RESEARCH

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GETTY

THIS WEEK'S RESEARCH QUESTIONS

1259 What is the efficacy and safety of varenicline for quitting smokeless tobacco?
1260 For how long must drivers be seizure free after a first seizure before they can drive again?
1261 Which congenital malformations are associated with carbamazepine exposure in early pregnancy?
1262 Did an early two dose measles vaccine strategy during a measles outbreak in Guinea-Bissau affect all cause mortality in babies?

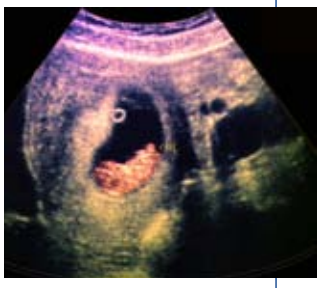
Varenicline and quitting smokeless tobacco

The use of oral smokeless tobacco is increasing in many countries; "snus" use is well established in Scandinavia, and the largest Western market for such products is the United States. Last year we published a meta-analysis of observational studies from these areas, which reported an increased risk of fatal myocardial infarction and stroke associated with use of smokeless tobacco (*BMJ* 2009;339:b3060). A recent clinical review notes that it's also a risk factor for head and neck cancer (*BMJ* 2010;341:c4684).

Users often view smokeless tobacco as less harmful than smoking, but reports suggest that many would like to quit. There's evidence that behavioural interventions can help them do so, but pharmacotherapy has so far shown little success.

In a multicentre randomised controlled trial, Karl Fagerström and colleagues investigated whether varenicline, a drug licensed as a smoking cessation aid, could also work for users of smokeless tobacco—mainly Norwegian and Swedish men who used snus (p 1259). They found that the drug was more effective than placebo at helping users achieve both short and longer term abstinence, and it had an acceptable safety profile. The study was funded by Pfizer, the manufacturer of varenicline.

Safety of carbamazepine in the first trimester


SOVEREIGN, ISM/SPL

A High Court action in England against Sanofi-Aventis over birth defects in children whose mothers took its anticonvulsant drug sodium valproate (Epilim) during pregnancy collapsed last month after legal aid was withdrawn (*BMJ* 2010;341:c6384). Lawyers for the families had argued that even though mothers were informed of this drug's risks, they would have risked their unborn babies' health by not taking an anticonvulsant.

So which anticonvulsant should women take? Carbamazepine seems to be the safest option in early pregnancy, but studies so far have lacked the power to detect risks for specific congenital malformations with the various drugs. Now Janneke Jentink and colleagues have analysed data from 19 European population based registers of congenital anomalies in the EUROCAT Antiepileptic Study Database, covering over 3.8 million births (p 1261). Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy, and the risk was smaller for carbamazepine than for valproic acid. The authors also found, in an extensive literature review, an overall prevalence for a major congenital malformation of 3.3% (95% confidence interval 2.7 to 4.2) after exposure to carbamazepine monotherapy in the first trimester.

Editorialist Irena Nulmnan agrees that carbamazepine is the drug of choice for pregnant women with epilepsy and asserts that seizure control, perinatal counselling, and careful management should produce favourable outcomes in more than 95% of such pregnancies (p 1229).

Non-specific benefits of measles vaccination in west Africa

Research from Africa, Bangladesh, and Haiti has shown that measles vaccination in infancy is associated with much greater reductions in mortality than would be expected simply from preventing measles. Given this, should WHO review its advice that measles vaccination should be given to 9 month old babies? Could more lives be saved by vaccinating sooner?

Two years ago we published an interim analysis of a randomised controlled trial in Guinea-Bissau suggesting that two doses of the Edmonston-Zagreb strain measles vaccine given as early as 4.5 months of age might be warranted in humanitarian emergencies or measles outbreaks (*BMJ* 2008;337:a661). In that trial the number needed to treat to prevent one case of measles during the epidemic was 7.2 (6.8 to 9.2). The treatment group tended to have lower overall mortality, but this was not significant.

Now Peter Aaby and colleagues' further analysis of this trial finds that mortality was significantly lower between 4.5 and 36 months of age for vaccinated girls but not boys (p 1262). This trial is just one of many intriguing studies arising from the long term Bandim Health Project on the population effects of vaccines, vitamin A supplementation, distribution of bed nets, and other interventions in Guinea-Bissau, one of the world's poorest countries (www.bandim.org).

