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Minimally invasive treatments for benign prostatic enlargement: systematic review of randomised controlled trials

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ABSTRACT

Objective To compare the effectiveness and risk profile of minimally invasive interventions against the current standard of transurethral resection of the prostate.

Design Systematic review and meta-analysis of randomised controlled trials.

Data sources Electronic and paper records up to March 2006.

Review methods We searched for all relevant randomised controlled trials. Two reviewers independently extracted data and assessed quality. Meta-analyses of prespecified outcomes were performed with fixed and random effects models and reported using relative risks or weighted mean difference.

Results 3794 abstracts were identified; 22 randomised controlled trials met the inclusion criteria. These provided data on 2434 participants. The studies evaluated were of moderate to poor quality with small sample sizes. Minimally invasive interventions were less effective than transurethral resection of the prostate in terms of improvement in symptom scores and increase in urine flow rate, with most comparisons showing significance despite wide confidence intervals. Rates of second operation were significantly higher for minimally invasive treatments. The risk profile of minimally invasive interventions was better than that of transurethral resection, with fewer adverse events. The results, however, showed significant heterogeneity.

Conclusion Which minimally invasive intervention is the most promising remains unclear. Their place in the management of benign prostate enlargement will continue to remain controversial until well designed and well reported randomised controlled trials following CONSORT guidelines prove they are superior and more cost effective than drug treatment or that strategies of sequential surgical treatments are preferred by patients and are more cost effective than the more invasive but more effective tissue ablative interventions such as transurethral resection.

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INTRODUCTION

Endoscopic removal of the inner part of the prostate gland by transurethral resection of the prostate has long been considered the most effective treatment for benign prostatic enlargement. This procedure has known disadvantages, including blood loss and physiological stress, and the need for high levels of technical skill and a three to five day stay in hospital.[1] These factors have encouraged the development of alternative treatments, including drugs, minimally invasive surgical techniques, and different forms of endoscopic prostatectomy.

We carried out a systematic review to summarise evidence of benefit and risk for seven promising minimally invasive technologies compared with transurethral resection using data from randomised controlled trials.

METHODS

Search strategy—We defined minimally invasive treatments as those that reduce prostate volume by delayed tissue necrosis using low energy heating devices. To identify published and unpublished reports of relevant randomised controlled trials we searched relevant databases and recent conference proceedings. Searches were not restricted by year of publication or language and included abstracts from conference proceedings. Reference lists of all included studies were also scanned. See bmj.com for further details.

Selection and study characteristics—We included randomised controlled trials if they compared minimally invasive interventions for benign prostatic enlargement with transurethral resection of the prostate. We excluded trials reporting on men without a clinical diagnosis of benign prostatic enlargement and comparisons against conservative management (table A on bmj.com). The primary outcome measure was change in symptom score 12 months after surgery, measured by the international prostate symptom score or the American Urological Association symptom index. Secondary outcomes were improvement in quality of life and increase in peak urine flow rate (for effectiveness); blood transfusion, urinary incontinence, urinary retention, urethral stricture, urinary tract infection, retrograde (loss of) ejaculation, erectile dysfunction (for morbidity); and duration of operation, length of hospital stay, and need for reoperation (for descriptors of care). We considered all reports of

prespecified complications regardless of their timing. Two reviewers (from TL and Angela Couts or Susan Wong or Ghulam Nabi) independently assessed each study. Differences were decided by an arbiter. See bmj.com.

Quantitative data synthesis—For meta-analysis we combined dichotomous outcome data using the Mantel-Haenszel relative risk method. For continuous outcomes we used inverse variance weighted mean differences and 95% confidence intervals. We mostly used a fixed effects mode but used a random effects model for symptom score and peak urine flow rate because of statistical heterogeneity, explored by χ^2 tests and I^2 statistics.

