease cycles. Each cycle consisted of a 30s rest block followed by a 60s increase block, during which subjects were trained to increase their rACC activity, followed by a 60s decrease block in which subjects were trained to decrease their rACC activity. To measure pain, the Visual Analogue Scale (VAS) was used. Participants rated their pain with a projected screen inside the scanner showing a 1-10 continuous VAS. The participants underwent three training runs and one post-test run. The post-test run and the training runs differed in that the VAS was rated immediately after the stimulus was given during the post-test run.

Besides the experimental groups there were also five control groups. Group I consisted of eight healthy volunteers who received identical instructions to the experimental group and the same period of training, except without rtfMRI information and attempted cognitive control over pain. Group II consisted of 8 healthy volunteers who received purely behavioral training for twice as long as the experimental group. Group III consisted of 8 healthy volunteers who received training identical to the experimental group, but they received rtfMRI information from a different region of the brain that is not involved in pain processing. Group IV consisted of four healthy volunteers who also received training identical to the experimental group, but they received the rtfMRI images that corresponded to the participants of the experimental group. Therefore they did not see their own rACC activity, but that from someone from the experimental group. There also was a patient control group which received autonomic biofeedback information rather than rtfMRI. They were trained to control their autonomic tone like heart rate, respiration etc.

In order to objectively measure pain intensity, the difference of the VAS score during increase and decrease blocks was used. Therefore no absolute pain intensity ratings were used, only pain intensity rating differences.

Figure 6A shows the activity of the rACC of the experimental group during each run. There is a significant difference between the first and third training run ($p<0.05$). Furthermore, there is a significant difference between the first run and post-test run ($p<0.05$). Figure 65A also shows that the more training runs a subject received the higher the rACC activity. The researchers concluded that the participants succeeded in controlling the activity of their rACC.

Figure 6



Along with the increase in activity, Figure 6B shows that the difference in pain ratings during each increase block increased and decreased during each decrease block. As in the previous figure, there is also a significant difference between the first and third run ($p<0.05$). During the post-test run, participants immediately rated the intensity of their pain using the VAS score, while in the training runs they rated their pain intensity after each training run. The difference between the post-test run and the first run is also significant ($p<0.05$). Figures 6A and 5B show a correlation between the rACC activity and the pain intensity rating difference. If the activity in the rACC increases, the pain intensity rating also increases. However if the activity in the rACC decreases, the pain intensity also decreases. Therefore the activity of the rACC is important in the experience of pain.

Figure 7

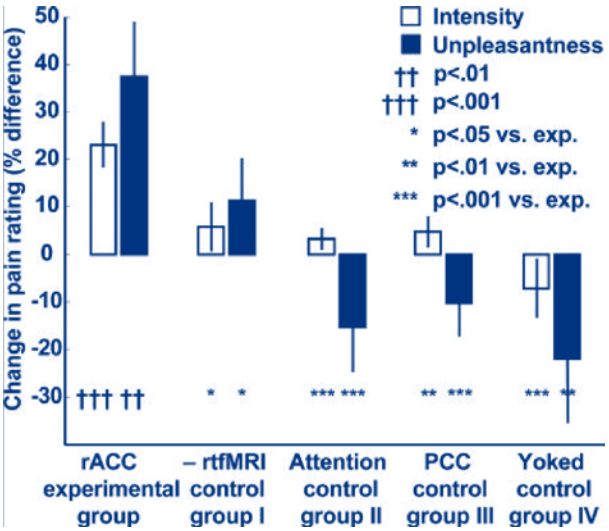
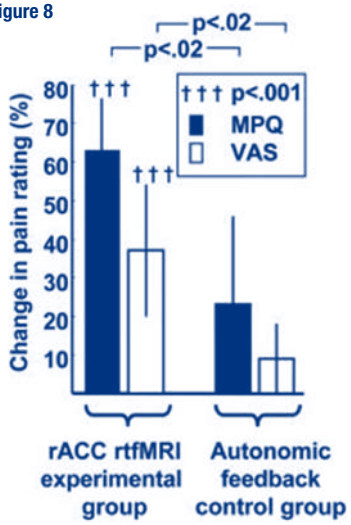


Figure 7 shows the change in pain rating difference after the training runs between the different groups. There is a significant difference in the intensity and unpleasantness of pain between the experimental group and all the other groups ($p<0.01$ for unpleasantness and $p<0.001$ for intensity). It should be noted that the rtfMRI control group also had a positive change in their pain rating, but it was less than the experimental group. The researchers concluded that the use of rtfMRI is important in training a subject to increase their pain intensity difference.

Figure 8 shows not only the VAS scores, but also the MPQ (McGill Pain Questionnaire). On the MPQ, participants rate their pain intensity by choosing different words to describe their pain.

Figure 8 shows the changes in pain ratings of the experimental group and the autonomic feedback control group. The differences in both the VAS score and MPQ are significantly higher in the experimental group ($p<0.02$). These results showed that neurofeedback is effective in increasing and decreasing the rACC activity and that this leads to an increase and decrease in the pain intensity rating difference.

Figure 8



DISCUSSION

More and more evidence has shown that it is possible to train people to regulate different areas of their brain with neurofeedback. The studies in our review examined the rACC, sACC and the insula. These areas are involved in the emotional perception and regulation of pain. Because it is possible to regulate the activity of these areas, this can influence pain perception. Although all the studies showed that neurofeedback can be used to increase and decrease the experience of pain which is beyond control, there are several limitations that need to be addressed.

In was unclear how the researchers determined the number of rtfMRI runs and why the studies ended after only one day. All studies stopped the training before the maximum of increasing/decreasing activity of a particular brain area had been reached. Speculating on the reasons, perhaps they stopped early because of the cost or physical discomfort of the patients.

However, none of the studies had a follow-up. It therefore remains unclear whether the participants were able to retain their ability to change the activity of a particular brain area. Moreover, it is unknown whether the participants continued to use neurofeedback after the tests.

The number of participants was very low. The study population ranged from 1 to 48 participants. So it is doubtful that the studies are representive of a larger population.

Another limitation is that no study investigated the correlation between the reduction of pain and the activity of the different brain areas (rACC, sACC, insula). Only one study (DeCharms RC. et al.) addressed the relationhip between decreasing the activity of the rACC and pain perception. However, they did not use absolute values for the measurements, but only the difference between the increasing and decreasing blocks, giving relative outcomes.

Concluding remarks

What can neurofeedback mean for pain management in the future? First of all, chronic pain patients will have more control over their pain. Nowadays, chronic pain patients have no autonomous control.

Second, patients could cope more easily with severe pain episodes. During pain episodes patients are now treated with rescue medication, which can be used if they still have severe pain despite treatment with slow-release morphine or a fentanyl-patch. Additional morphine can be administered to control the severe pain.

The disadvantage of these rescues is that the analgesic effect takes time. Neurofeedback could enable patients to immediately decrease their pain-related brain activity and thus reduce their pain.

