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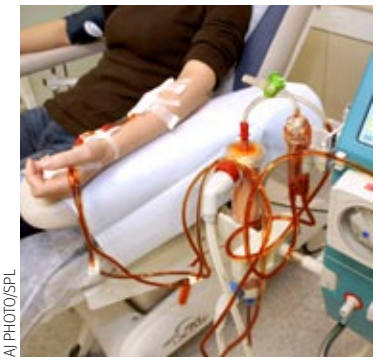
RESEARCH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THIS WEEK'S RESEARCH QUESTIONS

Effect of SSRIs on tamoxifen treatment in breast cancer

SSRIs are often prescribed to women being treated for breast cancer with tamoxifen. But because these antidepressants inhibit the enzyme that converts tamoxifen to its active metabolite, there's been concern that they might reduce its effectiveness. In a retrospective, population based cohort study, Catherine Kelly and colleagues saw that this appeared to be the case for paroxetine—longer co-treatment with the drug while receiving tamoxifen was associated with increased risk of death from breast cancer for women in Ontario, Canada (p 352). Although they found no such risk with other SSRIs, the authors caution that the sample size for those drugs may have been too small for an effect to be confidently ruled out. In view of the potential implications for practice, we were keen to publish this paper as speedily as possible. An editorial by Frank Andersohn and Stefan N Willich discusses how clinicians should respond to these findings (p 324).


ACTION PRESS/REX

Ventricular assist devices and survival after heart transplantation


HENNING DALHOFF/BONNIER PUBLICATIONS/SPL

These battery powered mechanical pumps, can get fragile patients with end stage heart failure to a point where they can receive a new heart, and they seem to prolong survival. But studies on this have been limited by small sample sizes, selection bias, and confounding. In this new prospective cohort study Jeffrey H Shuhaiber and colleagues tackled those limitations, using data from the United States Network for Organ Sharing Registry and propensity score matching (p 353). They found that post-transplantation survival wasn't affected by the installation of a device preoperatively. Comments in the authors' submission letter piqued our interest: "Insertion of the device requires surgery, exposure to blood products, prolonged hospital stay, and a dedicated team to manage its well documented complications of bleeding: thromboembolism and allosensitisation . . . The device is not cost effective per life saved according to some important public health studies. There is a tremendous financial incentive to continue adopting this technology with little long term understanding of its safety."

Treatment decisions in chronic kidney disease

Rachael Morton and colleagues did a systematic search of the relevant qualitative literature, assessed the retrieved studies' quality using the consolidated criteria for reporting qualitative research (COREQ) framework, and then did a formal thematic synthesis of the best and most relevant 18 studies. They found that patients tend to feel stuck with few options and pressured by peers, and, once a treatment has begun, they don't feel able to change their minds and try something else. And some patients say they heard about treatment options only while having their arteriovenous fistula created, so they assumed that dialysis was inevitable and any talk of options was hollow. The authors propose guidelines on when and how to make these shared decisions, and call for a range of formal care pathways. But Vishal Sharma, a senior resident in Delhi, added in a Rapid Response that in the developing world "it is a sad fact that for the majority of patients with chronic kidney disease palliative care becomes the de facto preference" (www.bmj.com/cgi/eletters/340/jan19_2/c112 - 229839).

RESEARCH ONLINE: For these and other new research articles see http://www.bmj.com/channels/research.dtl

Therapeutic hypothermia in newborns Several studies have investigated therapeutic hypothermia in neonates with hypoxic-ischaemic encephalopathy, but the findings do not provide unequivocal evidence of benefit. A David Edwards and colleagues' meta-analysis provides high level evidence of the efficacy of moderate hypothermia. Their assessment of three trials (767 infants) showed a reduction in death and neurological impairment at 18 months, whereas a larger analysis of 10 trials (1320 infants) showed a significant reduction in mortality. "These results will attract attention and may draw a line under a fairly high profile debate," says research editor Alison Tonks.