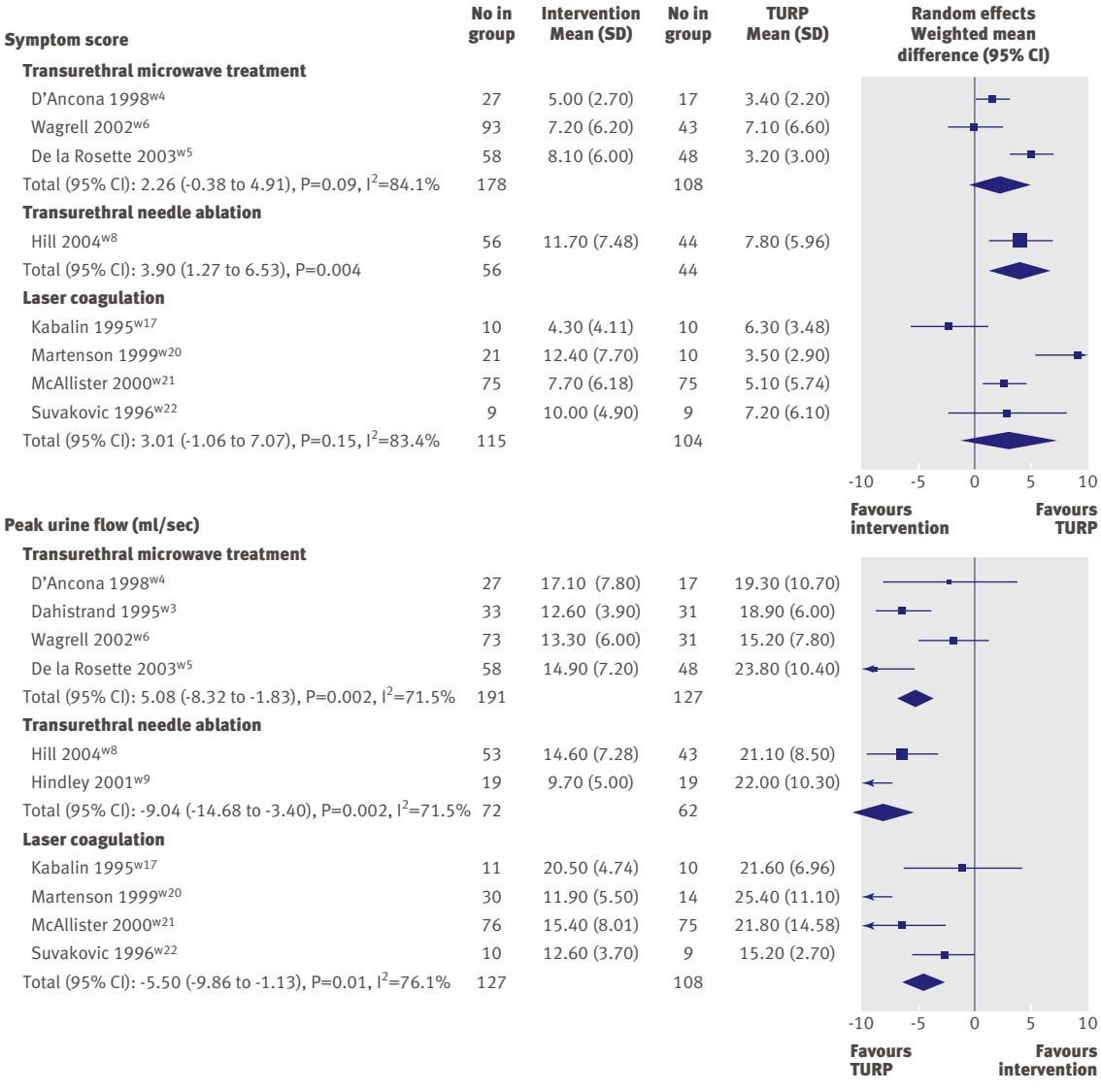
RESULTS

The initial search generated 3794 reports, of which 621 were selected for full assessment. Fifty four reports describing 22 trials met the eligibility criteria. We classed the 22 full text randomised controlled trials[w1-w22] as being moderate or poor quality (table B on bmj.com). Trial setting and baseline characteristics of the patients, varied across the included trials. Types of laser and delivery mode of laser coagulation also varied (table C on bmj.com). The eligible trials included 24 relevant comparisons involving 2434 participants.

Quantitative data synthesis

Symptom scores—Results from studies reporting change in symptom score from baseline to 12 months showed significant heterogeneity so we carried out random effect meta-analyses (figure). There was generally less improvement in symptom score for patients who underwent transurethral microwave treatment, transurethral needle ablation, and laser coagulation than transurethral resection of the prostate (table D on bmj.com).

Peak urine flow rate—The results for peak urine flow rate at 12 months were generally consistent with those for symptom scores (figure).



Symptom scores (international prostate symptom score or American Urological Association symptom index) and peak urine flow rate at 12 months (TURP=transurethral resection of prostate)

Quality of life—Two,[w5 w6] four,[w7-w10] and six[w10 w12 w15 w16 w18 w20] studies comparing transurethral resection with transurethral microwave treatment, transurethral needle ablation, and laser coagulation, respectively, reported on quality of life using various instruments. Scores after these interventions were generally poorer than after transurethral resection, but we could not undertake a formal meta-analysis (table D on bmj.com).

Blood transfusion—Blood transfusion was less common after minimally invasive treatments than after transurethral resection: relative risk 0.11, 95% confidence interval 0.01 to 1.98, P=0.13, after transurethral microwave treatment; 0.05, 0.01 to 0.32, P=0.002, after transurethral needle ablation; 0.11, 0.04 to 0.26, P<0.001, after laser coagulation). No patients undergoing transurethral microwave treatment or transurethral needle ablation required a blood transfusion.

Urinary retention—Laser coagulation was associated with a higher rate of urinary retention than transurethral resection (12.9% *v* 5.3%, relative risk 2.31, 1.11 to 4.80, P=0.02). No significant differences were seen between transurethral resection and transurethral microwave treatment or transurethral needle ablation.

Strictures—Men undergoing a minimally invasive treatment had a lower risk of developing strictures (0.6% *v* 6.5%, relative risk 0.20, 0.05 to 0.75, P=0.02, after transurethral microwave treatment; 0.5% *v* 6.8%, 0.14, 0.03 to 0.62, P=0.009, after transurethral needle ablation; 0.9% *v* 8.6%, 0.18, 0.06 to 0.56, P=0.003, after laser coagulation) (fig B on bmj.com).

Incontinence—The risk of postoperative incontinence was lower after transurethral needle ablation and laser coagulation than after transurethral resection (0.9% *v* 8.0%, relative risk 0.16, 0.05 to 0.51, P=0.002; 0% *v* 3.9%, 0.16, 0.04 to 0.71, P=0.02, respectively), while there was no significant difference after transurethral microwave treatment (4.9% *v* 8.3%, 0.61, 0.30 to 1.26, P=0.18) (fig B on bmj.com).

Urinary tract infection—There was no significant difference in rates of urinary tract infection after transurethral microwave treatment and transurethral needle ablation compared with transurethral resection (6.7% *v* 7.5%; 1.05, 0.53 to 2.08, P=0.90, after transurethral microwave treatment; 10.3% *v* 7.0%; 1.42, 0.69 to 2.91, P=0.34, after transurethral needle ablation). The rate of postoperative urinary tract infection, however, was higher in patients after laser coagulation (14.8% *v* 6.9%; 1.84, 1.22 to 2.79, P=0.004) (fig B on bmj.com).

Sexual dysfunction—Men undergoing a minimally invasive treatment were less likely to experience loss of ejaculation compared with those having transurethral resection. Also, after transurethral needle ablation or laser coagulation, sexually active men had a lower risk of experiencing erectile dysfunction, but the difference between transurethral microwave treatment and transurethral resection was not significant. See figure on bmj.com.

Descriptors of care—Compared with transurethral resection, transurethral needle ablation procedures were longer and laser coagulation procedures shorter. We had insufficient data to assess differences in duration of operation between transurethral microwave treatment and transurethral resection. Hospital stay was on average one day shorter for laser coagulation than for transurethral resection (95% confidence interval −1.68 to −0.98 days, P<0.001). This was consistent with results from other trials with data unsuitable for meta-analysis. Concerning transurethral needle ablation, two studies favoured transurethral resection of the prostate [w7 w9] and one favoured transurethral needle ablation.[w10] Patients undergoing transurethral microwave treatment were generally treated as day cases. The need for a second procedure was more common after a minimally invasive procedure (10.2% *v* 4.8%, 2.01, 0.96 to 4.18, P=0.06, after transurethral microwave treatment; 6.2% *v* 0.5%, 6.89, 1.58 to 29.95, P=0.01, after transurethral needle ablation; 7.9% *v* 2.0%, 3.21, 1.65 to 6.24, P<0.001, after laser coagulation).

DISCUSSION

Principal finding

Overall, our findings do not support a change in surgical treatment of benign prostatic enlargement away from the current standard of transurethral resection. On an individual basis, however, personal preference will influence choice of procedure and some patients might trade-off the lower efficacy and higher risk of a second operation for the decreased morbidity seen with minimally invasive treatment options.