One of the problems with using neurofeedback in the Netherlands is that the CVZ (the institute that reimburses medical expenses for patients) decided in 2008 that this treatment would no longer be reimbursed. Their main argument was that there is insufficient scientific evidence for the effectiveness of neurofeedback, and that the mechanisms are not sufficiently known [16].

Other imaging options, like modified EEG, should be studied to find a cheaper alternative to rtfMRI If this therapy were covered by health insurance, we expect that more patients would use self-regulation by neurofeedback to reduce their pain.

Our study shows that it is possible to change brain activity by using neurofeedback, and that neurofeedback with rtfMRI can be effectively used as a treatment for chronic pain. However, further research is necessary.

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Home or hospital: mothers should decide for themselves

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Perinatal mortality in the Netherlands is exceptionally high: approximately 10 deaths per 1,000 births according to the Peristat-II-study [1]. This is the third highest rate in Europe, and is exceeded only by France and Latvia. In recent years, extensive research has therefore been conducted into the causes of this relatively high mortality rate and ways to reduce it.

The Netherlands differs from other countries in another way: the large proportion of homebirths. Between 20% and 30% of the 180,000 annual births in the Netherlands take place at home [2,3]. This is very high in comparison to other industrialized countries, where homebirths often comprise only a few percent of total births [4].

In the Netherlands, a distinction is made between high-risk and low-risk pregnancies. This is done using the *Verloskundige Indicatielijst* (VIL) [5]. This is a list of medical conditions and risk factors that could increase the risk of complications during pregnancy. If a pregnancy is considered high risk, the mother is referred to a gynecologist, who can essentially compel the mother to deliver in a hospital. This leaves a group of women with low-risk pregnancies. Currently these women can decide for themselves whether they are going to give birth at home or in the hospital. Of course, should a complication occur during a planned home birth, the mother and infant are still taken to a hospital.

Because the Netherlands differs from other countries regarding both perinatal mortality rate and the proportion of home births, these two characteristics might be causally linked. Homebirths could increase the risk of complications and therefore the rate of perinatal deaths. If this were true, then the high level of perinatal mortality might be reduced by obligating all women to give birth in a hospital — not just those at risk for complications. Homebirth would then be prohibited entirely. A similar measure is already in effect in countries such as Finland, where it has been in force since 1972 [6].

In this essay I explore the pros and cons of implementing such a measure in the Netherlands and determine whether it would reduce perinatal mortality.

Mortality and morbidity

In 2009 the *British Journal of Obestetrics and Gynaecology* (BJOG) published an article by de Jonge et al. which showed that low-risk births in hospitals do not differ from planned homebirths [7] regarding mortality. These researchers conducted a retrospective cohort study comprising seven years of data from the Dutch national birth register concerning 529,688 pregnancies. The results of this study contradicted the assumption that a ban on homebirths would reduce the perinatal mortality rate.

However, in 2010 Evers et al. (BMJ) [8] concluded that there was a difference in mortality between homebirths and hospital births. According to their results, the risk of perinatal death during planned homebirths is almost twice as high low-risk hospital births. These findings appeared to support the proposition of mandatory hospital births, but the study also had some major flaws [9].

First, the study only examined a small region of the Netherlands, so it was doubtful that the results from this region could be generalized to the entire country. Second, there seemed to be a discrepancy between the area in which the number of births was measured and the area in which the number of perinatal incidents was measured [9]. Evers et al. used the national birth register to determine the number of births in the studied region. They then tried to determine the number of perinatal incidents by consulting hospitals and midwifery practices that were located inside this region. However, midwifery practices often provided care outside the studied region, especially those located near the edge of the region. This caused the total combined service area of the consulted practices to be larger than the actual studied region, which meant that perinatal incidents were taken into account that were not related to the homebirths in the studied region. This could have distorted the difference in mortality and morbidity between the different kinds of birth. Consequently, the results of this study cannot be used to support the proposition of mandatory hospital births.

Nijhuis et al. recently conducted a new analysis in which they confirmed the findings of de Jonge et al. [10]. Interestingly, despite the fact that mortality did not differ between planned homebirths and planned low-risk hospital births, significantly fewer cesarean sections and assisted vaginal deliveries (AVD) were carried out during births that intentionally started at home. More specifically, deliveries that started at home had a relative risk of 0.8 for a Cesarean and 0.9 for an AVD when compared to planned low-risk hospital births.

Choice and comfort

Besides risk, the autonomy of the mother plays an important role in this issue. By making hospital births mandatory, the freedom to choose where to give birth would be taken away from the mother and instead the choice would be made for her. However, our current midwifery system is largely based on the assumption that pregnancy and childbirth are physiological processes and should not be treated as a disease [5]. This is one of the reasons why medicalization of childbirth should be avoided as much as possible and the mother should have as much say as possible about pregnancy and giving birth.

One could argue that the autonomy of the mother is less important than the safety of the child. Because infants cannot make choices, as a society we are morally obligated to protect them against potentially bad choices of the mother. However, measures to protect infants are already in place. For example, if a pregnant woman is assessed in primary care with the VIL as high risk, she would be referred to a gynecologist, who can then compel her to give birth in a hospital. Combined with the results of Jonge et al. [7], it seems unlikely that banning homebirths would provide additional protection, which makes the autonomy of the mother in this case more important.

The mother's freedom of choice has additional advantages as well. Hendrix et al. researched the preferences of pregnant

women and their partners about the course of labor [11]. The most important aspect for women (and their partners) was to have a say in the course of events and to have the freedom to make their own choices about how the pregnancy would proceed. Other studies also showed that women greatly appreciate a certain level of autonomy during labor and being able to influence its course to some extent [12]. This makes choice an important determinant of happiness and satisfaction during childbirth.

Conclusion

The data lead to an unequivocal conclusion: pregnant women who are at low risk of complications should not be compelled to deliver in the hospital. This conclusion is supported by two arguments.

First, there is no reliable data to suggest that compulsory hospital birth will lower mortality. The results of Evers et al. from 2010 are disputed and cannot be used as support. In fact, there is reason to believe that this measure would cause morbidity to increase (due to the risk of a Caesarian or AVD).

Second, mothers should have the right to decide where they want to give birth. Labor is not only a physiological process; having a sense of control about the delivery greatly influences how comfortable mothers and their partners feel.

The high perinatal mortality rate in the Netherlands remains a problem without a clear assignable cause. However, banning homebirths is certainly not a solution and could even be a step in the wrong direction.

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Liberation treatment for MS: can a doctor refuse?

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The Liberation treatment

The "Liberation treatment" [1, 2], also known as the "Zamboni procedure", is a controversial treatment for multiple sclerosis (MS) based on the dissolution of occlusions in the jugular and azygos veins. It was developed by Dr. Paolo Zamboni [3, 4], vascular surgeon and professor at the University of Ferrara, Italy. Proponents consider it to be a breakthrough in MS treatment. They regard the procedure as safe, simple and effective. Opponents are very skeptical about the Zamboni procedure. They believe the scientific evidence for its efficacy is insufficient.

