

Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction

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Cardiovascular disease

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Medstead
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Diabetes

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Obstetrics and gynaecology

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Respiratory medicine

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Urology

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Cardiovascular disease

Fish oils show no benefit in patients with multiple CVD risk factors

Fish oils have no effect on cardiovascular morbidity and mortality in patients with multiple risk factors or atherosclerotic vascular disease, a large general practice-based study from Italy has found.

The Risk and Prevention Study was double-blind and placebo-controlled. A total of 12,513 patients were enrolled who had multiple cardiovascular risk factors or atherosclerotic vascular disease but none had had a myocardial infarction (MI). They were followed up by a network of 860 GPs.

Around half, 6,244 patients, were assigned to 1 g/day of n-3 fatty acids (polyunsaturated fatty acid ethyl esters with eicosapentaenoic acid and docosahexaenoic acid content not less than 85%) and 6,269 to placebo.

The primary end point was initially a composite that included death, nonfatal MI and nonfatal stroke but was later revised at one year after a blinded assessment showed a very low event rate. The revised primary end point was death from cardiovascular

causes or hospital admissions for cardiovascular problems. The median follow-up was five years.

There were no significant differences in death from cardiovascular causes or hospitalisations for CVD between the two groups: 11.7% in the fish oil group and 11.9% in the placebo group, adjusted hazard ratio (HR) with n-3 fatty acids, 0.97 (95% CI:0.88-1.08; P = 0.580). Furthermore, none of the secondary end points showed a significant effect of fish oils either: death, non-fatal MI or stroke (P = 0.64), death from cardiovascular cause or nonfatal MI or stroke (P = 0.59), fatal or nonfatal coronary event (P = 0.51) and death from coronary cause (P = 0.66).

Fish oils or more specifically n-3 polyunsaturated fatty acids are considered to be of benefit in patients with a previous MI or heart failure. This is based on the findings of the GISSI and GISSI-HF trials.

Patients and physicians may be tempted to extrapolate this data to consider that taking fish oil supplements may be of benefit in those with multiple cardiovascular risk factors or atherosclerotic vascular disease without prior MI. The Risk and Prevention Study has shown this not to be the case.

The dose of fish oil used was the same as in previous studies such as GISSI and GISSI-HF which did show a benefit in the reduction of sudden cardiac death postulated to be via suppression of ventricular arrhythmias. Other recent trials such as the Alpha Omega trial and the OMEGA trial have questioned the role of fish oils post-MI.

The fish oil supplements were well tolerated and did not appear to cause harm but the evidence base to support their use in patients at high risk of CVD is lacking and it is possible that this may soon extend to their use post-MI. »

DR PETER SAVILL

● **The Risk and Prevention Study Collaborative Group. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368:1800-1808**

Urology

Overactive bladder and irritable bowel syndrome often co-exist

The link between overactive bladder (OAB) and irritable bowel syndrome (IBS) suggests that it is worth GPs asking about bowel symptoms when assessing patients with symptoms suggestive of OAB, a study from Japan concludes.

The researchers investigated the prevalence of OAB and IBS using a

large-scale internet-based survey. Questionnaires were sent to 10,000 patients, 5,000 men and 5,000 women, with 1,000 of each gender represented from each decade from 20-29 through to 60 and over.

The severity of OAB symptoms was assessed using the OAB symptom score for the first time in a general population. Higher scores indicate greater severity: 3-5 mild; 6-11 moderate; 12-15 severe.

IBS symptoms were assessed using the well established Rome III criteria for functional gastrointestinal disorders. This also allowed classification according to subtype, i.e. diarrhoea- or constipation-predominant IBS.

Overall prevalence of OAB was 9.3% (9.7% in men and 8.9% in women)



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hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). **Very common:** epistaxis. Epistaxis was generally mild to moderate, with incidences in adults and adolescents higher in longer-term use (more than 6 weeks). **Common:** headache, nasal ulceration. **Uncommon:** rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness. **Rare:** hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. **Not known:** transient ocular changes, growth retardation. **Precautions:** Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. Consider additional systemic corticosteroid cover during periods of

with prevalence increasing with age. Of those affected, 59% reported mild symptoms, 40% moderate symptoms and 1% severe symptoms.

The prevalence of IBS was greater, with 21.2% of subjects reporting symptoms (18.6% of men and 23.9% of women). The incidence of IBS declined with age.