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Lifetime cardiovascular risk Validated risk prediction algorithms such as QRISK2 usually use a 10 year absolute risk of cardiovascular disease of 20% or greater to identify patients at high risk. But applying this threshold may miss people at younger ages who, despite a low absolute 10 year risk, have a high risk relative to their peers. In a UK cohort study, Julia Hippisley-Cox and colleagues aimed to develop, validate, and evaluate a new QRISK model to estimate lifetime risk of cardiovascular disease (doi:10.1136/bmj.c6624). Their approach identified younger people with a high lifetime risk who would not have been identified with 10 year risk estimates—such patients were more likely to be men, to be from non-white ethnic groups, and to have a family history of premature coronary heart disease. But although lifestyle interventions at an earlier age could help some people at high lifetime risk, it's unclear whether the benefits of earlier medical treatment would be outweighed by the associated risks and costs, say the authors.

Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial

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STUDY QUESTION

What is the efficacy and safety of varenicline—a drug used in smoking cessation—compared with placebo for quitting smokeless tobacco?

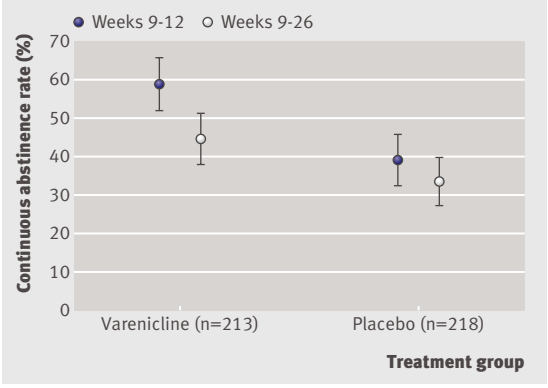
SUMMARY ANSWER

Varenicline 1 mg twice daily had an acceptable safety profile and was efficacious as an aid for quitting smokeless tobacco.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Use of smokeless tobacco is prevalent in some areas and current cessation options have focused on behavioural interventions. A drug used in smoking cessation, varenicline, can also help cessation of smokeless tobacco, and users can remain abstinent six months after quitting.

CONTINUOUS ABSTINENCE RATES WITH VARENICLINE AND PLACEBO AT END OF TREATMENT IN USERS OF SMOKELESS TOBACCO



Design

In this double blind, placebo controlled, multicentre, parallel group clinical trial with computer generated randomisation participants were randomised to receive either varenicline 1 mg or placebo twice daily for 12 weeks.

Participants and setting

Participants were men and women aged ≥18 who had been using smokeless tobacco at least eight times a day during the previous year (with no period of abstinence within three months before screening) and who were motivated to stop use of all tobacco products. Most participants were seen in primary care settings, with the remainder being seen either in secondary care or specialist smoking cessation clinics.

Primary outcome

The primary end point was the four week continuous abstinence rate, confirmed by cotinine measurements, at the end of treatment (weeks 9-12).

Main results and the role of chance

431 participants (213 varenicline; 218 placebo) were randomised. Demographics and baseline smokeless tobacco use were similar between groups (89% (189) and 90% (196), respectively, were men; mean age in both groups was 43.9; participants used smokeless tobacco products about 15 times a day, and about 80% first used smokeless tobacco within 30 minutes after waking). The continuous abstinence rate at week 9-12 was higher for varenicline than placebo (59% (125) *v* 39% (85); relative risk 1.60, 95% confidence interval 1.32 to 1.87, P<0.001; risk difference 20%; number needed to treat=5). The advantage of varenicline over placebo persisted through 14 weeks of follow-up (at weeks 9-26 the continuous abstinence rate was 45% (95) *v* 34% (73); relative risk 1.42, 95% confidence interval 1.08 to 1.79, P=0.012; risk difference 11.1%; number needed to treat=9).

Harms

The most common adverse events were nausea (35% *v* 6%), fatigue (10% *v* 7%), headache (10% *v* 9%), and sleep disorder (10% *v* 7%) in the varenicline versus placebo groups, respectively.

Bias, confounding, and other reasons for caution

Varenicline is currently not licensed for cessation smokeless tobacco. Further studies with longer follow-up will be needed to evaluate longer term efficacy.