On the forum of the ccsvi.nl website [5], MS patients appear to be predominantly positive about their experiences with the Liberation treatment. At the same time, they portray Dutch doctors as obstinate and disdainful towards this treatment [6, 7]. The doctors are accused of not taking Dr. Zamboni's research seriously; instead of opening their eyes to the success of this new therapy, they continue to prescribe expensive medication. But is this procedure really the breakthrough that MS patients have been waiting for? And are doctors simply being stubborn in refusing MS patients this new treatment, or are they justifiably skeptical?

The theory

In 2006 Dr. Zamboni published a revolutionary theory on the pathophysiology of MS: occlusions in the jugular and/or azygos vein and the reflux of blood and waste products caused by these stenoses can trigger an auto-immune reaction and lead to MS symptoms [8]. He calls this phenomenon "Chronic Cerebro-Spinal Venous Insufficiency" (CCSVI), and in 2009 he published data that caused quite a stir in the medical world [9]. He claimed that he found CCSVI in 100% of MS patients and in 0% of healthy controls.

Studies that tried to reproduce these data have yielded contradictory results [10, 11, 12]. In the Netherlands,

Wattjes et al. detected CCSVI in 50% of MS patients, but also in 50% of controls. They consequently rejected the hypothesis of an association between CCSVI and MS [13]. Dr. Zamboni commented on some of these studies by pointing out that only Doppler echography was used, which would be less sensitive in diagnosing CCSVI than Doppler echography and venography used together [14]. More important however, is that there are still no standardized criteria for the diagnosis CCSVI [15].

In their discussion Zamboni et al. mentioned that interpretation of Doppler-echography can be influenced by the examiner [9]. Blinding thus appears to be crucial. Nevertheless, they did not blind their examinations, nor did others [10, 11]. Studies that were blinded led to much lower CCSVI percentages [12, 16]. A triple blinded study by Mayer et al. did not find a single sign of CCSVI in twenty MS patients.

All in all, the current evidence for the existence of CCSVI seems insufficient. Consequently the debate is not just about the Liberation treatment itself, but also about the theory on which it is based.

The treatment

In 2009 Dr. Zamboni described balloon catheterization as a simple but effective procedure to resolve CCSVI [3]. This procedure has been used for years in interventional cardiology, but in CCSVI the dilatation is done in veins and not in arteries.

The study by Zamboni and his team was not a randomized controlled trial and follow-up of patients was limited to 18 months. Therefore, it was unclear whether the positive effects were more than just a placebo effect and how long the results persisted, because at the end of the study half of the patients showed restenosis in the jugular vein. Moreover, the improvements observed in this study appeared to apply primarily to MS patients with the relapsing-remitting type of the disease, so it remains doubtful whether this procedure can be justified in other types of MS. The results of this study alone are therefore insufficient to support evidence-based use of this therapy in MS.

More research is obviously required. Several studies which examine endovascular treatments in MS have begun, but no results have been published so far. And for the present, Dutch doctors still seem to have every right to refuse this treatment; they are simply being cautious, not stubborn.

The doctors' side

During a web forum, Drs. Zivadinov, a CCSVI researcher at the Buffalo Neuroimaging Analysis Center, brought up an important matter: the balance between scientifically rigorous research and the needs and rights of the patient [14]. In science it takes years of research before a treatment can be called evidence-based and is added to the existing options. But is it justifiable to withhold a possibly effective therapy from a patient who has had very few options for a very long time?

In this case the *primum non nocere* or "first do no harm" principle plays an important role for doctors. A procedure with unproven efficacy and unknown long-term effects could possibly do more harm than good. I believe that the role of a doctor in this matter is also to protect MS patients against themselves. MS is a very serious disease, causing patients to grasp at straws and sometimes lose their objectivity. A doctor's job is to stay objective and make sure the patient is properly informed. But what if a patient still decides he/she wants to undergo the Zamboni surgery? Is that part of the patient's right to self-determination?

In the Netherlands, the Zamboni procedure is currently only performed as part of scientific research. As a result, many patients seek treatment abroad, with the attendant risks. For example, proper follow-up cannot be guaranteed, traveling after an invasive procedure is risky, and variations in approach between individual surgeons – such as the use of stents – can make the procedure more hazardous [17].

The existing stents are only approved for use in arteries, and their use in veins can be dangerous. At Stanford University in California, a study was halted after two stent complications, one of which was fatal [18].
In October last year a Canadian man died after receiving Liberation treatment with stent placement in Costa Rica [19, 20].

Without stents, however, this procedure appears to be safe. It therefore seems contradictory that we do not allow patients to undergo this procedure, but instead compel them to go abroad to be exposed to possibly greater risks. Nevertheless, this is not a valid reason to perform the procedure here. Moreover, medication is available for which the efficacy, complications and long-term effects have been monitored [21]. Of course these therapies also have side effects and limitations, but at least their efficacy has been proven.

In some online discussion forums, however, people attribute the preference of doctors for prescribing medication to the assumption that they are being paid by pharmaceutical companies to do so [6, 7]. I believe that is not the case at all. Doctors simply want to prescribe the best treatments for their patients and prefer to be on the safe side. It does not make sense that Dutch doctors are accused of being mercenary, especially when the companies that offer the Liberation treatment appear to have commercial motives. It is no coincidence that companies like Prescan and Privatescan are involved [22].

The patients' side

MS patiënts are in a hurry to find effective treatment. In most cases, MS is a progressive disease. The sooner a new therapy is available, the more symptoms can be prevented. They are also supported by special interest organizations. For example, in July 2010, Mr. Frans Slangen, chairman of the Dutch MS Association, wrote a letter to Dutch neurologists, health care insurance companies and the Ministry of Health, Welfare and Sport [23]. In this letter he insisted on further research on the Liberation treatment.

Comments on various MS websites have emphasized the need of patients to be listened to and understood. They point out that a doctor should not respond with cynicism or rejection when a patient reports something about a new treatment he/she has read about, but should take the patient seriously and enter into a dialogue. A haughty attitude is a relic of the past. Nowadays, doctors and patients function more as a team, and cooperation is becoming more and more important.

Summary and remarks

Can a doctor refuse a patient the Liberation treatment? Yes, this justified. The evidence for this treatment is insufficient, and further research in the form of randomized placebo controlled trials with longer and better follow-up in homogenous patient and control groups is urgently needed. But first of all, in order to research the association with MS objectively, CCSVI must be studied in more detail, and clear criteria for its diagnosis must be established. Until then the Liberation treatment does not deserve a place in the list of accepted treatments for MS.

Scientific considerations aside, it is important to keep the patients' perspective in mind. Scientific literature is unreadable for many people and patients will mainly be guided by what appears in the media. Patients are also becoming more empowered and will demand specific treatments more often. Doctors and researchers should not be compelled into taking more risks as a result, but it is important for patients to feel that they are being taken seriously.

