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The role of dipeptidyl peptidase-4 inhibitors

Will be clearer once ongoing trials are complete

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Type 2 diabetes is a progressive disease and greater treatment intensity is needed over time to control increasingly abnormal glucose concentrations.[1] In the linked article, Karagiannis and colleagues present a systematic review and meta-analysis of the risks and benefits associated with one of the relatively new classes of oral hypoglycaemic drugs, the dipeptidyl peptidase-4 (DPP-4) inhibitors.[2]

DPP-4 inhibitors reduce the breakdown of the glucose responsive incretin hormones, mainly glucagon-like peptide 1 (GLP-1); they have multiple physiological effects that together normalise glucose homeostasis without increasing body weight.[3] Because GLP-1 is released in response to raised rather than normal glucose concentrations, DPP-4 inhibitors may be less likely to cause hypoglycaemia than other oral hypoglycaemic agents.[3] Increased GLP-1 activity is associated with favourable changes in cardiovascular risk parameters of weight, lipids, blood pressure, and ventricular function, but no trials of DPP-4 inhibitors that are powered to detect differences in cardiovascular events have been reported.[4]

Karagiannis and colleagues examined two potential roles of DPP-4 inhibitors in type 2 diabetes: as monotherapy (compared with metformin) and as dual treatment with metformin (compared with metformin combined with other hypoglycaemic agents). As monotherapy, DPP-4 inhibitors were less effective than metformin at lowering glycated haemoglobin (HbA_{1c}) and body weight. Combined with metformin, DPP-4 inhibitors were also generally less effective than metformin combined with other hypoglycaemic agents at lowering HbA_{1c}. However, the addition of DPP-4 inhibitors to metformin led to lower weight compared with the addition of sulfonylureas or pioglitazone, but not compared with the addition of exenatide, a GLP-1 agonist. The combination of metformin and DPP-4 inhibitor led to fewer episodes of hypoglycaemia than metformin combined with a sulfonylurea.


SATURN STILLS/SPL

DPP-4 inhibitors are less likely to cause hypoglycaemia

What role can DPP-4 inhibitors play in the management of type 2 diabetes? American, European, and UK guidelines recommend metformin as first line treatment for most patients with type 2 diabetes.[5 6] Karagiannis and colleagues' review confirms that DPP-4 inhibitors are inferior to metformin in this role. People with type 2 diabetes who need more than one drug have several options for second line treatment. The consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes ignores DPP-4 inhibitors and recommends adding insulin (the most effective option), a sulfonylurea (the least costly), or a glitazone (lowest risk of hypoglycaemia).[6] The National Institute for Health and Clinical Excellence (NICE) in England and Wales recommends a sulfonylurea as second line agent and insulin as third line agent, but suggests that DPP-4 inhibitors are considered as second line treatment if the patient has a high risk of hypoglycaemia or cannot tolerate a sulfonylurea, and as third line treatment if insulin is unacceptable.[7]

The findings of the linked paper support the approaches taken by the European and American consensus statements and by NICE. There is no compelling evidence that DPP-4 inhibitors play a major role in the management of type 2 diabetes, but the low incidence of hypoglycaemia associated with these drugs might be useful in certain patients. A difficulty for the producers of guidelines is that not all comparisons of all possible treatments or treatment combinations have been tested in randomised controlled trials. Pharmacodynamic interactions that occur when hypoglycaemic agents are given in combination may result in a different assessment of benefit and risk than for individual agents because the reduction in HbA_{1c} or the risk of hypoglycaemia may depend on which other hypoglycaemic drugs are used.[8]

Heterogeneity, the finding that trials of similar drugs have different results, is an important problem for clinicians when interpreting meta-analyses. Karagiannis and colleagues report prediction intervals—which take the full extent of heterogeneity into account[9]—alongside traditional confidence intervals. Other strengths of this meta-analysis are that it searched for and included unpublished data and it also captured results from extensions to trials, whereas previous reviews had access to short term glycaemic outcomes only.

Important questions remain. The risk of hypoglycaemia is an important consideration when deciding which hypoglycaemic agent to prescribe,[7] yet there is no standard definition of hypoglycaemia in diabetes trials, which precludes meta-analysis focused on this outcome.[2] Consequently, there are no pooled estimates of likely risk of hypoglycaemia with DPP-4 inhibitors, although there are pooled estimates of their benefit in terms of a reduction in HbA_{1c}. However, a meta-analysis of individual patient data would allow the pooled risk of hypoglycaemia to be estimated because the blood glucose results of individuals could be used and a consensus definition applied across trials.

