Health related quality of life after combined hormone replacement therapy: randomised controlled trial

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ABSTRACT

Objective To assess the effect of combined hormone replacement therapy (HRT) on health related quality of life.

Design Randomised placebo controlled double blind trial.

Setting General practices in United Kingdom (384), Australia (94), and New Zealand (24).

Participants Postmenopausal women aged 50-69 at randomisation; 3721 women with a uterus were randomised to combined oestrogen and progestogen (n=1862) or placebo (n=1859). Data on health related quality of life at one year were available from 1043 and 1087women, respectively.

Interventions Conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5/5.0 mg or matched placebo orally daily for one year.

Main outcome measures Health related quality of life and psychological wellbeing as measured by the women's health questionnaire. Changes in emotional and physical menopausal symptoms as measured by a symptoms questionnaire and depression by the Centre for Epidemiologic Studies depression scale (CES-D). Overall health related quality of life and overall quality of life as measured by the European quality of life instrument (EuroQol) and visual analogue scale, respectively.

Results After one year small but significant improvements were observed in three of nine components of the women's health questionnaire for those taking combined HRT compared with those taking placebo: vasomotor symptoms (P<0.001), sexual functioning (P<0.001), and sleep problems (P<0.001). Significantly fewer women in the combined HRT group reported hot flushes (P<0.001), night sweats (P<0.001), aching joints and muscles (P=0.001), insomnia (P<0.001), and vaginal dryness (P<0.001) than in the placebo group, but greater proportions reported breast tenderness (P<0.001) or vaginal discharge (P<0.001). Hot flushes were experienced in the combined HRT and placebo groups by 30% and 29% at trial entry and 9% and 25% at one year, respectively. No significant differences in other menopausal symptoms, depression, or overall quality of life were observed at one year.

Conclusions Combined HRT started many years after the menopause can improve health related quality of life.

Trial registration ISRCTN 63718836.

INTRODUCTION

The perception of the risks and benefits of hormone replacement therapy (HRT) has changed since the women's health initiative trial in 2002.[1] It did not find long term benefits on cardiovascular outcomes in women at an average of 13 years after menopause, and the impact of HRT on patient centred outcomes was questioned.[2 3] It reported a significant benefit of combined oestrogen and progestogen (combined HRT) in health related quality of life related to sleep disturbance, physical functioning, and bodily pain, but the differences were small, and for conjugated equine oestrogen no effect was found in women who had had a hysterectomy.[3] The smaller heart and oestrogen/progestin replacement study (HERS) found that menopausal symptoms modified the effect of HRT on health related quality of life.[4]

The women's international study of long duration oestrogen after the menopause (WISDOM) aimed to evaluate the long term benefits and risks of HRT. WISDOM was a placebo controlled, double blind randomised trial of HRT in postmenopausal women. It aimed to randomise 22 300 postmenopausal women aged 50-69 from primary care in the United Kingdom, Australia, and New Zealand to HRT or placebo for a median of 10 years. Recruitment began in 1999 and continued until October 2002, when the trial was closed after the announcement that the women's health initiative had been terminated early because the risks of combined HRT seemed to outweigh the benefits.[1]

We present findings from WISDOM for women with an intact uterus or subtotal hysterectomy who were randomised to combined HRT or placebo, focusing on health related quality of life measured at one year follow-up using both condition specific measures designed specifically for postmenopausal women and generic measures.

METHODS

Full details of the protocol, methods, and study participants are described elsewhere.[5-7] Combined HRT was oral conjugated equine oestrogen 0.625 mg daily, plus oral medroxyprogesterone acetate 2.5/5.0 mg daily. The trial was designed to treat participants for a median of 10 years with scheduled visits at four

weeks, 14 weeks, 27 weeks, 40 weeks, and 52 weeks, with annual visits thereafter. All participants were encouraged to continue attending annual interviews whether or not they had stopped taking study treatment. This report is limited to data collected a year after randomisation.

Outcome measures—We used a modified version of the women's health questionnaire, designed to assess physical and emotional wellbeing in middle aged women. We assessed the prevalence of individual symptoms related to menopause in the past four weeks using a 28 item symptom questionnaire. Depression was assessed with the Center for Epidemiologic Studies depression scale (CES-D). We used the European quality of life instrument (EuroQoL) which consists of the EQ visual analogue scale (EQ-VAS) and an overall health classification index (EQ-5D). All measures were administered at baseline and at annual visits. See bmj.com.