Finally, if patients decide to seek treatment abroad after all, their doctors should keep in touch and ensure proper follow-up.

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Influenza vaccination of healthcare workers should be mandatory

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Abstract

Many hospitalizations and deaths of the elderly and chronically ill can be prevented through vaccination of all healthcare workers. Despite guidelines and recommendations, the vaccination rate of healthcare workers remains extremely low. Higher vaccine rates can be achieved through mandatory vaccination. Based on the scientific, ethical and juridical aspects, influenza virus vaccination should be mandatory for all healthcare workers with direct patient contact. Implementation of this measure should follow certain tenets and be combined with an information and education campaign.

Introduction

Influenza is an acute respiratory infection caused by the influenza virus. Worldwide, between 3 and 5 million people per year become seriously ill from this virus, of which 250,000 to 500,000 die [1]. During influenza epidemics in the Netherlands, an average of 189 people die, according to data of the Central Bureau of Statistics (CBS) from 1998 to 2007. Moreover, the National Institute for Public Health and the Environment (RIVM) concluded that influenza mortality is underestimated. This because the immediate cause of death (decompensatio cordis for example) is registered [2], not the influenza that led to this condition.

Two groups are at high risk for hospitalizations and fatalities: the elderly (approximately 90 percent of the deaths involve people 65 years or older) and the chronically ill. In both of these groups,

influenza can exacerbate an existing condition [2]. These high-risk groups are especially represented in the patient populations of healthcare institutions.

Transmission of the virus from healthcare workers to patients has already been demonstrated [3,4]. Consequently, in April 2004 the Dutch association of nursing home physicians (NVVA) recommended attaining maximum vaccination levels in patients and healthcare workers. Before these recommendations went into effect, the vaccination rate of Dutch healthcare workers was 5% to 8% [5]. During the subsequent season (2004-2005) the vaccine uptake increased only to 10.5% [6]. A significantly higher vaccination rate can be reached by "a systematically developed multi-faceted intervention program" [7]. Because the effects of this intervention program are uncertain over the long term, a mandatory vaccination of all healthcare workers with direct patient contact must be considered. Such a measure maximizes the vaccination rate [8].

Aim of this essay

The aim of this essay is to critically examine the scientific, ethical and juridical aspects of mandatory vaccination of all healthcare workers with direct patient contact and to determine whether mandatory vaccination should be supported or rejected.

The evidence

Vaccination efficacy

Vaccinating care home staff against influenza has been shown to improve the health of the residents [9]. Moreover, in healthcare facilities an increased vaccination rate of healthcare workers was associated with a significant decrease of infections and deaths among the patients [10-12]. Vaccination of healthcare workers in long-term-care facilities reduced total patient mortality by 44% [12].

A linear relationship has been demonstrated between the vaccination rate of healthcare workers and the expected cases of illness among patients. A mathematical model has predicted that increasing the vaccination rate from 0% to 100% results in a reduction patient infections of approximately 60% [13].

Safety

Adverse side effects sometimes occur after an influenza vaccination, usually involving moderate, local adverse effects like pain, redness and swelling. Recipients of a vaccine suffered as often as recipients of a placebo from muscle aches, fatigue, headache, arthralgia, shivering and fever. Allergic reactions occurred rarely [14].

In 1976-1977, an increased incidence of guillain-barre syndrome (GBS) was linked to the influenza vaccination, but a causal relationship was not found. Subsequent studies could not provide a definitive answer either; lower or no correlation was found between GBS and influenza vaccination [15,16]. Moreover, since 1976 only flu strains that are not linked to this syndrome have been eligible for vaccine preparation [17].

The inactivated influenza vaccine has been proven safe and effective for pregnant women [18]. Therefore, pregnant healthcare workers can also be vaccinated with confidence.

Cost-effectiveness

An economic evaluation in the UK showed that vaccination is usually cost-effective. In the worst-case scenario, vaccination costs only 405 GBP per life-year gained [19].

Alternatives

Campaigns have regularly tried to increase vaccine uptake through voluntary immunization programs. The most effective strategies seemed to be "information and education" (1) and "easy access to free vaccine" (2). But even these methods have to overcome some barriers: a lack of knowledge about influenza, the role of healthcare workers in its transmission to patients, the patients' interest in and the adverse effects of vaccination [20].

According to a review of studies on attitudes and predictors, vaccine uptake depends on health belief factors of healthcare workers. The greater the expected effect, the greater the probability of vaccination [21]. On this basis, voluntary programs can still be improved. It is also important to realize that full herd immunity is not required to reduce the mortality and morbidity among patients. Even a modest increase in vaccination uptake results in a reduction [13].

Ethical arguments in favor of mandatory vaccination

A higher vaccination uptake among healthcare workers results in significantly lower morbidity and mortality among patients [10-12]. Mandatory vaccination of all healthcare workers with direct patient contact would therefore prevent infections and deaths. By preventing harm, the well-being of care-dependent individuals will be improved.

Non-maleficence (first, do no harm) is an ethical obligation for all healthcare workers. By requiring their vaccination, they would be prevented from causing harm to patients through influenza transmission.

One of the ethical goals of medicine is the prevention of disease/injury and the improvement and retention of health [22]. Vaccination of all healthcare workers is necessary to pursue this goal.

Finally, it is ethically inconsistent for healthcare workers to try to persuade patients about the usefulness of vaccination if they have not been vaccinated themselves [23].

Few fundamental objections

To estimate the number of people who have fundamental objections against mandatory vaccination, the immunization coverage in the National Immunization Program of the Netherlands was used. For babies born in 2008, the participation for the MMR, Hib and meningococcal C vaccination was 96%, for the DTaP-IPV and pneumococcal vaccination it was 95%. Data from the previous five years showed similar rates. The 96% of parents who have their babies vaccinated apparently have no fundamental objections. This means that no more than 4% would have such objections. It can be assumed that these parents are an accurate reflection of Dutch society at large, so the population of healthcare workers would be similar. Therefore, it can be assumed that the majority of healthcare workers would have no fundamental objections to vaccination [24].

Nevertheless, the majority of healthcare workers did not get vaccinated. Vaccine shortage was mentioned as a reason by 48%. This rate was 57% among physicians [25]. When vaccination is mandatory, the required number of doses (equal to the number of employees) can be determined more accurately, and this situation would be avoided.

Ethical arguments against mandatory vaccination

Autonomy

Mandatory vaccination would limit the autonomy of healthcare workers. Voluntary vaccination is preferred because it does not affect the privacy and liberty [26]. Vaccination should therefore not become mandatory until all voluntary alternatives have been exhausted. For example, educational intervention can increase voluntary vaccine uptake [27].

Non-maleficence

It is still unclear whether influenza vaccines cause GBS, but they can certainly harm by causing pain, redness and/or swelling. Although these adverse side effects are rare and usually moderate, they do constitute harm.