Treatment for UTI Look out for a cluster of four research articles on treatment options for urinary tract infection in women in primary care, including strategies to reduce the use of antibiotics (doi:10.1136/bmj.b5633, doi:10.1136/bmj.c199, doi:10.1136/bmj.c346, doi:10.1136/bmj.c279). An editorial draws the findings together (doi:10.1136/bmj.c657), and in a podcast, *BMJ* deputy editor Trish Groves talks to Paul Little, professor of primary care at Southampton University, about the papers (http://podcasts.bmj.com/bmj).


INOVA

The views of patients and carers in treatment decision making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies

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STUDY QUESTION What factors influence decision making in the treatment of chronic kidney disease from the perspective of patients and their carers?

SUMMARY ANSWER Factors influencing treatment decisions included the experiences of other patients (peer influence) and the problematic timing of information about treatment options and synchronous creation of vascular access, which appeared to predetermine centre based haemodialysis and inhibit the choice of pre-emptive transplantation, home dialysis, or palliative care.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Only one third of patients with chronic kidney disease receive information about treatment options after starting dialysis, contrary to current clinical guidelines. There is a strong preference for retaining the status quo and patients are reluctant to change treatments, which may explain why they often remain on their initial therapy. Formal care pathways for pre-emptive transplantation, home dialysis, and palliative management would facilitate provision of treatments more aligned with patients' preferences.

Selection criteria for studies

We searched Medline, PsycINFO, CINAHL, Embase, social work abstracts, and digital theses from database inception to week three October 2008 to identify literature using qualitative methods (focus groups, interviews, or case studies) in the area of decision making and choice for kidney dialysis, transplantation, or palliative care from patients' and carers' perspectives.

Primary outcome(s)

The comprehensiveness of reporting was assessed by using the consolidated criteria for reporting qualitative research framework. The domains of this checklist (research team and reflexivity, study design, and data analysis and reporting) provided a transparency of research methods that allowed readers to assess the trustworthiness and transferability of the primary study findings to their own setting. Studies were not excluded or weighted on the basis of the quality of reporting assessment. Thematic synthesis of the findings from the primary studies and development of analytical themes enabled the analysis of a substantive literature in decision making for all types of treatment for chronic kidney disease, as no single study provided perspectives on transplantation, haemodialysis, peritoneal dialysis, and palliative care.

Main results and the role of chance

Eighteen studies that reported the experiences of 375 patients and 87 carers were included. Fourteen focused on preferences for dialysis modality, three on transplantation, and one on palliative management. Four major themes were identified as being central to treatment choices: confronting mortality (choosing life or death, being a burden, living in limbo), lack of choice (medical decision, lack of information, constraints on resources), gaining knowledge of options (peer influence, timing of information), and weighing alternatives (maintaining lifestyle, family influences, maintaining the status quo).

Bias, confounding, and other reasons for caution

The review was limited to the experiences of patients in the 18 included primary studies and under-represented people from non-English speaking backgrounds and those seeking palliative care.

Study funding/Potential competing interests

RLM is supported by the National Health and Medical Research Council grants in population health (Nos 457281 and 571372). We have no competing interests.

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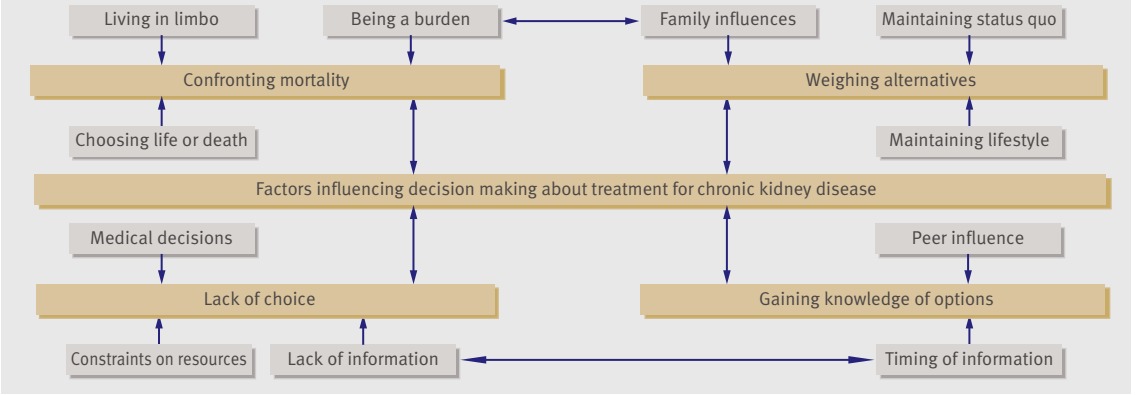
"It is a sad fact that for patients with chronic kidney disease, palliative care becomes the de facto preference. The reasons are lack of availability and the immense cost of the renal replacement therapies. Until the resource constraints are tackled, a realistic assessment of the choice of therapy will not be possible"
Vishal Sharma, senior resident at the University College of Medical Sciences, Delhi, in a rapid response

