RESEARCH

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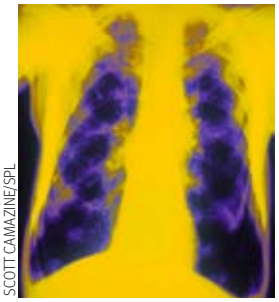
THIS WEEK'S RESEARCH QUESTIONS



SCOTT CAMAZINE/SPL

Palliative care for COPD

Chronic obstructive pulmonary disease (COPD) can be a serious terminal illness, but, according to qualitative research by Hilary Pinnock and colleagues, few patients, carers, or even healthcare professionals view the disease this way (p 268).

The 21 patients and 13 carers they interviewed described COPD as a "way of life," with only severe exacerbations classified as real illness. "Patients passively accept their lot and see the increasing disability as part of normal ageing," say editorialists Andrew Thorns and Declan Cawley of the study's findings (p 240).

The patients' "disease stories" were impossible to distinguish from their life stories, with no clear beginning and an unpredictable end, unlike patients with cancer, who often give a clear account of their diagnosis and how their life has been disrupted since.

This lack of a clear narrative and the fact that patients seem to passively accept the limitations imposed by COPD mean that it's hard to distinguish a point at which starting palliative care would be appropriate, say the authors. They suggest that clinicians should proactively assess the needs of patients with COPD at milestones such as starting long term oxygen therapy and admission to hospital for an exacerbation.

How to deal with exacerbations is discussed in some depth in a clinical review from *Drug and Therapeutics Bulletin* (p 271). The evidence behind the various pharmacological and non-pharmacological approaches available is reviewed, although unsurprisingly the most effective intervention is stopping smoking.

Vitamin D supplements for children's bones

Osteoporosis is a common and costly public health problem, and maximising bone mass early in life may be an important way to tackle it. Improving children's levels of vitamin D is one strategy that's been tested, but the results of randomised controlled trials of supplementation in young people have been inconsistent. Tania Winzenberg and colleagues did a meta-analysis to find out whether the evidence supported the use of vitamin D supplements to increase peak bone mass in children and adolescents (p 267). Their assessment of data from six studies, including almost 800 participants, showed no difference between vitamin D supplementation and placebo for effects on total body bone mineral content or on bone mineral density of the hip or forearm. A planned subgroup analysis suggested that supplementation could bring about clinically useful improvements, particularly in lumbar spine bone mineral density and total body bone mineral content, in children and adolescents who initially had a vitamin D deficiency. But the authors say that this finding requires confirmation.

Do NSAIDs protect against Parkinson's?

The idea that non-steroidal anti-inflammatory drugs (NSAIDs) might confer protection against Parkinson's disease has been around for a while, partly backed up by some epidemiological studies. But Jane Driver and colleagues found no evidence for any association (p 270).

This case-control study, nested within the prospective Physician's Health Study, included 22 007 US male physicians aged 40-84 followed up for 25 years. In all, 616 cases of incident Parkinson's disease were matched to 3080 controls by age, and for this comparison the drugs seemed to be protective. But, when the authors looked at 565 cases and 2458 controls matched by age and by scores for confounders (comorbidity and indicators of NSAID use), the apparent protective effect disappeared. Timing played a part too. Pain often precedes the main symptoms and signs of Parkinson's disease and, sure enough, use of NSAIDs by the patients in this study was clustered in the few years before their diagnosis of Parkinson's disease: without further adjustment this could have looked like a possibly causative link.

We particularly liked the way this study illustrates the perils of "confounding by indication." Anyone running a journal club would do well to read the paper's full discussion section on bmj.com.

CHASSENET/SPL

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Do women's magazines influence caesarean rates? Articles on caesarean section in Brazilian women's magazines provide an incomplete picture of the benefits and risks associated with the procedure and do not use optimal sources of information, according to research by Maria Regina Torloni and colleagues (doi:10.1136/bmj.d276). Their analysis of 118 articles published between 1988 and 2008 in the top selling women's magazines in Brazil, a country with one of the highest caesarean section rates in the world, found that almost all (94%) were written exclusively by journalists, although almost 80% cited health professionals as the main source of information. A total of 71% reported at least one benefit of caesarean section and 82% reported at least one short term maternal risk, but only a third mentioned any long term maternal risks or perinatal complications.