Juridical aspects

According to Article 11 of the Constitution of the Netherlands, everyone shall have the right to inviolability of his or her person, but without prejudice to restrictions laid down by or pursuant to an Act of Parliament [28]. Such restrictions could enable mandatory vaccination for healthcare workers. Extensive research is generally not required to convince courts of their validity; a plausible explanation is sufficient. However, It is obviously important that the policy would be in accordance with state interest (to improve public health) [29].

Conclusion

Influenza virus vaccination should become mandatory for all healthcare workers with direct patient contact. Implementation of this measure should follow certain tenets and should be combined with an information and education campaign.

This conclusion is supported by the following evidence:

- A higher vaccination rate will reduce morbidity and mortality among care dependent individuals
- Mandatory vaccination results in much higher vaccine uptake relative to voluntary measures.
- The costs of such an intervention are reasonable.
- The impact of the most common adverse side effects is limited.
- A causal relationship between influenza virus vaccination and GBS remains doubtful.
- The percentage of healthcare workers with fundamental objections is limited.
- Vaccine shortage will be avoided if mandatory vaccination is implemented.
- Based on ethical considerations, the preference is for mandatory vaccination.
- It is feasible to overcome the juridical barrier, which would enable the implementation of mandatory vaccination.

Regarding future implementation, the best method must still be determined. Introduction of this measurement should follow certain tenets: primarily exclusion criteria of a medical nature have to be established, and exclusion criteria based on theological or moral objection will be formulated. People could refuse vaccination if they believe it is contrary to the providence of God or if they invoke the integrity of the body. The latter criteria will be established for current healthcare workers only. The attention of prospective employees will be drawn to the mandatory policy and it will be emphasized that failure to comply may result in dismissal. If a prospective employee does not renounce his objection, he will be excluded from a medical career with patient contact [30].

In any case, the new policy must be preceded by information and education about the reason for mandatory vaccination and the implementation method.

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Abstract

Drug-eluting stents in STEMI-patients

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Background

Drug-eluting coronary stents are scaffolds coated with a polymer layer containing an anti-proliferative drug. Short- and long-term data showed that drug-eluting stents (DES) significantly decrease target-vessel revascularization (TVR) and major adverse cardiac event (MACE) rates compared to bare-metal stents (BMS). However, conflicting long-term data remains for patients with ST-segment elevated myocardial infarction (STEMI).

Objective

Our aim was to assess the 6-year clinical outcome of all patients undergoing primary percutaneous coronary intervention (PPCI) for a de novo lesion with exclusive use of BMS, sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES).
Methods: The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry was conducted from April 2002 until October 2002 in which 92 consecutive STEMI-patients were treated with only SES. From February 2003 until September 2003, 162 consecutive STEMI-patients were treated with the PES as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. These patients were compared with 80 BMS-patients, which were treated from October 2001 until March 2002. The three PPCI-cohorts were systematically followed for the occurrence of MACE.

Results

Very-late stent thrombosis was more common after the implantation of a SES as compared to PES or BMS (7.6%; 0.6%; 0.0%, respectively; p-value=0.001). Kaplan-Meier estimates indicate no statistically significant difference for mortality between the three stent types at 6-years (BMS=25%; SES=15% and PES=21%; Log-rank p-value=0.2) (table). After adjustment for differences in baseline characteristics mortality-, mortality/myocardial infarction (MI)- and MACE rates were significantly lower for SES compared to BMS (aHR=0.41, 95%CI:0.17-0.98; aHR=0.44, 95%CI:0.21-0.96; aHR=0.35, 95%CI:0.17-0.72, respectively), but not for PES. No differences were observed between the three stent types for TVR rates.

Conclusion

Neither SES nor PES improved safety or efficacy as compared to BMS in a STEMI-population at 6-years. After adjusting for baseline characteristics, the usage of SES resulted in a significant decrease in mortality, mortality/MI- and MACE rates as compared to BMS, in contrast to the usage of PES. SES and PES have a similar effectiveness and safety profile, although very-late stent thrombosis was more common with SES.

Table - Crude event rates and multivariable analysis stratified according to different stent types at 6-years.

	BMS (n=80)	SES (n=92)	PES (n=162)		SES vs. BMS	PES vs. BMS
	Number of events (%)				*Multivariate HR [95%CI]*	
MACE	28 (35.0%)	24 (26.1%)	46 (28.4%)		0.35 [0.17-0.72]	0.64 [0.37-1.08]
TVR	7 (8.8%)	10 (10.9%)	14 (8.6%)		0.84 [0.22-3.19]	0.91 [0.34-2.44]
Mortality	21 (26.3%)	14 (15.2%)	32 (19.8%)		0.41 [0.17-0.98]	0.67 [0.36-1.25]
Mortality/MI	23 (28.8%)	20 (21.7%)	38 (23.5%)		0.44 [0.21-0.96]	0.72 [0.40-1.30]
Early ST	1 (1.3%)	0 (0.0%)	4 (2.5%)	*(p-value=0.3)*		
Acute	0 (0.0%)	0 (0.0%)	1 (0.6%)	*(p-value=0.6)*		
Subacute	1 (1.3%)	0 (0.0%)	3 (1.9%)	*(p-value=0.4)*		
Late ST	1 (1.3%)	0 (0.0%)	2 (1.2%)	*(p-value=0.6)*		
Very-late ST	0 (0.0%)	7 (7.6%)	1 (0.6%)	*(p-value=0.001)*		
Total ST	2 (2.5%)	7 (7.6%)	7 (4.3%)	*(p-value=0.3)*		

BMS = Bare-Metal Stent; CI= Confidence Interval; HR = Hazard Ratio; MI = Myocardial Infarction; PES = Paclitaxel-Eluting Stent; SES = Sirolimus-Eluting Stent. ST = Stent thrombosis. Stent thrombosis occurring within 30 days post-stent implantation is defined as early stent thrombosis, categorized into acute stent thrombosis (within 24 hours) and subacute stent thrombosis (1-30 days). Late stent thrombosis is defined as stent thrombosis occurring within 30 days and 1 year. Stent thrombosis occurring after >1year after the index procedure is defined as very late stent thrombosis.

Brain perfusion patterns in familial frontotemporal lobar degeneration

Neurology. 2011 Jul 26;77(4):384-92. Epub 2011 Jul 13.
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Introduction
Frontotemporal lobar degeneration (FTLD) is a clinically, genetically and pathologically heterogeneous disorder. FTLD is characterized by a variable clinical presentation of progressive behavioural, language and executive dysfunction. Two major gene defects have been detected in familial FTLD; mutations in the *microtubule associated protein tau (MAPT)* and *progranulin (GRN)* genes. However, there still remain one or more familial forms of FTLD with unknown gene defect (UGD), in particular familial FTLD with motor neuron disease (FTLD-MND).