Although early and sustained improvement in HbA_{1c} is associated with a long term reduction in cardiovascular risk,[10] using HbA_{1c} alone as a short term surrogate is not a reliable indicator for reduction in cardiovascular risk.[11] Trials that are powered to detect differences in cardiovascular events in the long term are therefore needed. Three ongoing randomised trials and one observational study of DPP-4 inhibitors aim to investigate this research question.[4] Until we have the results of these studies, the position of DPP-4 inhibitors in treatment algorithms will remain peripheral and uncertain.

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RESEARCH, p 17

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- Head to head: Is it unethical for doctors to encourage healthy adults to donate a kidney to a stranger? Yes (*BMJ* 2011;343: d7140), No (d7179)
- Renal transplantation (*BMJ* 2011;343: d7300)

Does the fall in glomerular filtration rate in living kidney donors matter?

Probably not, in this rigorously selected, meticulously followed-up group

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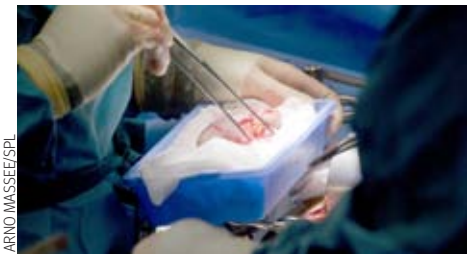

ARNO MASSEE/SPL

Harvested donor kidney

An estimated 32 201 living donor kidney transplants were performed worldwide in 2010.[1] This number will undoubtedly increase in coming years as demand for kidney transplantation grows and strategies to meet this demand, such as paired kidney exchange, gather momentum. Although living kidney donors have mortality outcomes and quality of life scores above population norms,[2 3] donor nephrectomy will always entail some degree of medical, social, financial, or psychological risk to the donor, and the transplantation community and the public must be satisfied that any risks are explicit and minimal.

The linked research paper by Garg and colleagues makes an important contribution to our understanding of the long term consequences of living kidney donation.[4] In patients with chronic kidney disease, there is an established association between reduced kidney function and cardiovascular events. Although donor uninephrectomy also results in a sizable decrease in glomerular filtration rate (GFR), evidence of an association between reduced GFR and cardiovascular events in living kidney donors is limited.[5 6] Long term data on outcomes for donors have been scarce,[3] and the identification of appropriate control groups against which to compare rigorously selected, highly screened living kidney donors has posed methodological difficulties. Garg and colleagues' population based matched cohort study applies a careful restriction matching protocol to define a comparator group that, as far as possible, satisfies acceptance criteria for kidney donation. The study found no evidence that living kidney donors had increased cardiovascular risk in the first 10 years after transplantation compared with the healthiest segment of the general population.

How can the findings of the current study, that an acute 50% reduction in GFR as a result of kidney donation does not increase cardiovascular risk, be reconciled with the well established observation that an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 is an independent risk factor for cardiovascular and all cause mortality in the general population?[7] A possible explanation, which the authors discuss, is that the association between chronic kidney disease and cardiovascular disease seen in epidemiological studies might not be causal but a consequence of the shared risk factors for both conditions. In contrast, living kidney donors are healthy people who develop reduced GFR in the absence of nephropathological and presumably cardiopathological processes. Furthermore, the observation that the outcomes for donors are superior to those for non-donors may be attributed to the quality of predonation screening for both renal and cardiovascular disease, and the difficulty of replicating all aspects of the donor selection process when trying to identify appropriate controls retrospectively. In addition, risks associated with uninephrectomy might be mitigated in Canadian donors whose ongoing management of risk factors for cardiovascular and chronic kidney disease through routine follow-up with primary care practitioners may be better than that received by donors in nations without universal health coverage.