Generalisability to other populations

Participants were almost exclusively Norwegian or Swedish, most were men, and all used a specific type of smokeless tobacco—namely, snus—so the results might not generalise to other settings or to users of different types of smokeless tobacco products, such as chewing tobacco. The primary addictive component of all of smokeless tobacco is nicotine, however, so the results should be replicated in studies of other types of smokeless tobacco.

Study funding/potential competing interests

This study was funded by Pfizer. MMet and MMes are employees of, and stockholders in, Pfizer. KF, ST, and HG have specified relationships with Pfizer.

Trial registration number

NCT00717093 (www.clinicaltrials.gov).

Risk of recurrence after a first seizure and implications for driving: further analysis of the Multicentre study of early Epilepsy and Single Seizures

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STUDY QUESTION

For how long must drivers be seizure-free after a first seizure before the risk of a recurrence is low enough to allow them to drive in the United Kingdom?

SUMMARY ANSWER

After a seizure-free period of six months following a first seizure the overall risk of a recurrence was low enough (below 20%) to allow people to resume driving, irrespective of whether they had started antiepileptic drugs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Reports have provided estimates for seizure recurrence from the date of a first seizure but not at subsequent time points. Our unadjusted analysis suggested that at six months after an index seizure the risk of recurrence within 12 months was significantly less than 20% for people who had started antiepileptic drug treatment, whereas multivariable analyses suggested that at this time point the risk was significantly more than 20% for people with a remote symptomatic seizure and abnormal electroencephalogram result, irrespective of treatment policy.

Participants and setting

The subset of participants from the Multicentre study of early Epilepsy and Single Seizures (MESS) used for this analysis comprised participants aged at least 16 years with a single unprovoked seizure. MESS was based in hospital outpatient clinics.

Design, size, and duration

MESS was a randomised controlled trial assessing the policies of immediate and deferred antiepileptic drug treatment. Overall, 637 of 1443 people randomised in MESS were suitable for analysis, 317 of whom were allocated to immediate treatment. Participants were recruited between 1 January 1993 and 31 December 2000 and were followed up until between 31 December 2001 and 30 June 2002.

Main results

The risk of seizure recurrence in the immediate treatment group after a seizure-free period of six months was 14% (95% confidence interval 10% to 18%), significantly below 20%. For the delayed treatment group the risk was 18% but the confidence interval (13% to 23%) did not exclude a 20% risk of recurrence. At 12 months the risk in the delayed treatment group was significantly below 20%, at 10% (6% to 15%).

Bias, confounding, and other reasons for caution

People were given the opportunity to enter MESS only if the clinician was uncertain about the need to start treatment; thus participants may not be representative of the general population of people presenting with a first seizure. Also, some patients who had had a first seizure had a second while waiting to see a specialist and possibly started treatment at that point rather than join the trial; thus MESS might have recruited people with a lower risk of a seizure recurrence than the general population. Participants were seen predominantly by neurologists who are experienced at identifying and classifying seizures, but a further challenge in outpatient based studies is that seizures are reported to the clinician by the patient and it is possible that patients under-report their occurrence.

Generalisability to other populations

MESS is the largest reported study of early epilepsy and single seizures. The results should be generalisable to anyone with a single unprovoked seizure.

Study funding/potential competing interests

This study is part of a programme that received funding from the National Institute for Health Research programme grants for applied research funding scheme. The original MESS trial was funded by the Medical Research Council. PRW and AGM sit on the advisory panel of the Driver and Vehicle Licensing Agency.

RISK OF SEIZURE RECURRENCE IN NEXT 12 MONTHS AT TIME POINTS AFTER A FIRST SEIZURE

	Risk of seizure in next 12 months (%, 95% CI)	
Seizure-free months after first seizure	Immediate treatment	Delayed treatment
6	14 (10 to 18)	18 (13 to 23)
12	7 (4 to 11)	10 (6 to 15)
18	8 (5 to 12)	12 (8 to 17)
24	7 (3 to 10)	10 (5 to 14)

Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study

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STUDY QUESTION With which specific major congenital malformations is carbamazepine exposure in the first trimester of pregnancy associated in published cohort studies and can this be confirmed in a population based case-control study?