Overall, 33% of patients with OAB also had IBS and this relationship was consistent in both men and women. Furthermore, 20% of patients without OAB were found to have symptoms of IBS according to the Rome criteria. IBS was reported in 33.3%, 32.8% and 38.5% of patients with mild, moderate and severe OAB, respectively. Prevalence of OAB was 14.6% in subjects with IBS and 7.9% in those without.

Several previous studies have demonstrated that the two disorders often occur concurrently, raising the possibility that these poorly understood conditions may share common pathological features.

The bowel and bladder are closely associated anatomically, share very similar innervation and have similar functions in terms of storage and voiding of bodily waste products.

Several theories have been put forward to explain the concurrence of OAB and IBS.

One is cross-organ sensitisation, whereby sensory innervation of the bladder and bowel interact. These interactions can occur at multiple levels, from the central nervous system to the periphery.

The link between these two conditions suggests that it is worth GPs asking about bowel symptoms when assessing patients with storage urinary symptoms suggestive of OAB.

To a lesser extent, it may be worth asking about urinary symptoms when assessing those with functional gastrointestinal symptoms suggestive of IBS. >>

DR JONATHAN REES

● **Matsumoto S, Hashizume K, Wada N et al. Relationship between overactive bladder and irritable bowel syndrome: a large-scale internet survey in Japan using the overactive bladder symptom score and Rome III criteria. *BJU Int* 2012;111: 647-652**



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Reference: 1. Maspero JF et al. *Allergy Asthma Proc* 2010; 31(6): 483-492.
Date of preparation: April 2013 UK/FF/0032/13

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Diabetes

Bariatric surgery improves weight loss and diabetic control

Patients with poorly controlled type 2 diabetes who underwent bariatric surgery, in addition to medical treatment, showed a significantly greater improvement in glycaemic

control and weight loss than those receiving medical therapy alone.

The trial, from the US, was a single site, open label, randomised 12-month study comparing intensive medical therapy with or without the addition of a surgical bariatric intervention (Roux-en-Y gastric bypass or sleeve gastrectomy) in 150 obese patients with poorly controlled type 2 diabetes. A single experienced surgeon performed the bariatric procedures. Mean age of the patients was 49 years, BMI 36 and average HbA_{1c} 9.2%. Two-thirds of the patients were women.

The primary end point was the proportion of patients with an HbA_{1c} ≤ 6% 12 months after treatment.

Surgery resulted in a significantly greater proportion of patients achieving an HbA_{1c} ≤ 6% at 12 months: 42% with gastric bypass and 37% with sleeve gastrectomy versus 12% with medical therapy alone.

Mean reductions in weight were: 29.4 kg with gastric bypass and 25.1 kg with sleeve gastrectomy compared with 5.4 kg in those receiving medical treatment alone.

All the gastric bypass patients who achieved the primary end point did so without antidiabetic medication, as did many of the gastrectomy patients. There was also a reduction in lipid lowering and antihypertensive therapy in both surgical groups. Clinical gains were most evident in the first 3 months following surgery and were retained throughout the 12 months of the study. The use of drugs to lower glucose, lipids and blood pressure increased in the group who received medical therapy alone.

Obesity is a worldwide epidemic that along with many other adverse health effects can lead to insulin resistance and type 2 diabetes. The potential complications of diabetes are well known and prevention of this disease by addressing the growing tide of obesity is key.

However, efforts to achieve significant weight loss are often labour intensive and many patients either fail to achieve or sustain long-term weight loss. Despite its short-term cost and invasive nature bariatric surgery offers a way to address this issue with the potential for long-term benefit.

This is certainly an encouraging study with impressive weight loss in the surgical groups which translates into an improvement in diabetic control in a previously poorly controlled and high-risk cohort. However, the period of follow-up was

quite short so it is not known whether the positive findings observed translate into longer-term benefit.

Furthermore, it would have been helpful to have the results stratified according to BMI particularly as this is the primary tool used by commissioners to decide if patients are eligible for such surgery.

DR PETER SAVILL

● Schauer PR, Kashyap SR, Wolski K et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012; 366:1567-76

Mental health

Antidepressants in pregnancy raise autism risk

Women who take antidepressants during the first trimester are almost twice as likely to give birth to children with autistic spectrum disorders, a nested case-control study has found.

The Stockholm youth cohort comprises all children aged up to 17 years resident within Stockholm County between 2001 and 2007. After exclusion of those with incomplete data, there were 4,429 cases of autistic spectrum disorder. For each case there were ten age- and sex-matched controls (n = 43,227).

Maternal or paternal depression before the birth of the child was identified from the Stockholm psychiatric outpatient register and the national inpatient register. For children born from 1995 onwards, maternal antidepressant use was identified from records of the first antenatal interview (median ten weeks' gestation).