COMPONENTS OF EACH THEME IDENTIFIED AS INFLUENCING TREATMENT DECISIONS



This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c112

Relation between hospital orthopaedic specialisation and outcomes in patients aged 65 and older: retrospective analysis of US Medicare data

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EDITORIAL by Lyman

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STUDY QUESTION Do hospitals with a greater degree of orthopaedic specialisation have improved surgical outcomes after total hip replacement or total knee replacement than those with less orthopaedic specialisation?

STUDY ANSWER Even after adjustment for patient characteristics, comorbidity, and hospital orthopaedic volume the odds of adverse outcomes was significantly lower among hospitals with greater orthopaedic specialisation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent studies have found improved outcomes in a limited number of hospitals (‹30) that focused on single diseases or procedures, but the broader relation between hospital specialisation and patient outcomes is uncertain. We found significant improvements in orthopaedic outcomes with increasing hospital specialisation, even after accounting for differences in patient characteristics and hospital volume.

Participants and setting

The study population comprised 1 273 081 Medicare beneficiaries age 65 and older who underwent primary or revision hip or knee replacement in 3818 US hospitals during 2001-5.

Design, size, and duration

The hospitals were stratified into fifths on the basis of their orthopaedic specialisation (lowest fifth, least specialised; highest fifth, most specialised). The primary outcome was a composite of one or more of pulmonary embolism, deep venous thrombosis, haemorrhage, infection, myocardial infarction, or death within 90 days of the index surgery. We compared patient characteristics, comorbidity, and hospital surgical volume across fifths of hospital specialisation. Multivariable generalised logistic models were used to compare the odds of adverse outcomes after accounting for differences in patient and hospital characteristics, and hospital procedural volume as hospital specialisation increased (highest fifth as reference category).

Main results and the role of chance

As hospital orthopaedic specialisation increased, the proportion of patients admitted to hospital who were women or black or who had diabetes or heart failure progressively decreased (P<0.001), while procedural volume increased. Compared with the most specialised hospitals, after adjustment for patient characteristics and hospital volume, the odds of adverse outcomes increased progressively with decreased hospital specialisation: fourth fifth, 1.10 (95% confidence interval 1.07 to 1.13); third fifth, 1.24 (1.21 to 1.28); second fifth, 1.32 (1.28 to 1.36); and first fifth, 1.59 (1.53 to 1.65).

Bias, confounding, and other reasons for caution

Hospital specialisation may capture different components of hospital quality than those components captured by hospital volume. These results should be interpreted with caution because we can not exclude the possibility that other unmeasured confounders related to socioeconomic status or other factors are responsible for the improved patient outcomes rather than hospital specialisation.

Generalisability to other populations

The results require replication outside the United States and among other diseases and procedures.

Study funding/potential competing interests

We have no competing interests.