SUMMARY ANSWER Of the five identified indications in the literature we could confirm only the association between carbamazepine exposure and spina bifida compared with no antiepileptic drugs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Carbamazepine exposure in the first trimester is known to increase the risk for major congenital malformations. This study could confirm this only for spina bifida, though the risk is less than with valproic acid.

Participants and setting
We searched PubMed, Web of Science, and Embase for papers about carbamazepine exposure in the first trimester of pregnancy and specific malformations. We used the EUROCAT Antiepileptic Study Database, including data from 19 European population based congenital anomaly registries, 1995-2005. The dataset included 98 075 registrations of malformations covering over 3.8 million births.

Design and size
In the literature search we identified eight cohort studies of 2680 pregnancies with carbamazepine monotherapy exposure. We identified key indications and carried out a population based case-control study to test these indications. The five indications identified were spina bifida, total anomalous pulmonary venous return, cleft lip (with or without palate), diaphragmatic hernia, and hypospadias (in boys). Our non-chromosomal and our chromosomal control group comprised 69 883 and 11 763 pregnancy outcomes, respectively.

Primary outcomes, risks, exposures
From the literature review we calculated overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester. In the Eurocat dataset we calculated odds ratios for malformations with exposure to carbamazepine among cases compared with two groups of controls: registrations of other non-chromosomal malformations and chromosomal syndromes.

Main results and the role of chance
The literature review yielded an overall prevalence for a major congenital malformation of 3.3% (95% confidence interval 2.7 to 4.2) after exposure to carbamazepine monotherapy in the first trimester. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy (odds ratio 2.6, 95% confidence interval 1.2 to 5.3, compared with no antiepileptic drug), but the risk was smaller for carbamazepine than for valproic acid (0.2, 0.1 to 0.6). There was no evidence of an association with the other malformations under study compared with no exposure to antiepileptic drugs. Further exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect. Despite the large dataset, there was not enough power to detect moderate risks for some rare major congenital malformations.

Bias, confounding, and other reasons for caution
Individuals in the control group with malformations related to carbamazepine—single ventricle and atrioventricular septal defect—were excluded and this did not essentially change our results. A limitation in our comparison of risks between exposures to different types of antiepileptic drug was that we did not have the information to adjust for type of epilepsy, frequency of seizures, used of folic acid, and dose of the antiepileptic drug.

Generalisability to other populations
We used a population based sample of European births for 1995-2005. We think that the teratogenicity of carbamazepine will be comparable in other populations (keeping in mind ethnicity).

Study funding/potential competing interests
The EUROCAT Central Database is supported in part by the European Public Health Programme, with various sources of public funding for individual registries. Additional funding was obtained from GlaxoSmithKline for a study of lamotrigine, during which the antiepileptic study database was constructed (all authors were involved in this study). GlaxoSmithKline was not involved in the present study.

MALFORMATION IN FETUS EXPOSED TO CARBAMAZEPINE MONOTHERAPY OR VALPROIC ACID MONOTHERAPY COMPARED WITH NO ANTIEPILEPTIC DRUGS

Malformation subgroup (No of cases)	Exposed to carbamazepine (n=16)	Odds ratio (95% CI) No antiepileptic drugs (n=69 534)	Odds ratio (95% CI) Valproic acid (n=102)
Spina bifida (n=2048)	8	2.6 (1.2 to 5.3)	0.2 (0.1 to 0.6)
Diaphragmatic hernia (n=755)	1	0.9 (0.1 to 6.6)	0.5 (0.0 to 4.5)
Hypospadias, boys only (n=5393)	6	0.7 (0.3 to 1.6)	0.2 (0.1 to 0.5)
Cleft lip (with or without palate) (n=3544)	1	0.2 (0.0 to 1.3)	0.3 (0.0 to 2.6)
Total anomalous pulmonary venous return (n=132)	0	—	—

Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial

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STUDY QUESTION

Does a 25% difference in mortality exist between 4.5 months and 3 years of age for children given two standard doses of Edmonston-Zagreb measles vaccine at 4.5 and 9 months of age compared with those given one dose of measles vaccine at 9 months?