Possible mechanism and implications for policy and practice

Although improvement in symptoms after minimally invasive treatments was inferior to transurethral resection of the prostate, it still represents a considerable treatment effect. It might be better to use these techniques earlier, possibly as alternatives to long term drug treatment. One randomised controlled trial showed superior efficacy in terms of symptom scores, peak urine flow rate, and quality of life with single transurethral microwave treatment at six months after treatment compared with terazocin, an α adrenergic antagonist.[2]

The durability of symptomatic benefit after minimally invasive treatments was poor compared with transurethral resection. This represents a major disadvantage of these techniques, particularly if the rate of treatment failure continues to increase with longer follow-up, as suggested by several studies reporting outcome at two and five years after transurethral microwave treatment.[w8 w9 w18 w20 w21] Their use might be favoured as a preliminary treatment, with transurethral resection for treatment failures.

Shorter duration of operation and hospital stay together with the lower risk of serious complications, suggests that minimally invasive treatments might offer significant cost savings over transurethral resection, but the importance of these savings would need to be set against differences in effectiveness and subsequent treatment costs such as need for a second operation and safety.

Strengths and limitations of the review:

We could not assess the extent of publication bias as most of the available evidence (53 randomised

WHAT IS ALREADY KNOWN ON THIS TOPIC

Transurethral resection of the prostate is the current standard surgical procedure for men with clinically benign prostatic enlargement

It provides a consistent high likelihood of improvement, which persists in the long term but is associated with relatively high risk of adverse events

Minimally invasive treatments have been tried in clinical practice

WHAT THIS STUDY ADDS

Minimally invasive treatments result in poorer improvement in symptoms and urodynamic parameters than transurethral resection but cause fewer adverse events

Rates of second operation are higher after a minimally invasive treatment than after transurethral resection

controlled trials) was excluded because it was reported only in abstract form. Unpublished reports tend to show less positive results[3] and so the exclusion of these abstracts might have introduced bias in favour of the newer interventions.

Heterogeneity in results for the primary outcome measure of reduction in symptom score presented problems in deriving a valid meta-analysis, which we overcame by using a random effects model.

Other methodological limitations resulted from variation in inclusion criteria, operative technique, and treatment protocols between trials investigating the same technology.

Our conclusions generally concur with the other recently published reviews.[4,5] One exception was the study by Bouza and colleagues that compared transurethral needle ablation with transurethral resection of the prostate.[4] The marked differences might be caused by different objectives and inclusion criteria and because they combined results from non-randomised and randomised studies to provide a single pooled estimate.

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Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study

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ABSTRACT

Objective To obtain large scale and generalisable data on the long term predictive value of cytology and human papillomavirus (HPV) testing for development of cervical intraepithelial neoplasia grade 3 or cancer (CIN3+).

Design Multinational cohort study with joint database analysis.

Setting Seven primary HPV screening studies in six European countries.

Participants 24 295 women attending cervical screening enrolled into HPV screening trials who had at least one cervical cytology or histopathology examination during follow-up.

Main outcome measure Long term cumulative incidence of CIN3+.

Results The cumulative incidence rate of CIN3+ after six years was considerably lower among women negative for HPV at baseline (0.27%, 95% confidence interval 0.12% to 0.45%) than among women with negative results on cytology (0.97%, 0.53% to 1.34%)). By comparison, the cumulative incidence rate for women with negative cytology results at the most commonly recommended screening interval in Europe (three years) was 0.51% (0.23% to 0.77%). The cumulative incidence rate among women with negative cytology results who were positive for HPV increased continuously over time, reaching 10% at six years, whereas the rate among women with positive cytology results who were negative for HPV remained below 3%.

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Conclusions A consistently low six year cumulative incidence rate of CIN3+ among women negative for HPV suggests that cervical screening strategies in which women are screened for HPV every six years are safe and effective.

INTRODUCTION

Meta-analyses and pooled analyses of cross sectional studies have established that tests for human papillomavirus (HPV) have higher sensitivity than cytology in detecting high grade cervical intraepithelial lesions (CIN)[1 2] and combined HPV and cytology testing has high negative predictive values for CIN.[3-5] Cost effectiveness modelling of screening strategies depends on reliable and generalisable estimates of the long-itudinal, long term predictive values of testing. Predictive values to be used for modelling should also ideally use CIN grade 3 or cancer (CIN3+) as the outcome as low and moderate grades of CIN often regress.[6]

To obtain large scale and generalisable data on long term predictive values for CIN3+, we obtained primary data from seven HPV screening studies in six EU countries, each investigating the predictive value of primary HPV screening for future CIN3+; assessed variability between studies; and estimated the overall long term predictive values for CIN3+.

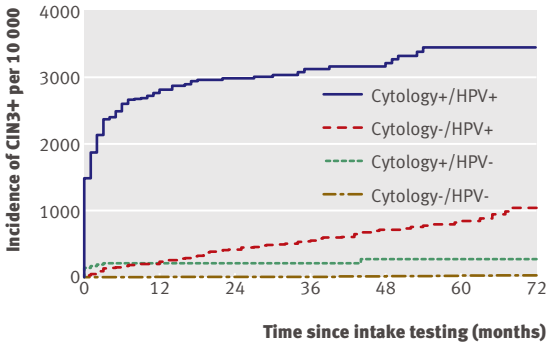
METHODS

The seven prospective HPV studies supplied data to a common database for joint statistical analysis and are shown in the table. All studies used routine cytology and the different HPV tests as currently practised in their country. For all studies the people executing either test were unaware of the results of the other test. Comparability and reproducibility of the two main HPV tests used (hybrid capture II and GP5+/6+ polymerase chain reaction) were evaluated with κ statistics. Recruitment was consecutive and data collection prospectively planned. See bmj.com for further details of the studies in each country.[3 7 8]

Statistical analysis

From the joint cohort, we included only women with adequate cytology and HPV tests at baseline and with at least one follow-up cytological or histological test. We regarded abnormal cytology as the equivalent of atypical squamous cells of uncertain significance or worse, for all the participating studies. Women were followed up from the date of the baseline test. Incidence depends on the number of person years of follow-up, and, for a disease detectable by screening, follow-up requires the person to have attended screening. Therefore, we censored follow-up at the date of diagnosis of the CIN3+ lesion (CIN3 or invasive cancer, including squamous and adenocarcinoma) or at the last registered testing date.