OUTCOME WITHIN 90 DAYS OF MAJOR JOINT REPLACEMENT ACCORDING TO HOSPITAL SPECIALISATION

	Fifths of specialisation*			
Variables	First (least specialised)	Second	Third	Fourth
Individual outcomes†:				
Deep vein thrombosis	1.76 (1.58 to 1.96)	1.46 (1.34 to 1.59)	1.32 (1.22 to 1.43)	1.16 (1.07 to 1.25)
Pulmonary embolism	1.16 (1.03 to 1.31)	1.12 (1.04 to 1.22	1.08 (1.00 to 1.16)	1.02 (0.95 to 1.09)
Haemorrhagia	1.65 (1.47 to 1.85)	1.3 (1.19 to 1.43)	1.29 (1.18 to 1.41)	1.14 (1.04 to 1.24)
Infection	1.98 (1.86 to 2.19)	1.52 (1.42 to 1.62)	1.28 (1.20 to 1.36)	1.14 (1.08 to 1.21)
Myocardial infarction	1.34 (1.16 to 1.55)	1.17 (1.06 to 1.29)	1.09 (0.99 to 1.20)	1.05 (0.97 to 1.15)
Mortality:				
Unadjusted	1.90 (1.73 to 2.08)	1.60 (1.51 to 1.69)	1.38 (1.31 to 1.45)	1.18 (1.13 to 1.24)
Adjusted†	1.57 (1.42 to 1.75)	1.44 (1.34 to 1.55)	1.29 (1.20 to 1.37)	1.14 (1.07 to 1.22)
Composite outcome:				
Unadjusted	1.60 (1.53 to 1.67)	1.30 (1.26 to 1.34)	1.27 (1.24 to 1.30)	1.10 (1.08 to 1.13)
Adjusted†	1.59 (1.48 to 1.72)	1.32 (1.24 to 1.40)	1.24 (1.17 to 1.32)	1.10 (1.04 to 1.17)

*Fifth fifth (most specialised) as reference category.
†Adjusted for age, sex, race, comorbid conditions, and hospital characteristics.

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c165

Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study

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EDITORIAL by Taylor

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STUDY QUESTION

Is venlafaxine use associated with an increased risk of sudden cardiac death or near death compared with other commonly used antidepressants?

SUMMARY ANSWER

Venlafaxine use was not associated with an excess risk of sudden cardiac death or near death compared with use of fluoxetine, dosulepin, or citalopram.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recent reports from the UK observed that the antidepressant venlafaxine was associated with an increased rate of fatal overdose compared to several selective serotonin reuptake inhibitors, a finding that some have hypothesised could be due to a pro-arrhythmic mechanism. Our study suggests that at pharmacological doses venlafaxine does not increase risk of life threatening arrhythmias.

Participants and setting

We used data from the UK general practice research database. Participants were new users of venlafaxine, fluoxetine, citalopram, and dosulepin between January 1995 and February 2005, aged 18 to 89 years, with a diagnosis of depression or anxiety.

Design, size, and duration

We conducted a nested case-control analysis within a cohort of 207 384 patients. Average follow-up was 3.3 years. For each case, 30 controls were matched on age, sex, calendar time, and indication.

Primary outcome, risks, exposures

The primary outcome was sudden cardiac death or near death identified from medical records indicating non-fatal acute ventricular tachyarrhythmia, sudden death due to cardiac causes, or out of hospital deaths from acute ischaemic cardiac events. We evaluated the risk of this outcome comparing current use of venlafaxine with current use of fluoxetine, citalopram, or dosulepin. We estimated relative risks from the adjusted odds ratios, calculated using conditional logistic regression.

Main results and the role of chance

568 cases of sudden cardiac death or near death were matched to 14 812 controls. The risk of cardiac death or near death was not elevated among venlafaxine users (odds ratio versus any of the three comparator antidepressants 0.77; 95% confidence interval 0.46 to 1.30).

ADJUSTED ODDS RATIO (OR) OF SUDDEN CARDIAC DEATH OR NEAR DEATH WITH CURRENT VENLAFAXINE USE RELATIVE TO CURRENT USE OF FLUOXETINE, CITALOPRAM, AND DOSULEPIN

	Cases (n=568)	Controls (n=14812)	Adjusted OR (95% CI)
Current use of venlafaxine	18 (3.2)	544 (3.7)	1.00
Versus fluoxetine	63 (11.1)	1281 (8.6)	0.66 (0.38 to 1.14)
Versus citalopram	39 (6.9)	1079 (7.3)	0.89 (0.50 to 1.60)
Versus dosulepin	35 (6.2)	1012 (6.8)	0.83 (0.46 to 1.52)
Versus any of the three	137 (24.1)	3372 (22.8)	0.77 (0.46 to 1.30)

Numbers of currently exposed cases and controls do not add up to column totals because the remaining cases and controls were past users of study antidepressants.