A history of maternal depression was associated with an increased risk of autistic spectrum disorder adjusted odds ratio (OR) 1.49 (95% CI:1.08-2.08). This association was restricted to those who reported antidepressant

use in early pregnancy. There was no association with paternal depression.

Antidepressant use in early pregnancy nearly doubled the odds of autistic spectrum disorder adjusted OR 1.90 (95% CI:1.15-3.14). The increased risk was seen with both SSRIs and tricyclics.

Cases were identified from secondary care registers so the results may not be applicable to patients with milder depression treated in primary care.

Failure to identify primary care patients also meant that for children born from 1995 onwards, the number of mothers with recognised depression was very small, 249, and of these only a small proportion were prescribed antidepressants, 36 of 249 (14%).

The study therefore lacked power and adjustment for confounders may not have been very effective.¹

The authors acknowledge the problem of confounding by indication i.e. those women who were prescribed antidepressants may have had more severe depression. Therefore, it is not possible to say whether the observed association between antidepressant use and autistic spectrum disorder is due to the medication or the severity of the depression.

Serotonergic neurones play an important role in the regulation of neurodevelopment, and animal studies suggest that intrauterine exposure to high serotonin levels may lead to autistic behaviours.² Therefore, a direct causal role of antidepressants is plausible.

However, even if this is the case, the authors estimate that less than 1% of autism cases can be attributed to antidepressant use.

Should we warn women that taking antidepressants in pregnancy may increase the risk of autism? The UK prevalence of autistic spectrum disorders is around 1%,³ so a doubling of risk would equate to an absolute risk increase of 1 in 100. However, if this increased risk is due to depression severity, antidepressants may in fact reduce the risk.

This study provides further evidence that we should be very wary of initiating antidepressant treatment during pregnancy, particularly during the first trimester.

For those women who become pregnant while taking antidepressants, it can be difficult to decide whether or not to stop treatment. Rapid discontinuation of antidepressants is associated with a high rate of relapse⁴

and this has to be set against the uncertain evidence of harm and the low level of absolute risk.

DR PHILLIP BLAND

● **Rai D, Lee BK, Dalman C et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autistic spectrum disorders: population based case-control study. *BMJ* 2013;346:f2059**

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- 3 Baron-Cohen S, Scott FJ, Allison C et al. Prevalence of autistic spectrum conditions: UK school-based population study. *Br J Psychiatry* 2009;194:500-9
- 4 Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid versus gradual discontinuation of antidepressants. *Am J Psychiatry* 2010;167:934-41

Addiction

Male injecting drug users who have sex with men at greater risk of HIV

Men who inject drugs (IDUs) and have sex with men (MSM) have a four-fold higher risk of HIV than those who only have sex with women (MSW), a national survey has found. Prevalence of hepatitis C (HCV) was also a third higher in the former group.

IDUs in England, Wales and Northern Ireland have been recruited into a voluntary unlinked anonymous cross-sectional survey annually since 1990. The survey includes an oral swab for HIV and HCV and a questionnaire on demographics and risk behaviours.

A total of 8,671 male IDUs who reported having had sex and injecting drug use in the previous 12 months took part in the survey for the first time between 1998 and 2007. Median age was 29 and median period of

injecting drug use seven years.

Prevalence of HIV was 0.9%, HCV 33% and HIV/HCV co-infection 0.5%. Less than two-thirds (61%) of those with HIV were aware of their infection. Half the respondents reported more than one sexual partner in the past 12 months and only 13% reported consistent use of condoms; 42% reported never or sometimes using condoms with multiple sexual partners.

Sexual intercourse with men in the preceding 12 months was reported by 4%. This proportion remained consistent in the 10-year period; 79% reported having sex with both men and women in the preceding 12 months.

Condom use was low during the previous 12 months among MSM-IDUs and MSW-IDUs with almost half of MSW-IDUs and two fifths of MSM-IDUs reporting never using a condom.

After adjusting for location, number of years injecting, number of partners and condom use, HIV prevalence among MSM-IDUs was four times that of MSW-IDUs; they were also a third more likely to have HCV than »

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Table 1**HIV, HCV and risk behaviours in male injecting drug users who have sex with men compared with those who only have sex with women**

	Adjusted OR	95% CI
HIV	4.08	1.9 – 8.5
HCV	1.34	1.1 – 1.8
Unprotected sex with multiple partners	3.78	2.9 – 4.9
Needle/syringe sharing*	1.72	1.3 – 2.2

*In those who injected in the 4 weeks prior to the study

MSW-IDUs. They were almost four times more likely to have unprotected sex with multiple partners than MSW-IDUs and nearly twice as likely to share needles or syringes (see table 1, above).