The study's findings are a reminder of our limited understanding of the natural course of early chronic kidney disease and of the need for more data on how age, albuminuria, GFR, diabetes, and blood pressure combine to predict progression to end stage disease, cardiovascular events, or death in the general population. Predictive instruments for chronic kidney disease are still in their infancy, and the current staging system based on eGFR is limited as a tool for clinical decision making.[7] Renal specific risk scores would enable eGFR to be interpreted in the context of individual patient characteristics, so that patients at greatest risk of progressive disease, cardiovascular events, and death can be distinguished from those more likely to follow a benign course. The ongoing refinement of existing markers of chronic kidney disease—such as combinations of eGFR, cystatin C, and microalbuminuria[8]—and the identification of new biomarkers with higher predictive accuracy for adverse outcomes—such as urinary podocyte loss, neutrophil gelatinase associated lipocalin, and fibroblast growth factor 23—have the potential to enhance the clinical management of chronic kidney disease through more accurate classification and assessment of prognosis.[9-11]

Although difficult to quantify, the excellent cardiovascular outcomes seen for this cohort of living donors might be attributable to regular medical follow-up and meticulous risk management as much as to careful donor screening and selection. What outcomes might patients with chronic kidney disease expect in a scenario of similarly rigorous medical management and optimal access to healthcare? Some indication is given by international comparisons of the association between the prevalence of chronic kidney disease and that of end stage disease. Despite a similar prevalence of chronic kidney disease in Norway and the United States, US patients have about twice the risk of progression to end stage disease after accounting for patient level factors.[12]

Recent years have seen a trend towards accepting living donors with less than optimal kidney function, mild glucose intolerance, hypertension treated with a single drug, and nephrolithiasis. Garg and colleagues' findings may not generalise to donors at and beyond the margins of current acceptance criteria, and this should be the subject of further investigation.

Living donor transplantation will always entail ethical tensions between the doctor's duty to do no harm, donor autonomy, and the unmistakable benefit to the recipient. Informed consent relies on explicit communication of the risks of donation, yet a lack of comprehensive data on long term outcomes leaves uncertainty about the full extent of risks assumed by living kidney donors. Garg and colleagues' findings are a important step towards resolving this uncertainty.

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RESEARCH, p 18

In the future, personalised medicine may allow risk profiles for cancer or neurodegeneration to be identified, allowing people to tailor their lifestyles according to genetic risk. If so, we may well look back and salute the epidemiologists who first spotted the connection

A reduced risk of Alzheimer's disease in those who survive cancer

Cold comfort for individual patients?

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In a linked population based cohort study, Driver and colleagues report that older adults who survived cancer had a lower risk of developing Alzheimer's disease than those who had never had cancer. Furthermore, people with Alzheimer's disease had a lower risk of subsequent cancer than those without the disease.[1] This report of an apparent mutually protective relation between Alzheimer's disease and cancer is intriguing although not unprecedented. Others have previously hinted at such a link,[2-4] and a similar pattern has been described for cancer and Parkinson's disease.[5] So, are neurodegeneration and cancer inversely associated? Should doctors tell their patients with newly diagnosed cancer that they have a reduced risk of Alzheimer's disease (or vice versa)?

Epidemiologists dream of discovering new risk (or protective) factors for disease. However, the path of analytical epidemiology is littered with observational findings that briefly made headlines but then failed to be replicated by other observational studies, or to be borne out by experimental studies. We should search diligently for alternative explanations for new observed associations because the inevitable backlash against results that are not confirmed by other studies tends to deepen scepticism about epidemiological research.[6]

Hazard ratios compare the hazard of disease in people who are exposed to the so called risk factor to the hazard of disease in unexposed people over a given period. The observed association provides a signal with varying signal to noise ratio. Although a factor might be statistically associated with an increased (or reduced) probability of developing disease, it might not be part of the causal pathway for that disease; instead it might mediate or modify the effect of another factor, it may be a confounder, or it might merely be associated through inadvertent bias.[7]

Driver and colleagues rightly consider the phenomenon of survival bias.[8] Is it possible that the observed negative association is not between cancer and neurodegeneration but rather between survival from cancer and neurodegeneration? Would people who died from cancer have developed dementia if they had lived long enough? If so, their removal from the pool could result in the spurious finding that cancer survivors have a reduced statistical probability of dementia.

Readers should also consider the possibility that a third factor associated with both cancer and neurodegeneration is the real protective factor. The current study found that the risk of Alzheimer's disease was especially low in survivors of smoking related cancers.[1] Smoking reduces life expectancy and is a well established risk factor for several cancers. The association between smoking and Alzheimer's disease is less clear. Cross sectional studies have shown a negative (potentially protective) association between smoking and Alzheimer's disease, which has been confirmed by some longitudinal studies but directly contradicted by others. A biologically plausible explanation is available for both observations. However, the phenomenon known as competing risk allows another explanation[9 10]—that patients who died from smoking related cancers may have developed smoking related Alzheimer's disease had they lived long enough.