Bias, confounding, and other reasons for caution

We accounted for potential confounders including body mass index, smoking, alcohol abuse, depression severity, medical comorbidity, and concomitant medications. The major limitation was inability to directly confirm that a ventricular tachyarrhythmia precipitated death. We did not have direct access to medical records for hospital or emergency care. We used prescription data as a proxy for antidepressant exposure and did not measure actual drug adherence; thus we cannot exclude the possibility of exposure misclassification, which may have varied by study drug. Selection bias is unlikely because drug data were recorded prospectively before events of interest.

Generalisability to other populations

We expect that results would apply to patients with depression or anxiety treated with study antidepressants in other primary care settings.

Study funding/potential competing interests

This study was sponsored by Wyeth, which produces and markets venlafaxine. The contract for this research specified that the non-company authors had ultimate control over all aspects of the study, including control over publication. All authors had access to the statistical reports and tables supporting the publication. DM is a full-time employee of Wyeth and owns company stock options. SS has participated in advisory board meetings, conferences and participating as a speaker in scientific meetings by various companies (AstraZeneca, Boehringer Ingelheim, Glaxo SmithKline, Pfizer, and Sepracor) and SS received research grants from AstraZeneca, Wyeth, and GlaxoSmithKline. TLA, SD'A, and CM have nothing to declare.

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The effect of maternal child marriage on morbidity and mortality of children under 5 in India: cross sectional study of a nationally representative sample

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STUDY QUESTION

How is maternal child marriage (marriage before age 18) associated with morbidity and mortality of infants and children under 5 in India?

SUMMARY ANSWER

The risk of malnutrition is higher in young children born to mothers married as minors than in those born to women married as adults.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Infants and young children in India are disproportionately affected by poor health. Girls married as minors are more likely to be poor, uneducated, and living in rural areas with low access to health care, and their children have increased mortality and ill health. In this study, infant and child malnutrition was associated with early maternal marriage, but low birth weight and infant and child mortality were not.

Participants and setting

We used data from the 2005-6 National Family Health Survey-3 in India. Women who reported births in the past five years who were ever married and aged 15-24 (n=19 302) were included in the analysis.

Design

Cross-sectional analyses of nationally representative household sample. Generalised estimating equation models were constructed to assess associations. Adjusted models included maternal and child demographics and maternal body mass index as covariates.

Primary outcomes

Primary outcome measures for children under age 5 included: mortality related infectious diseases in past two weeks (acute respiratory infection, diarrhoea); malnutrition (stunting, wasting, underweight); infant (age <1 year) and child (1-5 years) mortality; low birthweight (<2500 kg).

Main results and the role of chance

Response rate was 95% among the 124 385 women who participated in the original survey. The majority of births (73%; 13042/19302) were to mothers married as minors. Although bivariate analyses showed significant associations between maternal child marriage and infant and child diarrhoea, malnutrition (stunted, wasted, underweight), low birthweight, and mortality, only stunting (adjusted odds ratio 1.22, 95% CI 1.12 to 1.33) and underweight (1.24, 1.14 to 1.36) remained significant in adjusted analyses.

Bias, confounding and other reasons for caution

Most outcomes were based on self report, which is vulnerable to bias. Causality cannot be assumed. Birthweight data were available for only 40% of births in the past five years. Earlier maternal age at marriage was significantly associated with having older children under 5 years; inclusion of births to 15-17 year old mothers reduced this bias somewhat but not fully.

Generalisability to other populations

Births in the sample were restricted to births in the past five years to ever married 15-24 year olds; hence, findings are not generalisable to all births in the past five years but solely those to young mothers. Findings are specific to young women in India, and cannot be generalised to other national contexts and women of other age groups within India.

Study funding/potential competing interests

Analyses for this study and development of this paper were funded by the US National Institutes of Health and the Indian Council on Medical Research Indo-US Program on Maternal and Child Health and Human Development (Grant Number 1 R03 HD055120-01), as well as seed grant funding from Boston University School of Public Health. No competing interests declared.