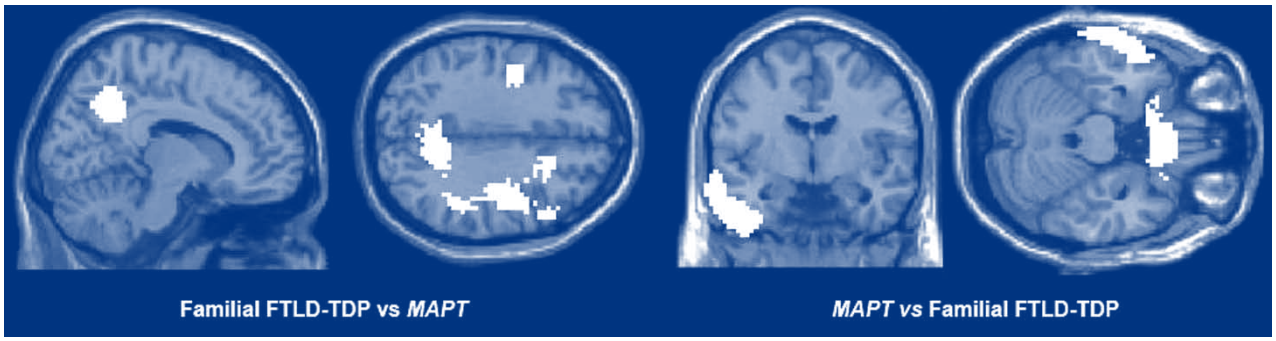
Histopathologically, *MAPT* is associated with FTLD with tau-positive inclusions (FTLD-tau), whereas *GRN* as well as familial forms with unknown genetic defect are associated with ubiquitin- and TDP-43 positive inclusions (FTLD-TDP). The aim of this case-control study was to compare clinical features and perfusion patterns on SPECT of patients with *MAPT* mutations and familial FTLD-TDP.

Methods
Patients were included if they had *MAPT* or *GRN* mutations, positive family history with pathologically-proven FTLD in the patient or first-degree relative, or were part of FTD-MND families. All patients and ten age- and gender-matched controls underwent measurement of brain perfusion using ^{99m}Tc-HMPAO SPECT. We used SPM8 to perform image processing and voxel-based group analyses (p<.001). Gender and age were included as nuisance variables in the design matrices.

Results
Of the 29 patients with familial FTLD, 19 had familial FTLD-TDP (GRN mutations in six), and 10 had *MAPT* mutations. At clinical presentation, familial FTLD-TDP patients were older at onset (p=.030) and had more memory deficits (p=.011), whereas MAPT had more naming deficits (p<.001) and obsessive-compulsive behaviour (p=.001).
The between groups SPECT analyses revealed significantly less perfusion in the right frontal lobe, precuneus, cuneus and inferior parietal lobule in familial FTLD-TDP, whereas significantly less perfusion was found in the left temporal and inferior frontal gyri in *MAPT*. Post-hoc analysis of familial FTLD-TDP with unknown genetic defect versus *MAPT* patients revealed less perfusion in the right frontal and parietal lobe.

Conclusion
Familial FTLD-TDP shows relatively more posterior hypoperfusion, including the precuneus and inferior parietal lobule, possibly related to significant memory impairment. *MAPT* patients were characterised by impaired perfusion of the temporal regions and naming deficits and obsessive-compulsive behaviour.

Figure 1 - Perfusion pattern of familial FTLD-TDP compared to *MAPT*



Relative hypoperfusion superimposed on a SPM8 canonical single subject template, with a threshold p<.001.

ITERATIVE REVIEWING AND EDITING FOR EFFECTIVE RESEARCH ARTICLES AND GRANT PROPOSALS

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This quotation from 1995 still applies today. Even after getting over the publishing hurdles, many scientific articles are never read nor cited—they are simply too tedious to read. For the same reason, excellent research may not get funded! Scientific papers do not have to be difficult to understand and tedious to read. To that end, the EJM provides a safe, but realistic, environment where students can take risks, make mistakes and learn to write.

At the professional level the stakes are higher, and an unbiased reviewer can help researchers to communicate more effectively. To that end, we have developed an approach we call *Iterative Reviewing and Editing* that helps authors to focus sharply on the relevance and credibility of their work; it makes complex science less tedious to read—even to non-specialists.

Relevant and credible writing

This approach emerged from Ed Hull's experience in teaching scientific writing and Charles Frink's experience in editing scientific texts. Ed explains, "My PhD students and postdocs assume that English language problems hamper their success in getting published and acquiring grants. Indeed, peer reviewers often comment 'have it edited by a native speaker.' But such comments can mislead authors. The real and more serious problem is usually fuzzy focus on the relevance and credibility of the research. This makes scientific papers tedious to read and, as Charles adds, "language editing alone cannot solve this problem."

How does *Iterative Reviewing and Editing* work?

Charles explains, "Working as a team with the author, Ed and I usually hold 3 iterations of reviewing and editing. (1) We first review an early draft of the text and suggest specific revisions to sharply focus on the credibility and relevance of the work, and improve its clarity to the non-specialist. These suggestions often have to do with organization and content. (2) After considering our suggestions, the author revises the text and returns it to us. (3) As a final step we 'polish up' the English. Throughout the process all parties interact with each other via e-mail and/or telephone."

This combination of review, structural revision, a built-in substantive check and language editing is efficient and results in a reader-friendly article or grant proposal. Want to know more? Please contact us.

"There is no form of prose more difficult to understand and more tedious to read than the average scientific paper." *Frances Crick*

Instructions for EJM authors

General

The instructions that follow have several purposes. First, we want to make life easy for you, the authors, and for the editors and peer reviewers, the layout (prepress) people, and the journal readers.

The Guidelines for the Storyline will help you to organize your article in a logical, credible and readable way. This will help you—it tells you what goes where—and, thus, save you time. It will help the editors and peer reviewers—they will easily see the credibility and relevance of your work— and, thus, save them from writing rejection letters. And, it will help readers to quickly and easily read and understand your work and see its value.

The section entitled Formatting Instructions will help you as well; the basic idea is to keep the formatting as simple as possible, so you can focus on content and not get involved with layout. The language editor and the prepress people will also be able to more efficiently do their jobs. Please follow these instructions. Please be aware that we will have to return papers that do not conform to these instructions to the authors.

What you can enter

Research articles - Research articles describe one study or analysis, usually from a fourth-year elective research project or one of the masters programs. Number of words: max. 3500 + 4 figures or tables.

Extended abstracts - Extended abstracts consist of a condensed presentation of complete final or temporary results of a study. Number of words: 350 words + 1 figure or table.

Research papers - Here researchers or teachers describe ongoing research projects at the Erasmus Medical centre for which they want to invite students to participate. Number of words: 350.

Reviews - Second year students can submit their review written in the second year elective course. Number of words: 1500 + 3 figures or tables

Opinion papers - These are papers that reflect the opinion of the author on a scientific topic. The author should be clear where evidence ends and personal opinion starts. A paper typically has a length of about 1000 words.