Statistical analysis—Treatments were compared with multiple or logistic regression analyses, including the measure of interest at baseline as a covariate to adjust for any differences between treatment groups at baseline. We evaluated the possible modifying effect of baseline vasomotor symptoms on effects of treatment at one year in health related quality of life by fitting an interaction term(s). Significance of the effect of combined HRT on individual outcomes at one year was judged by Bonferroni correction. Interaction tests were performed only if we identified a significant main effect and were used only to look at associations with baseline vasomotor symptoms.

RESULTS

At the end of the trial 3721 women with an intact uterus or subtotal hysterectomy had been randomised, 1862 to combined HRT and 1859 to placebo.[6] We excluded women who had been in the trial less than 40 weeks at trial closure in October 2002 or who had died within one year of randomisation (671 combined HRT; 666 placebo). Of the remainder, 148 and 106 women randomised to combined HRT and placebo, respectively, did not attend their one year interview and cannot contribute to the primary analyses. Mean age at randomisation in the 2130 women in the primary analyses was 63.8 years (SD 4.4). The median time between randomisation and one year interview was 368 days (90% interviews were 331-456 days after randomisation), and 21% of one year interviews (21% combined HRT; 20% placebo) were completed after trial closure.

At the first annual medical 290 (28%) women randomised to combined HRT were no longer taking trial treatment (214 had stopped permanently and 76 were on a temporary interruption of treatment). Of the 214 who stopped combined HRT permanently, 91 did so in the first 14 weeks and 177 did so in the first 27 weeks. Overall, trial treatment was supplied for 79% of follow-up time between randomisation and first annual medical. Correspondingly, at the first annual medical, 141 (13%) in the placebo group were not taking trial treatment (89 had stopped permanently; 52 were on a temporary interruption); trial treatment was supplied for 92% of follow-up time. The most common reasons for permanent discontinuation of combined HRT were vaginal bleeding (68/214, 32%) and breast tenderness (28/214, 13%). Of the patients who were not taking trial treatment at the first annual medical, 174 (60%) in the combined HRT group and 10 (7%) in the placebo group had previously reported bleeding to some degree, including spotting. Of those taking trial treatment at one year, 265 (37%) in the combined HRT group had reported bleeding at some time during the first year, including 65 (9%) since their last visit. Corresponding proportions in the placebo group were 36 (4%), including 9 (1%) since their last visit.

We reviewed the data on the women who did not attend their one year interview and therefore could not be included in the primary analyses. Most were known to have discontinued trial treatment. Again, the most common reasons for permanent discontinuation of combined HRT were vaginal bleeding (42/118, 36%) and breast tenderness (13/118, 11%.).

Women's health questionnaire—Participants in the combined HRT group experienced significant improvements in vasomotor symptoms compared with the placebo group at one year (table). Treatment differences were more marked in those with more severe baseline symptoms (P<0.001). Participants also reported significant improvements related to sexual functioning, and sleep problems. There was no evidence for a difference in treatment benefit by baseline vasomotor symptoms for sleep problems (P=0.78) or sexual function at one year (P=0.78).

Menopausal symptoms—At one year, with adjustment for differences at baseline, participants randomised to combined HRT experienced fewer vasomotor symptoms, including hot flushes (9% *v* 25%, P<0.001) and night sweats (14% *v* 23%, P<0.001) than those randomised to placebo. They were also less likely to report symptoms of aching joints and muscles (57% *v* 63%, P=0.001), insomnia (35% *v* 41%, P<0.001), and vaginal dryness (14% *v* 19%, P<0.001). Bloating was marginally less prevalent in the combined HRT group than the placebo group (21% *v* 24%, P=0.005), but significance was not achieved when we allowed for multiple testing. The combined HRT group reported higher rates of breast tenderness (16% *v* 7%, P<0.001) and vaginal discharge (14% *v* 5%, P<0.001) than the placebo group. The benefit of combined HRT was greater in those who had hot flushes or night sweats at baseline. The impact of combined HRT on other symptoms (aching joints and muscles, insomnia, vaginal dryness, breast tenderness, or vaginal discharge) did not vary according to baseline vasomotor symptoms (see bmj.com).