ASSOCIATIONS BETWEEN MATERNAL CHILD MARRIAGE AND INFANT AND CHILD HEALTH OUTCOMES

Infant/child health outcomes	% (number) Births to child marriage mothers (n=13 042)	Births to adult marriage mothers (n=6260)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Acute respiratory infection	–	–	1.03 (0.92 to 1.15)	1.04 (0.91 to 1.19)
Yes	10.6 (1221)	10.5 (588)	–	–
No	89.4 (10 805)	89.5 (5337)	–	–
Diarrhoea	–	–	0.86 (0.78 to 0.96)	0.95 (0.84 to 1.08)
Yes	9.9 (1221)	11.2 (683)	–	–
No	90.1 (10 825)	88.8 (5254)	–	–
Stunting			1.85 (1.71 to 1.99)	1.22 (1.12 to 1.33)
Yes	45.3 (4468)	32.2 (1495)	–	–
No	54.7 (5762)	67.8 (3507)	–	–
Wasting	–	–	1.19 (1.07 to 1.31)	1.09 (0.97 to 1.21)
Yes	17.7 (1754)	15.9 (739)	–	–
No	82.3 (8478)	84.1 (4263)	–	–
Underweight	–	–	1.87 (1.74 to 2.01)	1.24 (1.14 to 1.36)
Yes	50.9 (4912)	36.5 (1665)	–	–
No	49.1 (5318)	63.5 (3337)	–	–
Infant/child mortality	–	–	1.55 (1.35 to 1.78)	0.93 (0.79 to 1.10)
Yes	7.4 (934)	5.6 (296)	–	–
No	92.6 (12,108)	94.4 (5964)	–	–
Low birthweight infant	–	–	1.13 (1.004 to 1.26)	0.99 (0.86 to 1.13)
Yes	25.1 (1054)	22.2 (753)	–	–
No	74.9 (3275)	77.8 (2657)	–	–

The influence of preoperative use of ventricular assist devices on survival after heart transplantation: propensity score matched analysis

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STUDY QUESTION

Do survival rates after heart transplantation differ between those who do and do not receive a left ventricular assist device before transplantation?

SUMMARY ANSWER

Patients who received a left ventricular assist device before transplantation had comparable survival after transplantation to those who did not receive the device.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Ventricular assist devices can prolong the life of patients with heart failure before heart transplantation. In this study patients who received a left ventricular assist device had similar survival after heart transplantation to those who did not receive the device.

Participants and setting

Participants were 18 years or older who received a first heart transplant registered in the United Network for Organ Sharing registry from 1996 to 2004. The study included 2786 patients of status 1A or 1B requiring a heart transplant—that is, highest priority for heart transplantation with either some form of ventricular assist device, intravenous inotrope, or life expectancy of less than seven days.

Design, size, and duration

This was a prospective cohort study in which we compared survival after heart transplantation between patients who did and did not receive a left ventricular assist device before transplantation. Patients were assigned to one of five strata on the basis of the propensity score analysis. The first stratum consisted of patients most similar to those that had heart transplantation with no previous bridging using a left ventricular assist device and the fifth stratum consisted of patients most similar to those who received a left ventricular assist device before heart transplantation. A 1:1 propensity score matching analysis was also carried out as a sensitivity analysis. We compared survival distributions using the Kaplan-Meier method and estimated the risk ratios using the Cox proportional model.

HAZARD RATIOS BY PROPENSITY SCORE IN EACH STRATUM

Stratum	Variable estimate	SE	P value	Hazard ratio (95% CI)
First	−0.371	0.658	0.6	0.69 (0.19 to 2.51)
Second	0.314	0.342	0.4	1.37 (0.70 to 2.66)
Third	0.437	0.311	0.2	1.55 (0.84 to 2.85)
Fourth	−0.284	0.358	0.4	0.75 (0.37 to 1.52)
Fifth	0.176	1.014	0.9	1.19 (0.16 to 8.70)

Primary outcome(s), risks, exposures

The study outcome was survival after heart transplantation in heart transplant recipients who did and did not receive a ventricular assist device.

Main results and the role of chance

A stratified propensity score analysis of data within each stratum showed that the risk of death after heart transplantation was not significantly different between those who did and did not receive a left ventricular assist device. A 1:1 propensity score matching analysis also showed no significant difference in survival between the two groups (hazard ratio 1.18, 95% confidence interval 0.75 to1.86).