Statistical mechanisms used to adjust for these biases typically assume that the incidence of Alzheimer's disease would have been the same in those who died as in those who survived or make some other assumption to model competing risks. However, it currently is not possible to know the underlying distribution of incipient cancer, or incipient neurodegeneration, in those who do not survive long enough to develop the disease in question.

Cancer may also have been under-ascertained in this cohort because slow growing tumours had not become symptomatic or were not actively screened for, the detection of asymptomatic cancer not being part of the study. Survivors of cancer may be exceptionally hardy and able to resist for longer the ravages of neurodegeneration.

Is it impossible then to know whether surviving cancer truly protects against neurodegenerative disease in a population? It is hard to imagine a better population "laboratory" than the Framingham Study, which closely evaluates and monitors a large community based cohort over time, thereby minimising selection bias and recall bias. However, all potential biases and confounding effects cannot be accounted for in an observational study. The most promising approach to settling the matter might be so called life course epidemiology.[11] If reliable biomarkers were available for both cancer and Alzheimer's disease, and all participants could be repeatedly screened for both diseases from early adulthood, the true associations and temporal sequences could be determined with greater accuracy.

Assuming the associations seen in the current study are true, is there a plausible mechanism to explain a protective effect of cancer survival on Alzheimer's disease? The authors suggest that a biological mechanism common to both cancer and neurodegenerative disease may be inappropriate activation and regulation of the cell cycle, with uncontrolled proliferation underpinning one disease, and apoptosis (at the opposite end of the spectrum) driving the other. Other possibilities have also been proposed.[9 12] Which require further testing and may bring new understanding of the mechanisms of both diseases.

In the future, personalised medicine may allow risk profiles for cancer or neurodegeneration to be identified, allowing people to tailor their lifestyles according to genetic risk. If so, we may well look back and salute the epidemiologists who first spotted the connection reported here. Currently, however, patients who receive a new diagnosis of Alzheimer's disease or cancer will probably draw cold comfort from their reduced probability of developing the other disease if they live long enough. These results have no immediate implication at the individual level, but that they do offer some hope that new insights into disease mechanisms will lead to improved prospects for prevention and treatment.

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- News: NICE advises screening for TB in hostels and prisons to reduce UK cases (*BMJ* 2012;344:e2309)
- News: Health bill risks disrupting care for offenders leaving prison, warns peer (*BMJ* 2011;343:d5912)

Safer prescribing for prisoners

New guidance fails to deal properly with this complex area of practice

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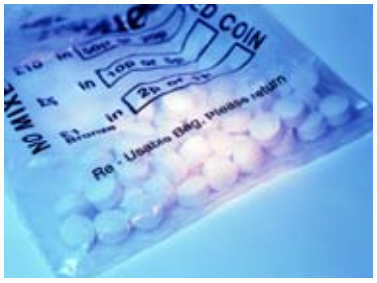
Most prisoner health services in developed countries are modelled on primary care, with nurse led health services. Prescribed drugs are a major component of clinical practice within prisons and usually form the central point of contact between the patient and prescribing medical staff; however, little information is available on how much care centres around prescribed drugs and the nuances of patient care in prisons. Much that supports the care of prisoners is excluded from public scrutiny because of generalised fears of disclosure of "in confidence" information. This impedes peer review and leaves a substantial void in an important area of primary care.

The Australian Institute of Health and Welfare is developing a surveillance system for prisoners in that country.[1] A survey conducted in 2010 showed that 40% of prisoners were prescribed drugs—on average 2.3 drugs per person—and that women were more likely to be medicated than men (47% *v* 39%). Antidepressants and mood stabilisers accounted for 18% of repeat prescriptions and anti-inflammatory drugs for 12%.



SPL

If not thoughtfully applied, guidance may lead to a worrying degree of complicity between healthcare practitioners and the prison authorities

Drug seeking behaviours in prison populations are underpinned to a large extent by psychological trauma, neuropathic pain, dependence on pain relief drugs, dependence on illicit drugs, mental illness, and oral (dental and gingival) disease, all of which are prevalent in prisoner populations.