CME

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Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis

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EDITORIAL by Shaw

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STUDY QUESTION

Does vitamin D supplementation improve bone mineral density in healthy children?

SUMMARY ANSWER

t is unlikely that vitamin D supplements are beneficial in children with normal vitamin D levels. Our planned subgroup analyses by baseline serum vitamin D levels suggest that vitamin D supplementation of deficient children could result in clinically useful improvements, particularly in bone mineral density of the lumbar spine and total body bone mineral content, but this requires confirmation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vitamin D deficiency is common in children and seems detrimental to bone health, but it is unclear if vitamin D supplementation improves bone density. This paper suggests that vitamin D supplements are unlikely to be beneficial in children with normal vitamin D levels, but that supplementation of deficient children could result in clinically useful improvements in bone density, although this requires confirmation in studies targeting deficient children.

Selection criteria for studies

We electronically searched up to August 2009, the Cochrane Central Register of Controlled Trials, Medline (1966 to present), Embase (1980 to present), CINAHL (1982 to present), AMED (1985 to present), and ISI Web of Science (1945 to present), and hand searched conference abstracts from key journals. Inclusion criteria were placebo controlled randomised controlled trials of vitamin D supplementation for at least three months in healthy children and adolescents (aged from 1 month to <20 years) with bone density or quantitative ultrasound outcomes.

Primary outcome(s)

Primary outcomes were bone mineral density at the hip, lumbar spine, and forearm, and total body bone mineral content.

Main results and role of chance

Overall, vitamin D supplementation had no statistically significant effects on total body bone mineral content or on hip or forearm bone mineral density. There was a trend to a small effect on lumbar spine bone mineral density (standardised mean difference 0.15, 95% confidence interval −0.01 to 0.31, P=0.07). The effects between studies of high and low serum vitamin D levels at any site did not differ, although there was a trend to a larger effect with low serum vitamin D levels for total body bone mineral content (P=0.09 for difference). In low serum vitamin D studies, significant effects on total body bone mineral content and lumbar spine bone mineral density were equivalent to about a 2.6% and 1.7% percentage point greater change from baseline in the supplemented group, respectively.

Bias, confounding, and other reasons for caution

The number of studies contributing data to the meta-analysis was small. We therefore could not assess fully the effects of important clinical factors that might influence supplementation outcomes. Additionally, although it would take a large study with a strongly positive result to cause a noticeable increase in effect size, the limited number of studies and relatively low overall numbers of participants could reduce the robustness of our findings.

Study funding/potential competing interests

TW received a national health and medical research training fellowship and GJ receives a national health and medical research practitioner fellowship. The funding body had no input into any aspect of this study.

EFFECTS (% CHANGE FROM BASELINE) OF VITAMIN D SUPPLEMENTATION BY BASELINE SERUM VITAMIN D LEVEL

	Low baseline vitamin D level (<35 nmol/L)			High baseline vitamin D level (≥35 nmol/L)		
Outcome	No of studies	No of participants	Standardised mean difference* (95% CI)	No of studies	No of participants	Standardised mean difference* (95% CI)
Hip bone mineral density	1	168	0.25 (−0.07 to 0.58)	3	471	−0.02 (−0.31 to 0.28)
Lumbar spine bone mineral density	2	189	0.31 (0.00 to 0.61)†	3	471	0.09 (−0.10 to 0.28)
Total body bone mineral content	3	413	0.21 (0.01 to 0.41)‡	2	259	−0.07 (−0.33 to 0.18)§
Forearm bone mineral density	1	168	−0.06 (−0.38 to 0.26)	2	259	0.12 (−0.62 to 0.85)

*Standardised mean difference of 0.3 regarded as small.
†P=0.05.
‡Statistically significant at 5% level.
§P=0.09 for difference.

Living and dying with severe chronic obstructive pulmonary disease: multi-perspective longitudinal qualitative study

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EDITORIAL by Thorns and Cawley

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STUDY QUESTION

What are the perspectives of people living and dying with severe chronic obstructive pulmonary disease (COPD) and of their carers, and what are the implications for provision of care?