We estimated the specific cumulative incidence rate of CIN3+ by original baseline group (cytology−/HPV−, cytology−/HPV+, cytology+/HPV−, and cytology+/HPV+) for each country, using the non-parametric Kaplan-Meier product limit estimator for log(hazard). To determine whether lack of homogeneity between the different studies in the joint cohort influenced results, we used bootstrap analysis. As a measure for heterogeneity, we compared the original cohort specific 95% confidence intervals with those obtained from the multilevel bootstrap. We calculated the test performance indices for cytology alone, HPV test alone, and cytology and HPV test combined (at least one of the two positive). Because we did not have complete data for all four original baseline groups, we excluded studies from Denmark and Tübingen from these analyses. See bmj.com.



Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in the first 72 months of follow-up in all seven countries

RESULTS

Out of 24 295 women included in the pooled analyses, 381 developed histologically confirmed CIN3+ during six years' of follow-up. The positive predictive value for future CIN3+ was highest among women with abnormal cytology and positive HPV test at baseline (cytology+/HPV+) (cumulative incidence rate 34%, 95% confidence interval 26.8% to 45.4%) (figure). Women with normal cytology but positive HPV test (cytology−/HPV+) had a continuously increasing cumulative incidence rate of CIN3+, eventually reaching 10% (6.2% to 15.1%) after six years. Women with abnormal cytology and negative HPV test (cytology+/HPV−) had a cumulative incidence rate for CIN3+ of 2.7% (0.6% to 6.0%). Women with both normal cytology and negative HPV test (cytology−/HPV−) had a low risk of future CIN3+ (0.28%, 0.10% to 0.47%). We compared the cumulative incidence rate of CIN3+ after being cytology−/HPV− with that of CIN3+ for normal cytology alone and negative HPV test alone. At six years of follow-up, the rate of CIN3+ was significantly lower among women negative for HPV (0.27%, 0.12% to 0.45%) than among women with negative cytology results (0.97%, 0.53% to 1.34%). By comparison, the rate of CIN3+ at the most commonly recommended screening interval in Europe (three years) was 0.51% (0.23% to 0.77%)

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for women with negative cytology results and 0.12% (0.03% to 0.24%) for women negative for HPV. At five and four years of follow-up, the rates were 0.25% (0.12% to 0.41%) and 0.19% (0.08% to 0.32%) for women negative for HPV compared with 0.83% (0.50% to 1.13%) and 0.69% (0.39% to 0.98%) for women with negative cytology results. There was little difference in rates for CIN3+ between women with negative results on both tests and women negative for HPV. The rate for CIN3+ among women positive for HPV was lower than for women with abnormal results on cytology but increased continuously and gradually approached the rate of women with positive results on cytology.

As the prevalence of HPV infection is highly age dependent and as cytological performance also varies with age, we analysed positive and negative predictive values, sensitivity, and specificity of the screening tests stratified by age group. The sensitivity and negative predictive value of cytology improved with age. Both cytology and the HPV test had higher specificity for women above 35 years but did not improve any further among women above 49. See bmj.com.

The seven studies included in the pooled analyses had estimates of cumulative incidence rate for CIN3+ that were not significantly different among cytology−/HPV−, cytology−/HPV+, or cytology+/HPV− women (scale parameters: 2.48, 1.80, 2.23; P values 0.14, 0.36, 0.1). The cumulative incidence rate of CIN3+ among women with positive cytology and HPV test, however, was clearly different between studies (scale parameter 4.77; P=0.01). See bmj.com.

DISCUSSION

Using pooled data from seven HPV screening studies in six European countries we estimated a cumulative incidence rate for future histologically confirmed CIN3+ during six years of follow-up. The uniformly low rate among women with negative results on both cytology and HPV tests suggests that double negativity confers a long lasting protective effect that is remarkably robust, considering that the participating studies used several different types of HPV tests in several different settings and in several different age groups. The long lasting protective effect was similarly low in women negative for HPV.

That several studies in different settings in different countries and with different infrastructure and intensity of follow-up gave largely similar results is a strength of the study, as it implies that the data are generalisable to various settings. Similarly, that we studied the actual cytology tests used in the different countries also implies that the data are generalisable.

Consistency with other studies

Our results agree with the results from a US cohort of 20 810 women that found that cytology−/HPV− women had a cumulative incidence rate of CIN3+ of 0.16% after 45 months and 0.79% after 122 months.[4] Similarly, in a German cohort of 4034 women, 0.7% of cytology−/HPV− women developed CIN3+ during

Study characteristics of seven European human papillomavirus (HPV) screening studies

Study	No initially screened	No analysed*	Age	Entry criteria	HPV test	Follow-up†	Histology
Germany-Hannover	4699	4107	≥30	No history of abnormal smear result, CIN, or treatment for cervical disease in past year and not pregnant	HCII	If cytology+ or HPV+ immediate and annual colposcopy‡ for 5 years. 5% of cytology−/HPV− to colposcopy after 5 years	Blinded central review
Germany-Tubingen	672	670	≥30	No history of abnormal smear result, CIN, or treatment for cervical disease in past year and not pregnant	HCII	Cytology−/HPV− to new tests after 5 years and if either positive referred to colposcopy	Blinded central review
Sweden	6448	5671	32-38	Participating in organised screening	GP5+/6+ PCR	Cytology−/HPV+ invited for new test >1 year later, if persistent HPV+ referred to colposcopy. Similar number of women randomly referred to colposcopy. Database linked with regional pathology registries	Regional pathology labs§
Denmark	2287	2274	20-29	No current evidence of cervical neoplasia	HCII	Study data base linked with the National Pathology Registry	Regional pathology lab§
UK	2720	2322	≥35	No previous cervical treatment or abnormal smear result within past 3 years	SHARP-PCR, HCI, HCII	SHARP-PCR+ or cytology+ referred to colposcopy	Blinded central review
France	17 247	7935	No age limits	No abnormal smear result or untreated cervical lesion in past 2 years. Not HIV positive	HCII	If cytology−/HPV+ new tests after 6-12 months and if persistent HPV+ referred to colposcopy. 15% cytology −/HPV− referred to colposcopy	Blinded central review
Spain	2012	1316	Matched to general population	Population registry or attending screening	HCII	Follow-up tests 1 and 5 years later. Persistently HPV+ referred to colposcopy	Regional pathology lab§

HCII=hybrid capture II; CIN=cervical intraepithelial neoplasia; PCR=polymerase chain reaction.
*Women with at least one follow-up cytology or histology.
†Follow-up procedures performed in addition to routine clinical practice.
‡Assessment by colposcopy.
§Blinded to HPV status.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cervical screening with HPV testing is more sensitive for detection of cervical intraepithelial neoplasia grade 3 or cervical cancer (CIN3+)

Cost efficiencies of cervical screening strategies combining cytology with HPV testing depend on the duration of the protective effect of negative testing as this determines the optimal screening interval