The main message of the recently published guideline on prescribing in prisons from the Royal College of General Practitioners and the Royal Pharmaceutical Society is that there is a standard of safe prescribing, guided by community norms, that should be deviated from only in certain circumstances.[2] Particular environmental issues and administrative concerns for custodial practices, as well as generalised attributes of the prisoner population, may need to be taken into account. For example, "The acquisition, misuse and onward trading of prescribed medication cannot be supported and should be discouraged as it presents risks in many ways." The guidance offers a traffic light framework (red: do not prescribe; orange: proceed with caution; green: safe to prescribe) to assess levels of acceptability of prescribing in the custodial environment.

The implications of these guidelines are clear for clinicians who practise in prison. The guidelines also contain useful information for primary care clinicians who provide care for patients in contact with the criminal justice system. For example, prescription for patients who will return to the custodial setting, where some drug classes are more strictly controlled, will need to be tailored. Opiate analgesia should be prescribed for as short a period as possible because the administration of opiates needs to be intensively supervised and this might disrupt the patient's reintegration into prison routine.

The guidelines advise that "Clinicians who choose to work within prison should . . . be familiar with the requirement of mandatory testing of prisoners for drugs and they should consider whether their prescriptions could mask illicit drug use, particularly with regard to the prescribing of opiates." The adverse health effects of mandatory testing in prison have been highlighted elsewhere.[3] Although the existence of a drug market (for both legal and illicit drugs) is widely acknowledged, the guidelines do not recognise the nature of such a market, which is opportunistic and variable. Prisoners can experience acute withdrawal when the supply of illicit drugs wanes, and healthcare practitioners should deal with such scenarios in a compassionate and non-judgmental way, without disclosing particular circumstances to custodial authorities. A recent report highlighted that responsible prescribing in prison reduced criminal recidivism.[4]

The guidelines recommend that pharmacists with experience in practising in secure environments are involved to optimise the use of the most appropriate drugs. This simple message deserves greater attention and a stronger evidence base.[5 6]

Health services on both sides of the prison gate must confirm that drugs dispensed to patients on one side are received or accounted for on the other side. It is currently unusual for a prisoner to enter custody with a letter from a community prescriber that details drugs prescribed, although it is more common for an ex-prisoner returning to society to have a letter detailing care received while in custody.

What impact might the recently published guidelines have on prison health services in the United Kingdom? Risk mitigation is the overarching principle of the guidelines, which seek to promote the creation of safe environments, to protect some prisoners from misguided attempts to overtreat existing or factitious health conditions, and to protect the prescriber. However, if not thoughtfully applied, the guidance may lead to a worrying degree of complicity between healthcare practitioners and the prison authorities.

Fishman acknowledged in 2006 that "drug abuse and undertreated pain are both public health crises," but he went on to say that "the solution to one need not undermine the other" and warned against "impos[ing] solutions that are insensitive to their collateral damages" and against "displac[ing] the regulation of medicine from . . . agencies responsible for health to those focusing on law enforcement."[7] The controversy regarding the best form of analgesia to use in people who have had a dependency on opiates will not be resolved by the current concise guidelines.[8]

The guidelines offer no advice on palliative care, saying merely, "The security implications of administering powerful opiates and benzodiazepines in the prison must be carefully evaluated." It is a shame that this is the final statement in a very useful document. Flexibility is needed—custodial authorities and health service providers must be able to offer a range of therapeutic options for intractable pain and end of life care. It is unconscionable that a person should not receive proper palliative care because he or she is in prison.

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- News: HIV epidemic in Europe is not under control, WHO says (*BMJ* 2011;343:d7848)
- News: More routine HIV testing is needed to reduce late diagnoses, says public health agency (*BMJ* 2011;343:d7794)

Increased HIV testing in men who have sex with men

The key to building effective HIV prevention strategies

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Health Protection Agency (HPA) data suggest that by the end of 2012 more than 100 000 people will be living with HIV in the United Kingdom.[1] Almost a quarter will be unaware of their infection. This figure may be small compared with countries in sub-Saharan Africa, but for a resource rich country it represents a serious failure in HIV prevention.

Men who have sex with men (MSM) remain the group most at risk of acquiring HIV in the UK, North America, Australasia, and much of western Europe. Annual HIV diagnoses in MSM have doubled over the past decade, with about 3000 new diagnoses in the UK in 2010.[1] One in four of these infections will probably have been acquired recently; and in men under 35 years, this figure is one in three. In London, one in 11 MSM is estimated to be HIV positive.[1]

Although at a population level no single intervention is likely to control HIV, effective prevention strategies should start with HIV testing. A negative test supports individual vigilance to remain uninfected. A positive test result opens up treatment options and enables planning to prevent partners from becoming infected. However, a community based survey of MSM in London in 2008-9 showed that about half had not had an HIV test in the past year, and about one in 10 had never been tested (D Mercey, personal communication, 2011).