Some practices provide enhanced services in substance misuse. In addition to opiate substitution and general physical health promotion, this study suggests IDUs – especially MSM – would benefit from regular screening for HIV and HCV. Interventions to reduce the risk of acquiring either HIV or HCV may include offering condoms and STI testing as well as prompt treatment of any diagnosed STI.

DR RICHARD MA

● **Marongiu A, Hope VD, Parry JV, Ncube F. Male IDUs who have sex with men in England, Wales and Northern Ireland: are they at greater risk of bloodborne virus infection and harm than those who have sex with women? *Sex Transm Infect* 2012;88:456-461**

Sexual health**Genital warts decline in wake of HPV vaccination**

A large study from Australia has demonstrated a significant reduction in genital warts following introduction

of the quadrivalent HPV vaccination programme in mid-2007.

Eight sexual health services provided retrospective data from 2004 to 2011. Data were collected on demographics, sexual behaviour and diagnosis of genital warts; two large clinics also collected self-reported HPV vaccination status of new patients from 2009. The number of patients diagnosed with new genital warts was presented as a proportion of new patients seen. The proportion of Australian born patients who tested positive for chlamydia was used as a comparison.

The proportion of women diagnosed with warts during the pre-vaccination period rose from 8.9% in 2004 to 9.6% in 2007; this fell to 2.7% in 2011 during the vaccination period.

For women under 21 the proportion diagnosed with genital warts dropped from 11.5% in 2007 to 0.85% in 2011 ($P < 0.001$). None of those who reported having had HPV vaccination were noted to have genital warts, compared with 10.5% in this age group in 2006 when all women were unvaccinated. For heterosexual men under 21, there was a dramatic decline in the proportion diagnosed with warts from 12.1% in 2007 to 2.2% in 2011 ($P < 0.001$).

There was no significant decline in the proportion of women aged 21-30 diagnosed with genital warts in the pre-vaccination period. However, this proportion declined from 11.3% in 2007 to 3.1% in 2011, a decrease of 72.6% ($P < 0.001$). Likewise, the proportion of heterosexual men with warts in this age group decreased from 18.2% to 8.9% ($P < 0.001$).

There was no significant trend in the proportion of women or heterosexual men aged over 30 diagnosed with genital warts before or during the vaccination period. The trend in proportion of men who have sex with men (MSM) diagnosed with warts appeared to have declined in the vaccination period by 24.7%, from 8.5% to 6.4%.

There was a significant increase in the proportion that tested positive for chlamydia in MSM, and women and heterosexual men under 21 in the vaccination period.

The authors concluded that the greatest decline in genital warts was seen in the group eligible for free quadrivalent HPV vaccine (women under 21 years); many of whom would have been vaccinated at school before becoming sexually active.

The more modest reduction in

women aged 21-30 may be explained by lower vaccination coverage. The fall in genital warts seen in two younger age groups of heterosexual men was likely to be due to herd immunity.

The small decline in genital warts in MSM might be explained by the increase in the number attending sexual health screening rather than protection conferred from herd immunity from young women (in the case of bisexual men or homosexual men who had ever had female partners).

In an accompanying editorial,¹ two UK consultants in sexual health gave the study findings a warm welcome. They state that the switch from bivalent to quadrivalent vaccine for the UK national programme in September 2012 should result in a substantial drop in workload for many sexual health clinics attributable to a fall in the incidence of genital warts in five to nine years' time. Also, the proven efficacy of quadrivalent vaccines against oncogenic HPV may result in reduction in HPV-16 and HPV-18 associated cancers such as cervical, oropharyngeal and other head and neck cancers.

The Australian government has started a publicly funded HPV programme in 2013 for 12 to 13-year-old boys with a catch up for 14 to 15-year-old boys. This decision was based on the increasing incidence of HPV-related oropharyngeal cancers in men and also the fact that young MSM would not benefit from heterosexual herd immunity.

Time will tell if the UK government will follow suit but it might not be long before those of us in primary care see the reduction in impact due to other HPV-related conditions such as cervical smear abnormalities and certain cancers.

DR RICHARD MA

● **Ali H, Donovan B, Wand H. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* 2013;346:12032**

REFERENCE

¹ Barton S, O'Mahony C. HPV vaccination - reaping the rewards of the appliance of science. *BMJ* 2013;346:12184

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