SUMMARY ANSWER

Patients tell a "directionless narrative" of a health problem, with no discernible transition point to a palliative care approach.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Models of palliative care for non-malignant disease, adapted from the traditional cancer model, are predicated on identifying "palliative" patients whose end of life care needs are then addressed. The lack of a discernible point of transition to palliative care in patients with COPD suggests that holistic assessment of needs linked with milestones throughout the patient's journey would be a better approach to end of life care in this group.

Rationale, design, and data collection method

We conducted serial qualitative interviews over 18 months with patients and their nominated informal and professional carers. We used our multi-disciplinary professional team, a lay advisory group, and an end of project national workshop to ensure balanced interpretation of the data.

Participants and setting

We interviewed 21 patients with end stage COPD, plus 13 informal carers (for example, a family member, friend, or neighbour) and 18 professional carers (that is, a key health or social care professional) nominated by the patients as important to their care, from Lothian, Tayside, and Forth Valley, Scotland, during 2007-2009.

Recruitment and sampling strategy

Primary and secondary care clinicians from general practices or from hospital and community specialist respiratory services identified patients. We purposefully sampled to recruit males and females with different ages, social class, rurality, presence within the home of an informal carer, and current smoking status.

Data analysis method

Interviews were transcribed and analysed both thematically and as narratives.

Main findings

The participants in our study described severe symptoms that caused major disruption to normal life, but often in terms implying acceptance of the situation as a "way of life" rather than an "illness" disrupting life.

Patients told narrative indistinguishable from their life stories, with an onset of symptoms that was so insidious as to be imperceptible, and an end described in terms reminiscent of normal expectations of death rather than as an anticipated consequence of their disease. Within the context of a lifetime condition with an uncertain prognosis, identifying a transition point to palliative care was meaningless and impractical for both patients and professionals.

Implications

Firstly, healthcare professionals need to recognise the risk of "passive acceptance" among patients with COPD, and services should be developed that proactively identify and seek to address needs. Secondly, rather than seeking a point of transition to palliative care, we propose linking holistic assessments of supportive and palliative care needs with milestones throughout the patient's journey, such as diagnosis, retirement on medical grounds, starting long term oxygen therapy, or hospital admission for an exacerbation of COPD.

Bias, confounding, and other reasons for caution

Our 21 participants may not fully represent the diversity of people with very severe COPD. In particular, none was from an ethnic minority background, although the study cohort encompassed a broad range of demographic, social, clinical, and healthcare backgrounds.

THE STORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: EXAMPLES OF CONTRASTING PERSPECTIVES

Patient perspective	Patient perspective: the exception (patient with α1 antitrypsin deficiency)	Professional perspective
A story with no beginning	**Well rehearsed story of a dramatic diagnosis**	**Insidious onset**
"How it started is anybody's guess; there is no way of knowing . . ." [T06.1]	"Day before the wedding we found out he was basically a dying man." [L06.1 wife]	"He has probably had COPD for years but official diagnosis was just about 18 months ago" [F07.1 nurse]
A middle that is a way of life	**Emotional upheaval and a quest**	**A way of life for clinicians?**
"I'm all right if I sit still. It's all just part of getting older I suppose." [T03.1]	"After I did the research on the internet we thought, well, we can't surely be the only people with this disease, there must be somebody else out there that we can ask or whatever." [L06.1]	"It [a consultation] is more reassurance about how he is and chatting generally and he just likes a bit of social discourse I think." [L04.1 GP]
An uncertain and unlooked for end	**Discussed and planned for**	**An uncertain and unlooked for end**
"Even the doctor said that, it won't get any better. What I thought, actually I could stay in the same sort of level . . ." [F07.3]	"It wasn't a difficult decision for me actually because having spoken about it at length before, you know, when he had bad episodes, about, you know, what we wanted to happen etc." [L06.1 wife]	". . . we are all going to die aren't we, but it is a case of picking the time and place [to discuss it]." [L06.1 hospital doctor]

Monitoring adherence to drug treatment by using change in cholesterol concentration: secondary analysis of trial data

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STUDY QUESTION

How accurate is cholesterol monitoring for detecting non-adherence with cholesterol lowering treatment?

SUMMARY ANSWER

Monitoring low density lipoprotein (or total) cholesterol is reasonably accurate for detecting complete non-adherence or non-persistence with pravastatin treatment but inaccurate for detecting partial non-adherence.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Adherence after starting lipid lowering treatment varies between patients, but the capacity of lipid monitoring to detect non-adherence is unknown.
Monitoring low density lipoprotein (or total) cholesterol concentration has modest ability to detect complete non-adherence or non-persistence with pravastatin treatment and weak ability to detect partial non-adherence.