Low and infrequent levels of testing have important consequences. People who are unaware of their HIV infection contribute disproportionately to transmission of the virus. A recent US study estimated that the 21% of HIV positive people who were undiagnosed were responsible for 50% of new infections.[2] Once on treatment, people with HIV are likely to be less infectious,[3] but simply being diagnosed HIV positive improves transmission risk behaviour. In San Francisco, unprotected insertive anal intercourse with partners who were HIV negative or of unknown serostatus decreased from 39% before diagnosis to 2% in the four weeks after diagnosis.[4] In London, 76% of gay male seroconverters posed no transmission risk three months after diagnosis.[5]

The effectiveness of antiretroviral drugs means that HIV positive people can now expect near normal life expectancy if diagnosed and treated early.[6] Late diagnosis is the single most preventable factor associated with HIV related death and disease in the UK, with death in the year after diagnosis being 10 times higher in those diagnosed late than in those diagnosed promptly (4.0% *v* 0.4%).[1] HIV treatment promises to be an important public health measure for the prevention of HIV transmission. A large randomised controlled trial showed early initiation of treatment reduced the risk of sexual transmission by 96%.[7] Although few MSM were enrolled in this trial, the results engender optimism that early treatment strategies could underpin future prevention. Importantly, the first trial of pre-exposure prophylaxis in MSM using orally administered antiretroviral drugs has also shown a protective effect.[8]

CHRIS GALLAGHER/SPL
HIV test using saliva sample

The above strategies can be successful for MSM only if they regularly test for HIV and thus know what interventions are appropriate for them as individuals. Epidemiological and modelling data suggest that annual testing at the minimum is needed to reduce transmission of HIV.[9-11] MSM who attend sexual health clinics may be at higher risk of acquiring HIV than other MSM, and testing these men more often may have additional benefit. In Glasgow and Edinburgh, HIV testing in a community sample increased from 33.2% in 2005 to 48.3% in 2008 (P<0.001) after testing became routinely offered in sexual health clinics. Among HIV positive men, undiagnosed infection fell from 41.7% in 2005 to 26.3% in 2008 (P<0.08).[12] Robust efforts can therefore produce large changes in the uptake of testing.

The promotion of regular and frequent HIV testing as a means of limiting the transmission of infection is a core component of prevention efforts in the United States. The Centers for Disease Control and Prevention has recommended that routine HIV testing should be performed in all healthcare settings. In the UK, HIV testing has played a smaller part in prevention, but its promotion has been central to recent campaigns. The chief medical officer of England has advocated extension of HIV testing to all healthcare settings, and the UK national guidelines for HIV testing and recent National Institute for Health and Clinical Excellence guidelines are designed to facilitate this.[13 14] The HPA's 2011 report recommends prioritising the implementation of routine universal HIV testing for general medical admissions and new registrants in general practice in areas of high HIV prevalence. MSM, as the group most at risk of HIV infection, should consider annual or more frequent testing.[1]

Establishing a culture of frequent HIV testing in distinct (and sometimes hidden) population groups such as MSM will require sustained intervention at multiple levels, and there is little evidence to guide strategies. Social marketing and enhanced community mobilisation should be used to increase opportunities for and awareness of HIV testing among gay men in specific communities. Increased community testing and availability of home sampling kits need to be evaluated for their clinical and cost effectiveness.

The year 2012 marks the beginning of the fourth decade of AIDS in the UK. Increasing the frequency and numbers of MSM tested for HIV could help improve HIV prevention in the group in which the disease was first recognised.

