these 434 were excluded on various grounds, including inappropriate inclusion criteria, lack of observational study design, lack of diabetes outcomes, absence of shift work exposure, subjects already with a diagnosis of diabetes or a study design that did not allow the association between diabetes and shift work to be assessed.

Fourteen studies remained, of which one had been reported in two or more papers. This left 12 eligible studies with 28 independent reports involving 226,652 participants and 14,595 patients with diabetes.

The studies were from a range of countries (Japan, Sweden, United States, Belgium and China), eight studies included men only and two women only. There were seven prospective cohort studies, one retrospective cohort study and four cross-sectional studies. The number of participants ranged from 475 to 107,915.

Four studies were classified as rotating shifts, two irregular or unspecified shifts, three night shifts and three mixed or evening shifts only.

- The results showed a pooled adjusted odds ratio (OR) for the association between any exposure to shift work and diabetes risk of 1.09 (95% CI: 1.05-1.12)
- Sub-group analysis showed a stronger association between shift work and diabetes for men OR 1.37 (95% CI: 1.20-1.56), than for women OR 1.09 (95% CI: 1.04-1.14)
- Further sub-group analysis showed that evening shifts and mixed shifts did not increase the risk of diabetes, but all other shift patterns did
- The rotating shift pattern showed the highest risk OR 1.42 (95% CI: 1.19-1.69)

Several observational studies had previously noted an increased risk of diabetes in shift workers, but none had used quantitative techniques to estimate risk.

The headline finding from the analysis is that exposure to shift work increases the risk of diabetes by 9%, and that men may be more at risk than women.

Shift work can disturb health in two main ways. First, it has an effect on physiology, when normal circadian rhythms are overridden. There is some evidence that insulin resistance is increased and that circadian disruption can increase the development of type 2 diabetes in susceptible individuals.[1]

Second, it interferes with normal social interaction, and may be associated with less exercise and unhealthy patterns of eating, as well as continual low-level stress.

This meta-analysis did include a very heterogeneous group of research papers, and although I am not a statistical expert, I would be cautious about the strength of the results. Allowing for this, the findings appeal strongly to the commonsense of those of us who work on the front line with diabetes patients. Achieving good control always seems more of a challenge in patients who work shifts, at every level of diabetes treatment. The complex regimens of insulin-dependent shift workers would suggest that diurnal rhythms might well have a significant effect on this aspect of metabolism.

DR MATTHEW LOCKYER

- **Gan Y, Yang C, Tong X et al. Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occupat Environ Med* (2014) doi:10.1136/oemed -2014-102150**

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Mental health

Antidepressants may increase suicide risk

Patients prescribed mirtazapine or venlafaxine are more likely to attempt or complete suicide, a UK study has found.

Data were obtained from more than 600 contributing practices that use the EMIS medical records system. There were 238,963 participants who were aged between 20 and 64 years and had a first recorded diagnosis of depression between 1 January 2000 and 31 July 2011. The follow-up period ended on 1 August 2012.

Antidepressant exposure was measured from electronic prescribing data. Suicides were identified from linked death certificates; both open and suicide verdicts were classified as suicide. Attempted suicide or self-harm events recorded using the appropriate Read codes were identified from the medical records.

During follow-up (median 5.2 years), 87.7% of the cohort received at least one prescription for antidepressants. The median duration of treatment was 221 days (7.3 months). During the first five years of follow-up, there were 198 cases of suicide and 5,243 cases of attempted suicide or self harm.

- Compared with SSRIs, the suicide rate was significantly increased during periods of treatment with 'other antidepressants' (mainly mirtazapine and venlafaxine; adjusted hazard ratio (HR) 2.64 (95% CI: 1.74-3.99) but not with tricyclics
- The absolute annual risk of suicide was highest with mirtazapine (0.19%) and lowest with amitriptyline (0.02%)
- Similarly, when compared with SSRIs, the rate of attempted suicide or self harm was significantly increased with 'other antidepressants' adjusted HR 1.80 (95% CI: 1.61-2.00) but not with tricyclics

Compared with citalopram, the adjusted HRs for attempted suicide or self harm were significantly increased:

- Venlafaxine 1.85 (95% CI: 1.61-2.13)
- Trazodone 1.73 (95% CI: 1.26-2.37)
- Mirtazapine 1.70 (95% CI: 1.44-2.02)

The majority of open verdicts are thought to be suicides and it is standard practice to include them in studies of suicide. However, not all open verdicts are suicides and it has been suggested that those cases in which suicide is unlikely on the grounds of probability should be excluded.[1] This does not appear to have been attempted in the present study. Even with the inclusion of open verdicts, the total number of suicides was low and the results for completed suicide should be treated with caution. For example, the 95% confidence intervals for absolute suicide risk with mirtazapine and amitriptyline overlap.