SUMMARY ANSWER

An early two dose measles vaccination strategy was associated with a non-significant 22% reduction in all cause mortality between 4.5 and 36 months; the effect was statistically significant for girls.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vaccines may have non-specific and sex differential effects on all cause mortality. This two dose schedule may have beneficial non-specific effects on survival, particularly for girls and for children who have not received neonatal vitamin A.

Design

This was a randomised controlled trial. We randomised children to receive Edmonston-Zagreb measles vaccine at 4.5 and 9 months of age (group A), no vaccine at 4.5 months and Edmonston-Zagreb measles vaccine at 9 months (group B), or no vaccine at 4.5 months and Schwarz measles vaccine at 9 months (group C).

Participants and setting

We included 6648 children aged 4.5 months who had received three doses of diphtheria-tetanus-pertussis (DTP) vaccine at least four weeks before enrolment. A large proportion (80%) had previously taken part in randomised trials of neonatal vitamin A supplementation. The trial took place at the Bandim Health Project, Guinea-Bissau.

Primary outcome(s)

This was the mortality rate ratio between 4.5 and 36 months of age for group A compared with groups B and C.

Main results and the role of chance

In the intention to treat analysis, the mortality rate ratio of children who received two doses of Edmonston-Zagreb vaccine at 4.5 and 9 months of age compared with those who received a single dose of Edmonston-Zagreb vaccine or Schwarz vaccine at 9 months was 0.78 (95% confidence interval 0.59 to 1.05); the effect was significant for girls (0.64 (0.42 to 0.98)). In children who did not receive neonatal vitamin A supplementation, the two dose measles vaccine schedule was associated with a mortality rate ratio of 0.59 (0.39 to 0.89) between 4.5 and 36 months. The effect was again significant for girls but not statistically significant from the effect in boys. When we censored measles cases, the mortality rate ratio was 0.65 (0.43 to 0.99).

Harms

The intervention was not associated with any harms.

Bias, confounding, and other reasons for caution

Given previous evidence that receiving DTP after measles vaccination shortens children's survival, we enrolled only children who had already received the third DTP vaccine. More children in the control groups received measles vaccine early elsewhere and had to be censored because we did not know the strain and quality of measles vaccine used. This may have influenced the estimated effect of early measles vaccination. The effect of early two dose measles vaccine interacted with neonatal vitamin A supplementation, so the effect should be tested in populations that are not receiving vitamin A.

Generalisability to other populations

Observational studies from Africa, Asia, and America have given strong indications of such effects, so we also believe that our results can be generalised.

Study funding/potential competing interests

This study was funded by DANIDA and the Danish National Research Foundation. The Bandim Health Project received support from DANIDA. PA holds a research professorship grant from the Novo Nordisk Foundation.

Trial registration number

Clinical trials NCT00168558.

MORTALITY RATES AND MORTALITY RATE RATIOS (95% CI) OF RECIPIENTS OF EARLY TWO DOSE MEASLES VACCINE COMPARED WITH MEASLES VACCINE AT 9 MONTHS AMONG ALL CHILDREN (4.5-36 MONTHS; N=6417)

	ITT mortality per 100 person years (deaths/person days)					
Children	Early two dose measles vaccine (group A)	Measles vaccine at 9 months (groups B and C)	ITT mortality rate ratio (A/(B+C))	ITT mortality rate ratio (A/(B+C)) (with censoring for measles infection)	PP mortality rate ratio (A/(B+C))	PP mortality rate ratio (A/(B+C)) (with censoring for measles infection)
Boys	1.5 (36/904 841) (n=1084)	1.5 (75/1 789 303) (n=2151)	0.95 (0.64 to 1.42)	1.05 (0.70 to 1.57)	0.82 (0.54 to 1.25)	0.90 (0.59 to 1.37)
Girls	1.2 (29/881 883) (n=1045)	1.9 (90/1 755 448) (n=2137)	0.64 (0.42 to 0.98)	0.67 (0.44 to 1.02)	0.59 (0.38 to 0.91)	0.61 (0.39 to 0.95)
All	1.3 (65/1 786 724) (n=2129)	1.7 (165/3 544 751) (n=4288)	0.78 (0.59 to 1.05)	0.84 (0.63 to 1.12)	0.70 (0.52 to 0.94)	0.74 (0.55 to 1.00)

ITT=intention to treat analysis; PP=per-protocol analysis.