Comments - In this section editors, or faculty staff, as well students are invited to write a short critical comment on a paper, putting it into perspective for a broader medical public readership. Number of words: 350.

Letters to the editor - The editorial board encourages students to write a letter to the editor to comment on published papers, or on the journal in general. These will be published on the website of the journal. Letters should not exceed 200 words and may be abbreviated by the editor.

The review process

Papers may be submitted to one of the editors, or to the editorial office. Please indicate which author will act as corresponding author. We expect this author to maintain contact with the other authors and to speak and decide on their behalf.

Each paper will be assigned to a team consisting of a managing editor and an associate editor. Each submitted paper will be checked for compliance with the author instructions. If this is not the case, the paper may be returned to the author. When the paper is taken into review, it will be sent out to two external reviewers, a student and a staff member of Erasmus MC. Based upon these reviewers comments, their recommendations and the opinion of the editorial team, a decision will be made: reject, major revision, minor revision, accept with or without minor changes.

The paper will then be returned to the corresponding author, along with the recommendation. We try to return papers within 3 weeks after submission. When a paper is rejected, it cannot be resubmitted, but we encourage resubmissions when we recommend major or minor changes to a paper. Resubmitted paper will be reviewed again by the same reviewers and editorial team.

When a paper is accepted for publication, it will often be forwarded to our language editing and restructuring editors. They will each in turn give recommendations and ask the author adapt the paper accordingly. When this phase is completed, the paper will be forwarded to the publisher. Page proofs will be sent to the author for a final check.

Formatting instructions

Entry format - Papers should be submitted by email, to ejm@erasmusmc.nl. Word 2003 files are preferred for the initial submission. The file should include all figures and tables.

Title page - The title page should clearly identify the authors, the institute where the research project was carried out, as well as the staff member who supervised the project. The corresponding author name (first name and family name), email address, student id, should be clearly indicated. In case of multiple authors, state functions and departments only in superscript in alfabetical values. Example:

First name A.G. Family name[a] and First name W.F. Family name[a]
Supervisor: First name R. Lastname[b]
[a] Medical students, Erasmus MC University Medical Center Rotterdam, the Netherlands
[b] Dept. of Internal Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands
Correspondence: First name A.G. Family name, email: Firstname-Familyname@me.com.

Structure - Please use the following sections in all papers (except in comments and opinion papers): Abstract, Introduction, Methods, Results, Discussion, References, Tables, Figures.

References - Number references in order of appearance. References should have the following format:
Rothwell, P. M. Medical and surgical management of symptomatic carotid stenosis. Int.J.Stroke. 2006; 1: 140-149. (I.e. year;vol:ppp-ppp)
In case of more than 3 authors, name the first 3 and insert "et al.". Limit the number of references to 30. References should appear in the text as follows treatment is of proven benefit.[1]

Tables and figures - Tables and illustrations (both numbered in Arabic numerals) should be prepared on separate pages. Number tables and figures separately and consecutively. Tables require a heading and figures a legend, also prepared on a separate page and should be formatted with a text editor (example). Figures should be submitted electronically. B/w half-tone and color illustrations must have a final resolution of 300 dpi after scaling, line drawings one of 800-1,200 dpi (jpg and tiff is an acceptable format). Please note that all color-figures will be converted to gray tones. Please adapt graphs to suit this format, i.e. make use of dotted and dashed lines and hatched bars instead of colored items.. The final submission should contain figures as JPG or TIFF files.

Instructions for EJM authors

Page layout
- Standard margins
- no headers or footers
- no columns
- left align (ragged right)
- font: 12pt Arial
- single line spacing
- main headings 14 pt bold; subheading 12 point italic
- indent every paragraph, except after headings, tables, bulleted lists or figures

Other formatting
- number all tables and figures sequentially
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- no text boxes
- no footnotes or end notes
- do not submit figures with text as drawing objects (they cannot be edited)
- limit the use of italics and do not use italics for simple emphasis; do not italicize quotations; quotation marks are sufficient
- do not use italics for commonly understood Latin expressions such as "in vitro"
- use italics for other foreign words, such as expressions in Dutch
- no "sub-paragraphs"
- no hyphenation (afbreking)

Language
US English spelling and punctuation

Guidelines for the storyline of a scientific article

Authors of scientific articles often write in a style that was very successful at school but, unfortunately, does not work well in the "real" world. The reason? Readers of scientific journals -"real world readers" - when reading your papers have much different goals than your instructors had. Real world readers do not care how smart you are, or if you have done the homework, and they are not going to "grade" your papers. They do not count words to see if you met the minimum length of the paper. They read journal articles because they are looking for information and ideas that they can use in their own work. In other words, they are looking for something of value. In fact, when you read journal articles you are also a real world reader. Do you care how smart the authors are, or if they did their homework? Probably not. Are you impressed with long complicated sentence constructions and abstract ideas that only seem to fill up space? Do you count words? Probably not.

You probably are impressed, however, when you read an easy to understand article that clearly presents credible and relevant science. You can write that way too. But you need to get "out of the box" of what I call "academic" writing style. These guidelines will help you to get outside the box. The guidelines are based on one very simple concept: give you readers something they can use. Note that this requires a different mode of thinking. At school you probably never thought of giving your instructors something they could use. You wrote to receive something - a good grade. These guidelines will take you step by step through the process of writing a readable scientific article that presents relevant and credible science.

The first step is to write the "storyline" of your article - a readable story that logically ties all of your main ideas together. It focuses on the logical thread that credibly presents the point and the value of your research. It is to be short, logically linked and easily understood by non-specialists. It contains few technical or theoretical details. This requires another shift in your mode of thinking. It requires you to forget, for the moment, the technical and theoretical details and problems that you focus on day-in and day-out. Rather, you need to think in terms of what the reader wants to know - the point and value of your research.

Your storyline will become a "skeleton" for your entire article. After getting the storyline clear, take the second step and add the "muscles" to turn this skeleton into a complete entity - a readable and credible scientific article. The "muscles" are, of course, the technical and theoretical details.

Below, is a short (fictitious) example to illustrate the storyline. In this example, 6 key elements of the standard scientific article form the basic structure of the storyline. You can use this example as a template for your storyline. Under each heading, delete the example text and paste in a similar text about your own work.

Fictitious Example

"Predicting Malaria Epidemics in Ethiopia"

Key element 1: the point of the research - why should the editors and readers care about the study?

'Malaria is still the number one killer of all infectious diseases. Most deaths could be prevented, however, if adequate medical facilities and medicines were available at the beginning of an epidemic. After an outbreak of malaria, getting adequate medical facilities and medicines to the local area can take many weeks. Obviously, this time is truly lost time and, for many victims, fatal. If, however, malaria epidemics could be predicted in local areas, medical facilities and medicine could be mobilized where they will be needed and, thereby, save many lives. Predicting where and when an epidemic can be expected is, however, currently not possible.'