WHAT THIS STUDY ADDS

A joint analysis of seven different studies in six European countries consistently found a low six year cumulative incidence rate of CIN3+ among women negative for HPV

Cervical screening strategies with HPV testing every six years is safe and effective

five years of follow-up,[5] and in a Dutch cohort of 2810 women there was only one case of CIN3+ among women with negative results on both tests during 4.6 years of follow-up.[9]

Limitations and other considerations

The HPV test was less specific than cytology. The higher specificity in women aged over 35 suggests that restricting HPV testing to older women would reduce overdiagnosis. With increasing length of follow-up, however, the cumulative incidence rate for CIN3+ increased more among women positive for HPV than among women with positive cytology results. This implies that the problem of HPV based screening resulting in increased overdiagnosis, with women unnecessarily referred for clinical procedures, is attenuated in evaluations with longer follow-up—some of the HPV positivity that seems to be false positivity in cross sectional evaluations will turn out to be true, but earlier, detection of CIN3+.

Nevertheless, as assessment of the incidence of CIN3+ by baseline group during follow-up depends on the intensity of screening our estimates should be interpreted as relative rather than absolute.[10] We included only women who had been screened at least once during follow-up, and the follow-up time was longer than the recommended screening intervals in all the included countries.[11]

As prevalence of CIN3+ is associated with prevalence of HPV some heterogeneity between studies might be explained by differences in prevalence of HPV. Another possible source of variability is the fact that five of the countries used hybrid capture II for HPV detection, while the Swedish study used polymerase chain reaction. However, the agreement between the two is substantial. The most obvious source of heterogeneity between countries was the variability in interpretation of cervical smear tests, as the proportions of positive cytology results ranged from 2% in Sweden to over 4% in Hanover and Spain, 5% in the UK, and 7% in France; these differences cannot be entirely explained by the observed differences in the prevalence of HPV.

In conclusion, these joint European data suggest that screening intervals could safely be lengthened to six years among women with a negative result on an HPV test. This could at least partly compensate for the increased referral rate resulting from HPV based screening strategies.

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Competing interests: K-UP has received speaker's honorarium from Digene and Roche and research grants from Digene; TI has received speaker's honorarium from Digene; JC is on the speaker's bureau of Digene and the advisory board for Roche and has received research grants from Roche; SK is on an advisory board for Merck and has received research grants from Merck and SPMSD; CM has received travel grants from Merck; SdeS has received travel grants from Digene and GSK and research grants from GSK and Merck/Sanofi Pasteur. The Department of Public Health of the Erasmus MC in Rotterdam, Netherlands, has received a research grant from GSK.

Ethical approval: All studies were approved by the ethical review boards in their respective countries.

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Prevalence of depression and anxiety in patients requesting physicians' aid in dying: cross sectional survey

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ABSTRACT

Objective To determine the prevalence of depression and anxiety in terminally ill patients pursuing aid in dying from physicians.

Design Cross sectional survey.

Setting State of Oregon, USA.

Participants 58 Oregonians, most terminally ill with cancer or amyotrophic lateral sclerosis, who had either requested aid in dying from a physician or contacted an aid in dying advocacy organisation.

Main outcome measures Diagnosis of depression or anxiety according to the hospital anxiety and depression scale and the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders.

Results 15 study participants met "caseness" criteria for depression, and 13 met criteria for anxiety. 42 patients died by the end of the study; 18 received a prescription for a lethal drug under the Death with Dignity Act, and nine died by lethal ingestion. 15 participants who received a prescription for a lethal drug did not meet criteria for depression; three did. All three depressed participants died by legal ingestion within two months of the research interview.

Conclusion Although most terminally ill Oregonians who receive aid in dying do not have depressive disorders, the current practice of the Death with Dignity Act may fail to protect some patients whose choices are influenced by depression from receiving a prescription for a lethal drug.

INTRODUCTION

In 1994 the voters of Oregon passed the Death with Dignity Act, which legalised the practice of physicians' aid in dying for terminally ill patients. This law authorises a physician to prescribe a lethal dosage of drug, usually a short acting barbiturate, to a competent, requesting patient for the purposes of self administration.[1] Several safeguards in the law ensure that patients are adult, competent, terminally ill, and choosing to end life voluntarily but not impulsively (box).

For people at the end of life, depression, hopelessness, and psychosocial distress are among the strongest correlates of desire for hastened death.[2-9] Physicians, hospice professionals, and family members of patients in Oregon who pursue aid in dying generally do not believe that depression influences choices for hastened death.[10-12] In 2007 none of the people who died by lethal ingestion in Oregon had been evaluated by a psychiatrist or a psychologist.[1] Healthcare professionals, however, often fail to recognise depression, particularly among medically ill patients.[13-15] The goal of this study was to determine the prevalence and severity of psychological distress, including major depressive disorder, in Oregonians who request aid in dying.

METHODS

We used several sources to notify patients of the opportunity to participate in our study (see bmj.com). The study psychologist (ERG) administered all measures in the participant's home, including the hospital anxiety and depression scale and the current mood disorder section of the structured clinical interview for American Psychiatric Association Diagnostic and Statistical Manual-IV axis I disorders (SCID-I), a standard research instrument for diagnosing mental disorders.[16 17] The SCID interview was audiotaped and the tapes were reviewed by a research psychiatrist (SKD) who did not know if the patient had requested aid in dying (19 audiotapes from terminally ill patients who had not requested aid in dying were randomly interspersed). Based on studies by Chochinov and colleagues,[18] the severity of depressed mood or anhedonia needed to be at least moderate for the two weeks before the interview in order to reach the threshold for diagnosis.

We obtained information on outcomes—whether the study participant received a prescription of a lethal drug or died by lethal ingestion—six months or more after all other data collection was complete. See bmj.com for more details of methods.

RESULTS

The mean age of the 58 patients requesting aid in dying was 66 (SD 12) years. Thirty one participants were women, 22 were married, and 21 were enrolled in a hospice at the time of the interview. The most common terminal diseases were cancer (n=44) and amyotrophic lateral sclerosis (n=7). At the time of the study interview 46 patients had explicitly requested aid in dying from a physician and 47 had contacted Compassion and Choices to obtain information about aid in dying.

Fifteen participants met our criteria for depression by being depressed on the SCID or having a hospital anxiety and depression scale depression score of 11 or higher. The mean desire to die among depressed participants was 5.7 (SD 3.0) on our 11 point scale. Seven of the depressed group did not attribute their pursuit of aid in dying to depression at all (score=1), but six felt that depression somewhat or strongly influenced their preference for hastened death (scores=3, 4, or 5). An offer to facilitate counselling was made to all depressed patients, but only one participant (patient C below) agreed.