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Three recent cluster randomised trials in primary care have added greatly to what is known about effective interventions for women who do disclose that they experience IPV

Responding to domestic violence in primary care

We know more about what works, but questions remain

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The recent publication of findings from the first randomised controlled trial in the United Kingdom on domestic violence marks a suitable opportunity to take stock of what we know about responding to domestic violence in primary care.[1] Abuse against women by intimate partners (intimate partner violence; IPV) is a major public health problem worldwide.[2] More than one in four women experience IPV at some time in their lives,[3 4] and these women and their children have an increased risk of severe short term and long term health consequences, both physical and mental.[4] The social and economic costs of IPV are enormous; in 2008 the annual cost of IPV in the UK was estimated to be £15 730m (€18 720m; $24 740).[5]

The primary care response to women who experience IPV is important, not least because a meta-analysis of qualitative studies has highlighted that such women see healthcare professionals as potential sources of support.[6] Although several recently published randomised controlled trials and systematic reviews have advanced our knowledge about effective responses in primary care, our understanding of how best to manage this complex and challenging problem remains incomplete.

Whether sufficient evidence exists to recommend screening for IPV in healthcare settings is debateable.[7] Structured instruments have been designed to help identify women who are experiencing IPV in the primary care setting. A recent systematic review found that the HITS instrument, which comprises four questions, had the best predictive power and reliability.[7] Some clinicians recommend adopting a low threshold for asking direct questions about abuse (which is effectively case finding). Any inquiry process forms a brief intervention in itself when accompanied by information about the reason for asking ("because the problem is common"), or the availability of specialised services, or when doing so offers a clear message about the practitioner's willingness to discuss the problem and provide support.

Some studies have shown positive effects of inquiry alone. A Canadian randomised trial conducted in settings including primary care found no harm from inquiry. It also found that both the intervention and control groups improved in terms of the primary outcomes "repeat IPV" and "quality of life" up to 18 months after screening in analyses adjusted to account for women lost to follow-up.[8] All women (intervention group and control group) were given a card with information on specialised services, and all were asked by researchers to self complete a screening tool, so all experienced a form of inquiry. The difference between the groups was that the intervention group completed the screening tool before seeing the clinician, and if the woman screened positive results were passed to the clinician for possible use in the consultation.

A systematic review of screening studies that focused on programme mechanisms identified four components that increased rates of disclosure or identification of IPV. These were a commitment to investment and support for screening implementation at high levels in the organisation or institution concerned, effective screening protocols, thorough initial and ongoing training of healthcare staff, and the facility to immediately access or refer to onsite or offsite support services (or both).[9]

KEVIN CURTIS/SPL

Three recent cluster randomised trials in primary care have added greatly to what is known about effective interventions for women who do disclose that they experience IPV. The recent Identification and Referral to Improve Safety (IRIS) trial conducted in the UK evaluated an intervention that comprised training for clinicians, a computer prompt to ask about abuse within the medical record, and a referral pathway to a named IPV advocate—an earlier systematic review having shown the effectiveness of advocacy services.[1 8] It showed increased referral to an advocate.

The Australian Mothers' AdvocateS In the Community (MOSAIC) trial that examined the effect of non-professional mentor support for pregnant and recent mothers found a significant difference in mean abuse scores at 12 months, with weak evidence of effectiveness for other outcomes.[10] A trial conducted in family planning clinics in an urban area in northern California, United States, that examined the effects of an intervention comprising education, harm reduction strategies, and provision of information on further local resources showed that reports of a partner applying psychological pressure to become pregnant or sabotaging contraception were significantly reduced in the intervention group compared with controls.[11] Women in the intervention group were also more likely to report ending their relationship because it was unhealthy or because they felt unsafe. However, only four clinics were included in the study and the duration of follow-up was only three months, so the findings should be interpreted with caution.

Debates about the clinical importance of some of these effects are ongoing. A systematic review also found that psychological interventions delivered to women and children may be helpful.[8] A brief counselling intervention delivered by general practitioners that is based on the "readiness to change" concept[12] is currently being evaluated in an Australian trial that plans to report later this year. Translational research is needed to inform implementation of interventions on a larger scale and enable interventions to be tailored to different health service systems.

Many questions remain to be answered by both primary research and secondary analysis of primary studies through systematic review and meta-analysis. The cost effectiveness of interventions aimed at reducing exposure to and the effects of interpersonal violence needs further exploration. The usefulness of screening or routine inquiry regarding IPV in men (both perpetrators and victims) in the primary care setting should be investigated, along with the potential of offering interventions in primary care for men who want to change their behaviour.

A major barrier to preventing IPV is that it is still a stigmatising and often hidden problem. This silence could be broken by clinicians routinely enquiring about the problem, and the growing evidence of the effectiveness of interventions accessed from primary care indicates that a strategy of routine inquiry about IPV in primary care should be more widely adopted.

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