Bias, confounding, and other reasons for caution

The propensity score matching was done to control for potential selection biases that can lead to a false association (or false lack of association) between receipt of a left ventricular assist device and survival. Although we attempted to minimise bias through propensity score matching, some could potentially remain hidden because of other relevant known as well as unknown covariates not available in the United Network for Organ Sharing database.

Generalisability to other populations

The population included patients aged 18 and older who had had a first heart transplant. Two different ventricular assist devices were considered as a bridge to transplantation: Heartmate (XVE Thoratec, CA) and Novacor (World Heart, UT). The results should generalise to the population of patients waiting for heart transplantation who are considering use of these two devices, and provide estimates of what may be expected for future designs of ventricular assist devices.

Study funding/potential competing interests

We have no competing interests.

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c392

Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study

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bmj.com
For an interview with the author David N Juurlink, visit podcasts.bmj.com/bmj

STUDY QUESTION

Do some selective serotonin reuptake inhibitor (SSRI) antidepressants reduce the effectiveness of tamoxifen in treating breast cancer?

SUMMARY ANSWER

Use of paroxetine with tamoxifen is associated with an increase in risk of death from breast cancer that correlates with the duration of co-prescription.

WHAT IS KNOWN AND WHAT THIS STUDY ADDS

Tamoxifen is important in the endocrine treatment of breast cancer and is converted by cytochrome P450 2D6 (CYP2D6) to its active metabolite endoxifen. SSRIs are widely prescribed to women with breast cancer taking tamoxifen, but inhibit CYP2D6 to varying degrees. We found that use of paroxetine (a potent, irreversible CYP2D6 inhibitor) during tamoxifen treatment increases subsequent risk of death from breast cancer. No such risk was found with other SSRIs.

Participants and setting

Female residents of Ontario, Canada, aged 66 years and older.

Design, size, and duration

Retrospective cohort study of 2430 patients with breast cancer who were treated with tamoxifen and a single SSRI between 1 January 1993 and 31 December 2005. Patients were followed up from completion of tamoxifen treatment until death or the end of the study period (mean 2.38 years, SD 2.59).

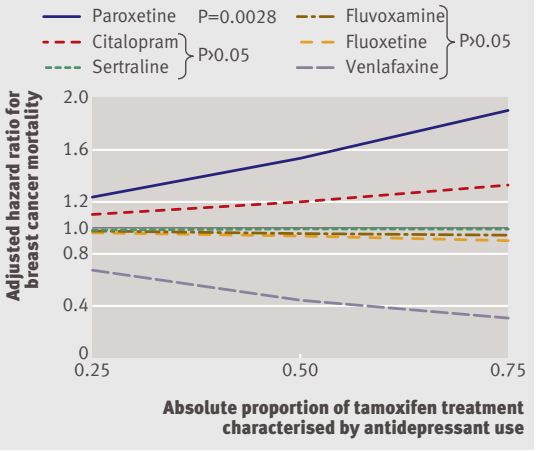
Main results and the role of chance

374 (15.4%) women died of breast cancer during follow-up. Absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk of death from breast cancer, respectively (P<0.05 for each comparison). No such risk was seen with other antidepressants. We estimate that use of paroxetine for 41% of tamoxifen treatment—the typical overlap in our sample—would result in one additional breast cancer death within five years of stopping tamoxifen for every 19.7 (95% confidence interval 12.5 to 46.3) patients so treated.

Bias, confounding, and other reasons for caution

We could not assess the indication for antidepressants, which are sometimes used to treat hot flushes, a purported marker of better response to tamoxifen treatment. We also lacked information on cancer stage, but because our analysis focused on within-drug comparisons, this did not threaten our conclusions. Finally, fluoxetine and its metabolite are also inhibitors of CYP2D6, yet we found no association between fluoxetine use and breast cancer mortality among women taking tamoxifen. This may reflect insufficient sample size, and our results should not be viewed as evidence that fluoxetine can be safely used in combination with tamoxifen.

RISK OF BREAST CANCER MORTALITY ASSOCIATED WITH ANTIDEPRESSANT USE DURING TAMOXIFEN TREATMENT



Generalisability to other populations

Whether the conclusions apply to younger women with breast cancer is unknown.

Study funding/potential competing interests

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