Among the 42 participants who died by the end of the study, 18 received a prescription for a lethal drug and

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Legal requirements of the Oregon Death with Dignity Act[1]

The attending physician who is responsible for care of the patient's terminal illness must ensure that:

- The patient is aged 18 years or above
- The patient is a resident of the state of Oregon
- The patient has made one written and two oral requests separated by 15 days
- The patient understands the risks of aid in dying and the alternatives, including hospice and comfort care
- The patient is assessed by a consulting physician
- Information about the patient is reported to the Oregon Department of Human Services

The attending and consulting physicians must ensure that:

- The patient is capable of making and communicating healthcare decisions
- The decision is voluntary
- The patient has a terminal illness that would, within reasonable medical judgment, cause death within six months
- The patient is referred to a psychologist or psychiatrist if concern exists that the patient has a psychiatric disorder including depression that may impair judgment

Information from statistical reports is compiled by the Oregon Department of Human Services and published yearly[1]

nine died by lethal ingestion. Among decedents, no significant differences existed between those who received a prescription for a lethal drug and those who did not on measures of psychosocial distress, except that those who received a prescription had (surprisingly) a lower desire to die and a trend toward lower hopelessness scores (table 1).

Three of the 18 participants who received a prescription for a lethal drug met our criteria for depression on either the SCID or hospital anxiety and depression scale (table 2), and 15 did not. All three died by lethal ingestion in their home within two months of the interview. None had been evaluated by a mental health professional before participation in the research (see bmj.com).

Table 1 | Comparison of deceased participants who received and did not receive prescription for lethal drug. Values are mean (SD) unless stated otherwise

Measure	Received prescription (n=18)	Did not receive prescription (n=22)	P value (*t* test)
Hospital anxiety and depression scale—anxiety*	4.8 (3.2)	7.0 (5.1)	0.12
Hospital anxiety and depression scale—depression†	5.7 (3.4)	7.3 (4.4)	0.19
Hospital anxiety and depression scale—total‡	10.5 (5.4)	14.3 (8.6)	0.10
Beck hopelessness scale§	5.0 (3.0)	7.5 (5.4)	0.08
Desire to die¶	1.5 (2.6)	4.7 (3.7)	0.004
Suffering**	3.7 (2.7)	4.5 (2.9)	0.36
Quality of life††	4.0 (1.8)	5.1 (2.9)	0.13

*Scores range from 0 (no anxiety) to 21 (severe anxiety).[16]
†Scores range from 0 (no depression) to 21 (severe depression).[16]
‡Sum of anxiety and depression scales.[16]
§Scores range from 0 (not hopeless) to 20 (very hopeless).[19]
¶11 point scale: 0=I desire to live as long as possible; 10=I have a strong desire to die soon.
**11 point scale: 0=I have not suffered in the past two weeks; 10=I have suffered severely in the past two weeks.[20]
††11 point scale: 0=quality of life in past two weeks is as good as it can be; 10=quality of life in past two weeks is terrible, very bad.

DISCUSSION

Among patients who requested a physician's aid in dying, one in four had clinical depression. However, more than three quarters of people who actually received prescriptions for lethal drugs did not have a depressive disorder. Our findings also indicate that the current practice of legalised aid in dying may allow some potentially ineligible patients to receive a prescription for a lethal drug; two of those who ultimately died by lethal ingestion had depression at the time they received a prescription for a lethal drug and died by ingesting the drug. A third patient was depressed at the time that she requested a physician's aid in dying and probably received her prescription; she was successfully treated for her depression before she died by lethal ingestion.

Strengths and limitations

Although many investigators have examined the degree to which depression is associated with a desire to die among terminally ill patients,[2-9] we believe that our study is the first to use standardised measures to examine the prevalence and severity of depression and anxiety in a group of patients who have actually requested and are potentially eligible to receive aid in dying.

Use of an inclusive approach to categorise somatic symptoms, which, if present, were attributed to depression and not to terminal disease, carries the risk of inflating the prevalence of depressive disorder. In addition, only 28% of invited patients who requested aid in dying agreed to participate; uncertainty exists about the degree to which our data are generalisable to the entire population of patients who request physicians' aid in dying.

The possibility remains that the three depressed patients who died by lethal ingestion satisfied the requirements of the Death with Dignity Act if the attending physician determined that depression was present but not influencing their judgment. Although diagnosing depression can be relatively straightforward, determining its role in influencing decision making is more difficult, even by expert assessment.

Depression and desire for death

Physicians in Oregon who received requests for aid in dying from 143 patients after enactment of the Death with Dignity Act reported that 20% were depressed—a proportion comparable to what we found in this study. None of the depressed patients on whom they submitted information received a prescription for a lethal drug.[21] Our study suggests that in some cases depression is missed or overlooked.

In contrast, studies of interest in euthanasia from populations outside of Oregon suggest that depression and psychosocial distress are prominent among patients who endorse an interest in hastened death. For example, in a study of 200 terminally ill inpatients

Table 2 | Measures of psychological distress in depressed participants who received a physician's aid in dying

Measure	Case A	Case B	Case C
SCID depression*	–	+	+
Hospital anxiety and depression scale—anxiety†	7	4	8
Hospital anxiety and depression scale—depression‡	12	10	9
Hospital anxiety and depression scale—total§	19	14	17
Beck hopelessness scale¶	9	NA	9
Desire to die**	6	8	5
Suffering††	4	8	5
How much depressed mood influenced decision‡‡	1	1	3

NA=not available; SCID=structured clinical interview for American Psychiatric Association Diagnostic and Statistical Manual-IV
*+ indicates major depressive disorder present; – indicates major depressive disorder absent.[17]
†Scores range from 0 (no anxiety) to 21 (severe anxiety).[16]
‡Scores range from 0 (no depression) to 21 (severe depression).[16]
§Sum of anxiety and depression subscales.[16]
¶Scores range from 0 (not hopeless) to 20 (very hopeless).[19] Case B declined to complete this scale.
**11 point scale: 0=I desire to live as long as possible; 10=I have a strong desire to die soon.
††11 point scale: 0=I have not suffered in the past two weeks; 10=I have suffered severely in the past two weeks.[20]
‡‡1=depressed mood not at all important in decision to request prescription; 5=depressed mood very important in decision to request prescription.

with cancer, the prevalence of depressive syndromes was 59% among patients with a serious and pervasive desire to die but only 8% among patients without such a desire.[6]

Whether findings from these patient groups can be extrapolated to patients who have actively requested legal physicians' aid in dying has remained uncertain—although 17% of Oregonians are potentially interested in aid in dying, only 1-2 % actually request it.[21,22] Our surveyed participants had taken active steps to pursue a physician's aid in dying in one of the few jurisdictions where it is legal.