Participants and setting

The long term intervention with pravastatin in ischaemic disease (LIPID) is a randomised controlled trial that compared the effects of pravastatin with placebo in 9014 patients with previous coronary heart disease and a plasma total cholesterol concentration between 4.0 and 7.0 mmol/L.

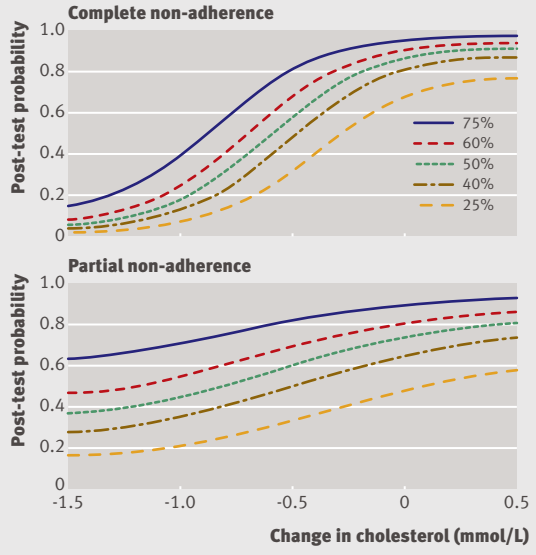
Design, size, and duration

This was a secondary analysis of data on cholesterol concentration from the LIPID study. The discriminatory power of change in low density lipoprotein and total cholesterol concentration from randomisation to one year was analysed by using two measures of complete non-adherence (discontinuation of treatment, allocation to placebo arm) and one of non-adherence (less than 80% of pills taken).

Main results and the role of chance

Cholesterol monitoring had modest ability for detecting complete non-adherence. One year after the start of treatment, 50% (1957/3937) of the non-adherent patients and 6% (253/3944) of adherent patients had a rise in concentration of low density lipoprotein cholesterol. Accuracy was reasonable (area under the receiver operating characteristics curve 0.89). Cholesterol monitoring had weak ability for detecting partial non-adherence. One year after starting treatment, 16% (34/213) of partially adherent and 4% (155/3585) of fully adherent patients had a rise in concentration. Accuracy was poor (area under the curve 0.65). The figure illustrates the post-test probabilities for typical pre-test probabilities of non-adherence. The curves range from low pre-test probability (25%) to high pre-test probability (75%). A patient with no change in concentration has a post-test probability of being completely non-adherent of between 67% and 95% and a post-test probability of being partially non-adherent of between 48% and 89%. A patient with a decrease of 1.0 mmol/L has a post-test probability of being completely non-adherent of between 7% and 40% and a post-test probability of being partially non-adherent of between 21% and 71%.

PROBABILITY OF NON-ADHERENCE WITH STATINS BY CHANGE IN LOW DENSITY LIPOPROTEIN CHOLESTEROL AND PRE-TEST PROBABILITY (25%, 40%, 50%, 60%, OR 75%)



Bias, confounding, and other reasons for caution

Analysis was limited to adherence at one year. Partial adherence was defined as taking less than 80% of pills.

Generalisability to other populations

Our results could be generalised to the effects of other statin drugs of similar dose in patients with similar baseline lipid concentrations.

Study funding/potential competing interests

This study was funded by the Australian National Health and Medical Research Council (Program Grant No 402764). The LIPID trial was supported by a grant from the Bristol-Myers Squibb Pharmaceutical Research Institute and conducted under the auspices of the National Heart Foundation of Australia.

Use of non-steroidal anti-inflammatory drugs and risk of Parkinson's disease: nested case-control study

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STUDY QUESTION

Does regular use of non-steroidal anti-inflammatory drug (NSAIDs) decrease the risk of Parkinson's disease?

SUMMARY ANSWER

Men with Parkinson's disease were more likely than controls to have been regular users of non-aspirin NSAIDs in the years before their diagnosis, but this positive association was attenuated after matching on scores for comorbidity and indicators of NSAID use.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Results from epidemiological studies of the relation between NSAID use and Parkinson's disease risk are conflicting. This study found no evidence that regular use of non-aspirin NSAID or aspirin decreased the risk of Parkinson's disease. The positive associations observed between NSAID use and Parkinson's disease might have been due to confounding by indication, as such NSAID use was clustered in the few years before diagnosis of Parkinson's disease.