Notice that the above statements clearly present a BIG health-related problem. And, an "if" sentence focuses on a strategy to help solve that problem. In only 3 sentences we know the point, and potential value, of the research. Now it is time to focus on what is known, and prepare the reader to understand the specific research question. For example,

'Malaria epidemics are known to be related to weather conditions. Previous research has shown that malaria epidemics seem to be related to specific meteorological factors (refs.). Smith and Jones (1995) have shown... Adams (1997) found that ... The correlations between these meteorological factors and subsequent malaria epidemics, however, have never been systematically investigated.

If such correlations do indeed exist, meteorological factors might be used to predict local epidemics. In this study we take a first step in developing a predicting model.'
At this point, the reader should have a good idea of the focus of the research. Now it is time to "zero in" on the specific research questions.

Key element 2: the specific research questions - the basis of credible science
'The purpose of this study was to answer the following questions. (1) What retrospective meteorological factors, and what combinations of factors, correlate significantly with the occurrence of subsequent malaria epidemics in Ethiopia? (2) To what extent do they explain the variance of occurrence of subsequent epidemics?'
Notice that the research questions are stated in terms of the variables that were measures or observed, in this case, meteorological factors (the independent variables) and occurrence of epidemics (dependent/outcome variable). Furthermore, the questions state the relationships sought between the variables: correlations and explanation of variance of the dependent variable. Such specific research questions tie the story together—they focus on credible science.

Key element 3: a description of the methods you used to answer your research questions.
This section will later become your Methods section. For the storyline, avoid details and make it understandable to the non-expert. Note that it is in past tense - factual information about what you did in this study.
'In a retrospective study, we collected meteorological data for 10 local areas in Ethiopia. The data included rainfall, temperature, sunshine, AAA, BBB, CCC, and DDD and... We also collected data concerning malaria epidemics for the same areas. This data covered the years 1963 to 2006. We developed a statistical model to determine correlations, and find factors and combinations of factors explaining the variance of epidemics. Using an independent subset of the data collected, we determined the predictive power of the model.'
Notice that in this section the authors report 2 types of information: (1) how they collected data, and (2) how they determined relationship between the variables.

Key element 4: the major findings
This will later become your Results section.
'We found that factors AAA, BBB, and CCC correlated significantly with subsequent epidemics in all 10 of the local areas studied. In 3 of the areas, the combination of CCC and DDD correlated significantly.'
Notice that in this section the authors report the relationships between the variables that they found. These are historical facts and, therefore, reported in past tense.

Key element 5: the answers to the research questions - your interpretation of the factual findings.
This will become the beginning of your Discussion section.
Notice that the answer to the research question uses exactly the same words used to state the question. And, notice that it is not a summary of results, but the authors' interpretation of the results about how the world IS and, therefore, stated in present tense. Of course, in a pilot study such as this, the authors cannot yet present definitive answers, and they indicate that with the words "suggest" and "may."
'The results of our study suggest that factors AAA, BBB, and CCC correlate significantly with subsequent malaria epidemics in Ethiopia. Furthermore, the combination of factors CCC and DDD may account for about XX% of variance in some areas. If we can generalize our findings to other areas, our model will have a predictive power of...'

Key element 6: the consequences of the answers—the value of your work.
This will become the Conclusion section and it relates directly back to the first key element, the original big health-related problem. A Conclusion is NOT a summary of results, but it describes how the study helps to solve the problem—it ties the end back to the beginning. And, it suggests a next step toward solving the problem - it gives direction to research.

'We conclude that local meteorological data can be used to predict malaria epidemics. Our statistical model, developed in this pilot study, has a predictive power of about 30%. Although this is certainly a first step toward predicting malaria epidemics, we would like to considerably increase the predictive power. We think that inclusion of groundwater level might increase the model's predictive power. This factor is, however, not available in the databases we used and will have to be determined by other means. Furthermore, our model still needs to be validated in other areas.'

The example as running text - a stand-alone story that focuses on the point and value of the research.

'Predicting Malaria Epidemics in Ethiopia'

Introduction

Malaria is still the number one killer of all infectious diseases. Most deaths could be prevented, however, if adequate medical facilities and medicines were available at the beginning of an epidemic. After an outbreak of malaria, getting adequate medical facilities and medicines to the local area can take many weeks. Obviously, this time is truly lost time and, for many victims, fatal. If, however, malaria epidemics could be predicted in local areas, medical facilities and medicine could be mobilized where they will be needed and, thereby, save many lives. Predicting where and when an epidemic can be expected is, however, currently not possible.
Malaria epidemics are known to be related to weather conditions. Previous research has shown that malaria epidemics seem to be related to specific meteorological factors. The correlations between these meteorological factors and subsequent malaria epidemics, however, have never been systematically investigated.
The purpose of this study was to answer the following questions. What retrospective meteorological factors, and what combinations of factors, correlate significantly with the occurrence of subsequent malaria epidemics in Ethiopia? To what extent do they explain the variance of occurrence of subsequent epidemics?

Methods

In a retrospective study, we collected meteorological data for 10 local areas in Ethiopia. The data included rainfall, temperature, sunshine, AAA, BBB, CCC, and DDD and... We also collected data concerning malaria epidemics for the same areas. This data covered the years 1963 to 2006. We developed a statistical model to determine correlations, and find factors and combinations of factors explaining the variance of epidemics. Using an independent subset of the data collected, we determined the predictive power of the model.

Results

We found that factors AAA, BBB, and CCC correlated significantly with subsequent epidemics in all 10 of the local areas studied. In 3 of the areas, the combination of CCC and DDD explained XX% of the variance in occurrence of subsequent epidemics.

Instructions for EJM authors

Discussion

The results of our study suggest that factors AAA, BBB, and CCC correlate significantly with subsequent malaria epidemics in Ethiopia. Furthermore, the combination of factors CCC and DDD may account for about XX% of variance in some areas. If we can generalize our findings to other areas, our model will have a predictive power of about 30%.

Conclusion

We conclude that local meteorological data can be used to predict malaria epidemics. Our statistical model, developed in this pilot study, has a predictive power of about 30%. Although this is certainly a first step toward predicting malaria epidemics, we would like to considerably increase the predictive power. We think that inclusion of groundwater level might increase the model's predictive power. This factor is, however, not available in the databases we used and will have to be determined by other means. Furthermore, our model still needs to be validated in other areas.

As a running text, it is now a short (452 words) and understandable story that forms the skeleton for the journal article. All we need to do now is to fill in the scientific and technical details - without destroying the storyline. To ensure that your article clearly presents the point of your research, write a similar short storyline for your study. Then fill in the details (theory, references, methods, data, tables, figures etc.) needed to support that storyline.

Do not underestimate the difficulty of getting out of that box of technical details. The author of the above example was also in a box, a box full of complex statistical methods and computer algorithms to design his model. And, as a consequence, he had lost all sight of the health-related problem he was helping to solve - malaria. I hope this example will help you to get started.

- Ed Hull -

Erasmus Journal of Medicine