Conclusions

Our results suggest that most patients who request aid in dying do not have a depressive disorder. However, the current practice of the Death with Dignity Act in Oregon may not adequately protect all mentally ill patients, and increased vigilance and systematic examination for depression among patients who may access legalised aid in dying are needed. Tools for screening for depression such as those used in our study are easy to administer and may help to determine which patients need further evaluation by a mental health professional. Further study is needed to determine the effect of treatment of depression on the choice to hasten death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The state of Oregon legalised physicians' aid in dying in 1997

Physicians, hospice professionals, and family members of patients who request a lethal drug do not believe that depression is an important reason why patients pursue aid in dying

WHAT THIS STUDY ADDS

Among terminally ill Oregonians who participated in our study and received a prescription for a lethal drug, one in six had clinical depression

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Retrospective analysis of hospital episode statistics, involuntary admissions under the Mental Health Act 1983, and number of psychiatric beds in England 1996-2006

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ABSTRACT

Objective To analyse the number of voluntary and involuntary (detentions under the Mental Health Act 1983) admissions for mental disorders between 1996 and 2006 in England.

Design Retrospective analysis.

Setting England.

Main outcome measures Number of voluntary and involuntary admissions for mental disorders in England's health service, number of involuntary admissions to private beds, and number of NHS beds for patients with mental disorders or learning disabilities.

Results Admissions for mental disorders in the NHS in England peaked in 1998 and then started to fall. Reductions in admissions were confined to patients with depression, learning disabilities, or dementia. Admissions for schizophrenic and manic disorders did not change whereas those for drug and alcohol problems increased. The number of NHS psychiatric beds decreased by 29%. The total number of involuntary admissions per annum increased by 20%, with a threefold increase in the likelihood of admission to a private facility. Patients admitted involuntarily occupied 23% of NHS psychiatric beds in 1996 but 36% in 2006.

Conclusions Psychiatric inpatient care changed considerably in the decade from 1996 to 2006, with more involuntary admissions to fewer NHS beds. The case mix has shifted further towards psychotic and substance misuse disorders, which has changed the milieu of inpatient wards. Increasing proportions of involuntary patients were admitted to private facilities.

INTRODUCTION

Between 1955 and 1995 deinstitutionalisation resulted in the number of beds for mental illness and learning disability in England's health service (NHS) decreasing from over 150 000[1] to fewer than 55 000. Although some evidence suggests that crisis teams and services for early intervention in psychosis can reduce the number of admissions for mental disorders compared with traditional psychiatric provision,[2 3] one study[4] found that crisis teams reduce the number of voluntary admissions but not involuntary admissions—detentions under the Mental Health Act 1983. Observers are debating whether a new era of reinstitutionalisation has begun.[5]

We examined changes in the number of psychiatric admissions in England from 1996 to 2006, explored any associations between reductions in NHS bed numbers and involuntary admission rates, and calculated the proportion of involuntary inpatients being treated in non-NHS facilities.

METHODS

We submitted a request to the NHS Information Centre for data on admissions to NHS hospitals in England from hospital episode statistics. We obtained information on admissions for all mental and behavioural disorders (codes F00-F99, international classification of diseases, 10th revision). To estimate the number of psychiatric beds we combined data on the number of available mental illness and learning disability beds from hospital activity statistics.[6]

Cross sectional data on numbers of involuntary inpatients in NHS hospital and private facilities on 31 March each year were derived from the Department of Health.[7] We calculated the total number of involuntary admissions per annum by combining the numbers of patients detained under the Mental Health Act—civil, forensic (patients involved in criminal proceedings), and place of safety. Patients whose status changed (from place of safety to civil) were included only once, in the estimates for place of safety. The "count me in census" (the number of patients admitted for mental disorders in NHS and independent hospitals in England and Wales counted on one day each year) provided data on ethnicity of voluntary and involuntary psychiatric inpatients on 31 March 2006. We carried out statistical analyses using Pearson correlations.

RESULTS

Admissions to NHS hospitals for mental disorders peaked in 1998, at 214 326. Over the study period from 1996 to 2006, yearly admissions declined by 11%, from 207 050 to 183 699. The reductions were confined to three subpopulations (figure): patients with learning disabilities (admission decreased by 58%), unipolar depression (33%), or dementia (28%). Since 2003, admissions for drug and alcohol related disorders increased by 29%, whereas admissions remained relatively stable for other groups—for example,

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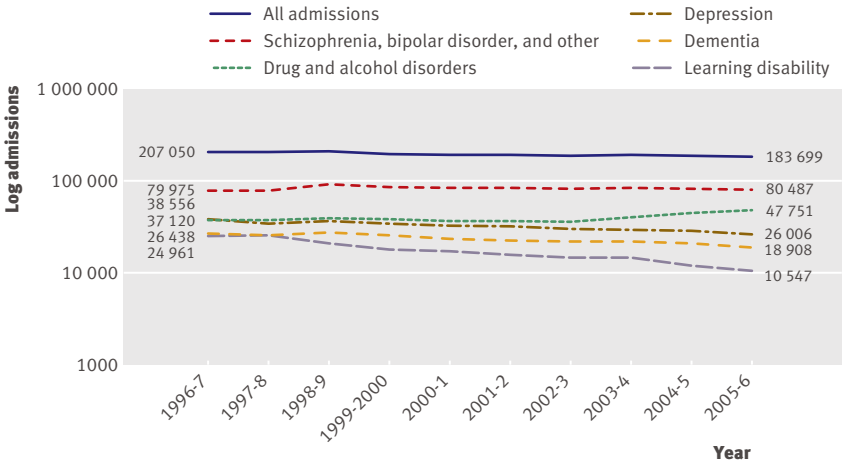

Changes in admission rates (on logarithmic scale) to NHS hospitals for different diagnostic groups of mental disorders, 1996-2006

30 639 patients were admitted for schizophreniform disorders in 1996 compared with 30 852 in 2006.