Participants and setting

This case-control study, nested within the prospective Physician's Health Study, included 22 007 US male physicians aged 40–84 years without indications for or contraindications to regular NSAID use and free of Parkinson's disease at baseline. Up to five controls were matched to each case by age alone or by age and scores for confounders (comorbidity and indicators of NSAID use).

Design, size, and duration

Using information collected during 25 years of follow-up, we matched 616 cases of incident Parkinson's disease to 3080 controls by age, and 565 cases to 2458 controls by age and the confounder scores. Parkinson's disease was self reported by the physician participants, and information on NSAID use was collected prospectively.

Primary outcome(s), risks, exposures

We calculated the odds of having been exposed to prior non-aspirin NSAID or aspirin use by participants with Parkinson's disease and by their controls in each case-control set.

Main results and the role of chance

Participants who had ever used non-aspirin NSAIDs had an increased risk of Parkinson's disease in the age matched group (odds ratio 1.28 (95% CI 1.05 to 1.56)) but not in the group also matched for confounder scores (odds ratio 1.17 (0.94 to 1.46)). There was an increased risk of Parkinson's disease in men who had 1–2 years of regular use of non-aspirin NSAIDs (odds ratio 1.35 (1.07 to 1.70)), a finding that remained significant after matching for confounder scores (odds ratio 1.35 (1.05 to 1.75)) (see table). In contrast, the significant association of use of non-aspirin NSAIDs for ≥5 years (odds ratio 1.48 (1.05 to 2.09)) in the age matched group was entirely attenuated in the group also matched for confounders (1.03 (0.70 to 1.53)). There was also a suggestion that men who regularly used aspirin had an increased risk of Parkinson's disease. The positive associations between use of non-aspirin NSAIDs or aspirin and risk of Parkinson's disease tended to disappear when analyses were limited to drug use ≥5 years before the disease diagnosis.

Bias, confounding, and other reasons for caution

While the study design allowed us to control carefully for confounding by indications for NSAID use and comorbidity, our results may be limited by residual or unmeasurable confounding.

Generalisability to other populations

Our cohort is homogeneous with respect to sex, ethnicity, and profession, which may limit generalisability to different populations. The participants' median age of onset of Parkinson's disease (73.8 years) is older than in many other studies.

Study funding/potential competing interests

This research is funded by a grant from the Parkinson's Disease Foundation. The Physicians' Health Study is supported by grants from the National Cancer Institute and from the National Heart, Lung, and Blood Institute, Bethesda, MD. The authors were independent from the funders in all aspects of the study design, analysis of data, and writing of the manuscript.

RISK OF PARKINSON'S DISEASE BY CUMULATIVE REGULAR USE OF NON-ASPIRIN NSAIDS

Years of regular drug use	Cases	Controls	Odds ratio (95% CI) by drug use: At index date	5 years prior*
Controls matched by age				
0	417/616 (68%)	2232/3080 (72%)	1.00	1.00
1–2	121 (20%)	492 (16%)	1.35 (1.07 to 1.70)	1.30 (0.99 to 1.69)
3–4	29 (4.7%)	174 (5.7%)	0.91 (0.60 to 1.37)	0.74 (0.45 to 1.23)
≥5	49 (8.0%)	182 (5.9%)	1.48 (1.05 to 2.09)	1.31 (0.82 to 2.09)
Controls matched by age and confounder scores†				
0	386/565 (68%)	1789/2458 (73%)	1.00	1.00
1–2	111 (20%)	370 (15%)	1.35 (1.05 to 1.75)	1.12 (0.84 to 1.50)
3–4	27 (4.8%)	137 (5.6%)	0.82 (0.52 to 1.29)	0.75 (0.42 to 1.36)
≥5	41 (7.3%)	162 (6.6%)	1.03 (0.70 to 1.53)	0.81 (0.46 to 1.43)

*Excluding drug use within 5 years before index date (when Parkinson's disease diagnosed in case).
†Confounder scores=modified Charlson comorbidity score, score for indicators of NSAID use, and score for NSAID side effects.