The variation in suicide rates was not explained by the relative toxicity of antidepressants in overdose. A UK study found that tricyclics were by far the most toxic (case fatality rate ratio of 13.8 as compared with 2.5 for venlafaxine, 1.9 for mirtazapine and 0.5 for SSRIs).[2] »

The authors acknowledge that the results may have been caused by channelling bias e.g. venlafaxine may have been more likely to be prescribed to patients at increased risk of suicide (as it is recommended as a third-line treatment for resistant depression) whereas tricyclics may have been less likely to be prescribed (because of their toxicity in overdose). They tried to reduce this bias by adjusting for attempted suicide at baseline, but were unable to adjust fully for depression severity.

NICE recommends generic SSRIs as first-line treatment for depression. For those who do not respond adequately, NICE recommends switching to either a different SSRI or a 'better tolerated newer-generation antidepressant' i.e. mirtazapine.

If patients still do not respond, third-line treatment with venlafaxine, a tricyclic or an MAOI can be considered.[3]

It is unclear how the results of this study should be interpreted. However, as the risk of suicidal behaviour associated with antidepressant use appears to be strongly age dependent, I would suggest that we avoid prescribing mirtazapine and venlafaxine to young adults (under 25 years).[4] Lofepramine is thought to have a very low toxicity, comparable with that of the SSRIs,[5] and may be preferred to mirtazapine as a second-line treatment.

Suicide rates were highest in the first 28 days after starting treatment: if we do prescribe mirtazapine or venlafaxine, we should monitor patients closely during this initial period.

DR PHILLIP BLAND

● **Coupland C, Hill T, Morriss R et al. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* 2015;350:h517 doi:10.1136/bmj.h517**

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Cardiovascular disease

Does renal denervation improve BP control in resistant hypertension?

Renal denervation plus a standardised stepped care antihypertensive treatment (SSAHT) regimen reduced ambulatory blood pressure more than the drug regimen alone in the DENERHTN trial, published in the *Lancet*.

The study was a prospective, open-label randomised controlled trial with blinded endpoint evaluation in patients, aged 18-75 years, with resistant hypertension. It was carried out in 15 French tertiary care centres specialising in the management of hypertension.

Patients received indapamide 1.5 mg, ramipril 10 mg (or irbesartan 300 mg), and amlodipine 10 mg daily for four weeks to confirm treatment resistance by ambulatory blood pressure monitoring before randomisation.

Patients were then randomly assigned to receive renal denervation plus SSAHT or SSAHT alone as a control group. The stepped medication regimen involved sequentially adding spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day from months two to five if home blood pressure was more than or equal to 135/85 mm Hg.

The primary endpoint was the mean change in daytime systolic blood pressure from baseline to six months measured by ambulatory blood pressure monitoring. The authors also analysed safety outcomes such as the incidence of acute adverse events following the renal denervation procedure and the change in renal function, by eGFR, from baseline to six months.

There were 101 patients with completed endpoints (48 in the renal denervation group, 53 in the control group).

The mean change in daytime ambulatory systolic blood pressure at six months was:

- −15.8 mm Hg (95% CI: −19.7 to −11.9) in the renal denervation group
- −9.9 mm Hg (95% CI: −13.6 to −6.2) in the group receiving SSAHT alone
- This represented a difference of −5.9 mm Hg (95% CI: −11.3 to −0.5; P = 0.0329)

The number of antihypertensive drugs used was similar between the two groups as was drug adherence at six months.

There were three minor renal denervation-related adverse events and a mild and similar drop in eGFR in both groups.

Renal denervation has rather fallen from grace as a strategy for the management of resistant hypertension. This is largely due to the disappointing results from the SYMPLICITY HTN-3 randomised trial which failed to show a reduction in systolic blood pressure with renal denervation when compared with medical therapy alone.

The DENERHTN trial provides further hope for supporters of this interventional therapeutic option in the battle against resistant hypertension.

The authors conclude that renal denervation plus a stepped care antihypertensive treatment regimen reduces ambulatory blood pressure more than the same drug regimen alone at six months. They postulate that this may contribute to a reduction in cardiovascular morbidity if maintained in the long term after renal denervation.

Whether or not commissioners and clinicians will be enthused by this new data remains to be seen.

DR PETER SAVILL

● **Azizi M, Sapoval M, Gosse P et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015. pii: S0140-6736(14)61942-5**