Over the decade the total number of involuntary admissions per annum increased by 20%, from 42 844 to 51 361; the number of civil detentions increased by 13%, from 38 938 to 43 820, and place of safety detentions increased by 189%, from 2037 to 5877, whereas forensic detentions decreased by 11%, from 1873 to 1664. The table shows that on 31 March each year the number of involuntary inpatients in hospital increased by 27%, from 11 500 to 14 625, with noticeable increases in the numbers admitted to private facilities compared with NHS facilities (256% *v* 12%). The odds of an involuntary patient being admitted to hospital in a private facility increased threefold (odds ratio 3.2, 95% confidence interval 2.9 to 3.5), from 0.06 to 0.21 (700/10 800 patients *v* 2493/ 12 132).

As the number of psychiatric beds decreased by 29% (47 333 to 33 729), the proportion of NHS beds occupied by involuntary patients increased, from 23% to 36% (table). A negative correlation was seen between the number of NHS beds and the number of involuntary patients in private facilities ($r=-0.98$, $P<0.001$) or in NHS facilities ($r=-0.64$, $P=0.046$).

The "count me in census" on 31 March 2006 identified 30 023 patients with mental disorders in NHS hospitals and 4262 in private facilities in England; 40% of NHS inpatients compared with 58% of private inpatients were involuntary. Ethnic minority groups comprised 21% of NHS inpatients, 19% of private inpatients, and 28% of all involuntary inpatients.

DISCUSSION

The number of involuntary admissions for mental disorders in England per annum increased by 20% from 1996 to 2006, whereas the total number of admissions and number of NHS psychiatric beds decreased. Reductions in admissions have largely been confined to patients with depression, learning disability, or dementia. The increase in numbers of involuntary inpatients has been most noticeable in private facilities: in 1996-7 involuntary patients were 15 times more likely to be in an NHS facility than a private facility, but by 2006 only five times more likely.

Limitations of the study are that findings only apply to England and most data sources warned of difficulties in comparing year on year estimates—a problem likely to be amplified by our comparisons across databases. That the data derived from disparate sources indicate similar trends, however, suggests that we are observing real changes in inpatient activity.

These findings support previous studies showing an increase in number of involuntary admissions[8 9] against a background of reductions in numbers of NHS beds. Psychotic and affective disorders account for over 50% of all NHS occupied psychiatric bed days in England; but changes in acute admissions were primarily accounted for by reductions in voluntary admissions for depression, a group with the shortest length of stay (data available on request). Although this may reflect the redirection of patients with depression to crisis teams, the impact on acute inpatient wards has been dramatic, with shifts in case mix (toward psychoses and drug and alcohol misuse) and extended lengths of stay (involuntary inpatients).

The increase in number of involuntary admissions to private facilities is noteworthy as the NHS purchases

Number of beds for mental illness and learning disability, and number of involuntary inpatients between 1996 and 2006, in England

Variable	1996-7	1997-8	1998-9	1999-2000	2000-1	2001-2	2002-3	2003-4	2004-5	2005-6	% change	Pearson correlation*
No of NHS beds for mental disorders and learning disability	47 333	44 798	43 183	41 007	40 530	38 477	37 791	37 464	35 701	33 729	29% reduction	—
Involuntary inpatients on 31 March:												
No in NHS facilities	10 800	11 800	11 823	11 473	12 150	11 566	11 589	11 708	12 148	12 132	12% increase	r=−0.64; P=0.046
No in private facilities	700	850	1170	1382	1679	1893	1999	2292	2533	2493	256% increase	r=−0.98; P<0.001
Total No	11 500	12 700	12 993	12 855	13 829	13 459	13 588	14 000	14 681	14 625	27% increase	r=−0.94; P<0.001
% of NHS beds occupied by involuntary inpatients†	23	26	27	28	30	30	31	31	34	36	—	—

*Correlation with number of NHS beds for mental disorder and learning disability.
†Number of involuntary patients in NHS facilities on 31 March divided by number of NHS beds for mental disorders and learning disability and multiplied by 100.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Rates of involuntary admissions under the Mental Health Act 1983 increased in the 1980s and '90s

The number of psychiatric beds in the NHS has been decreasing since the 1950s

WHAT THIS STUDY ADDS

The number of patients admitted to the NHS with mental disorders peaked in 1998 and is now decreasing

The number of psychiatric beds in the NHS has continued to fall and rates of involuntary admissions have continued to rise

A greater proportion of psychiatric inpatients are now involuntary and are being treated in private facilities

about 80% of private psychiatric provision. One of the largest growth areas has been in the provision of private medium secure beds even though NHS forensic facilities have expanded. The decrease in forensic involuntary admissions is therefore surprising. A question for further research is whether the changes identified in this study have applied across demographic and diagnostic groups and NHS regions for the duration of the Mental Health Act 1983.

Conclusions

Psychiatric inpatient care changed considerably from 1996 to 2006, with more involuntary patients admitted to fewer NHS beds and increasing proportions of involuntary patients admitted to private facilities. The decrease in acute general adult admissions has been confined to voluntary patients with depression. The inpatient case mix has shifted further towards psychotic and substance misuse disorders, which has changed the milieu on inpatient psychiatric wards.

Reuse of information from the "count me in census" and other datasets was covered by the public sector information licence held by Newcastle University.

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A curious thing

Many of us who have had an influenza infection will know that we aren't at our sharpest mentally when ill with flu. So, when I and other psychiatry researchers were invited by virology colleagues to test this hypothesis, we jumped at the opportunity. Twenty healthy volunteers were quarantined for 10 days and infected with influenza virus. We administered a number of validated neuropsychological tests assessing various aspects of memory and concentration before and after exposure to the virus.

So far, so good. However, when we came to analyse the results we were very surprised: most subjects performed better after exposure to influenza than before. For example, the story recall test required the participants to recount a lengthy multipart story immediately and then again later. A significant decay in the score is the norm, but our volunteers performed better on delayed recall in the post-exposure tests. How was this possible?

As the volunteers were quarantined, we had no access to them during the study. However, the answer to the conundrum became apparent when we spoke to the research assistants who had been locked in with the volunteers. Being bored, cooped up away from the world, and yet curious as to what "those psychiatrists" were up to, the volunteers had joined forces and, as a group, tried to remember as much of the story as possible before re-testing. They knew from the pre-exposure assessments (when a different version of the story recall test was given to them) that they would be required to recount the story they had been told earlier.

As psychiatrists, we had underestimated human nature —the influence of boredom, curiosity, the Hawthorne effect (improved performance when tasks are observed by others),[1] and a social desirability bias on how people behave. Perhaps we had inadvertently conducted an elegant covert social psychology experiment rather than a poorly designed psycho-immunology study.

We were minded of the following quote: "The cure for boredom is curiosity. There is no cure for curiosity" (Dorothy Parker (1893-1967), US author and humorist).

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