Depression—Assessment of depression with the CES-D at one year showed no significant difference between the combined HRT (median 3, interquartile range 0-7) and placebo groups (median 3, 1-8; P=0.51 for difference, adjusted for baseline score) and no difference in the proportion of individuals who

Mean (SE) scores on health related quality of life as measured with women's health questionnaire by treatment group

Component	Baseline		One year		Adjusted† difference at one year (95% CI)	P value
	Combined HRT (n=1043*)	Placebo (n=1087*)	Combined HRT (n=1043*)	Placebo (n=1087)*		
Depression	0.803 (0.004)	0.797 (0.004)	0.803 (0.004)	0.805 (0.004)	0.00 (−0.01 to 0.01)	0.39
Somatic	0.755 (0.006)	0.764 (0.006)	0.775 (0.006)	0.781 (0.006)	0.00 (−0.02 to 0.01)	0.80
Memory	0.730 (0.010)	0.721 (0.009)	0.759 (0.009)	0.757 (0.009)	0.00 (−0.02 to 0.02)	0.88
Vasomotor	0.766 (0.012)	0.771 (0.011)	0.926 (0.007)	0.833 (0.010)	0.09 (0.07 to 0.12)	‹0.001‡
Anxiety	0.882 (0.006)	0.882 (0.006)	0.894 (0.006)	0.904 (0.006)	0.00 (−0.02 to 0.00)	0.18
Sexual	0.679 (0.012)	0.679 (0.013)	0.764 (0.0110	0.721 (0.012)	0.05 (0.02 to 0.08)	‹0.001‡
Sleep	0.637 (0.010)	0.657 (0.010)	0.740 (0.009)	0.703 (0.009)	0.05 (0.02 to 0.07)	‹0.001‡
Menstrual	0.906 (0.005)	0.905 (0.005)	0.905 (0.005)	0.907 (0.005)	0.00 (−0.01 to 0.01)	0.77
Esteem	0.546 (0.004)	0.544 (0.004)	0.559 (0.004)	0.553 (0.004)	0.00 (−0.01 to 0.02)	0.40

*No in each group at each time point for any measure except sexual function (n=591 for combined HRT group (588 at one year) and 580 for placebo group (569 at one year) for women who attended interview).
†Adjusted for baseline score.
‡Significant at Bonferroni corrected α level of 0.001; actual unadjusted P values presented.

experienced high depressive scores (CES-D >16 units) between the two treatment groups (8% *v* 9%; P=0.51, adjusted for baseline).

Quality of life—There were no differences in self assessed health measured by the EQ visual analogue scale at one year follow-up. Participants randomised to combined HRT had a marginally higher health classification index score compared with those randomised to placebo (difference between treatment groups adjusted for baseline score 0.016 units, 95% confidence interval 0.003 to 0.028, P=0.02) but the difference was not significant when we applied the Bonferroni correction.

Generic visual analogue scale—At four weeks women in the combined HRT group had a slightly lower overall quality of life than those in the placebo group (difference, adjusted for baseline values, −1.6 units, −2.7 to −0.4, P=0.006). This difference was reduced at 14 weeks (P=0.03), and there were no differences between the combined HRT and the placebo groups after 14 weeks. We lacked power to investigate the extent to which the early reduction in visual analogue score associated with combined HRT declined because women who experienced a negative impact of combined HRT on quality of life stopped trial treatment early.

DISCUSSION

In this randomised controlled trial women who started taking combined HRT many years after menopause experienced improved sleep and reduced vasomotor symptoms. They also reported fewer aching joints and muscles, less vaginal dryness, and improved sexual functioning, but breast tenderness and vaginal discharge increased. The beneficial changes in sleep and sexual functioning were independent of the presence of baseline vasomotor symptoms. For most other condition specific measures there were no differences between placebo and combined HRT groups.

These improvements in health related quality of life for postmenopausal women were detected only by using the outcome specific women's health questionnaire and a symptoms questionnaire. The improvements seen in WISDOM are consistent with results from the women's health initiative, showing improvement in vasomotor symptoms, sleep, and bodily pain after one year of combined HRT.[2] Self reported sleep problems have been associated with both the perimenopause and postmenopause. Aches and stiff joints are commonly reported by menopausal women, and self reported arthritis is associated with menopausal status.[8]

For women taking combined HRT there was a significant improvement on the three item sexual functioning domain of the menopause specific women's health questionnaire. The result is consistent with the recent findings from the COGENT study, a randomised controlled trial using combined HRT for four months.[9]

Neither WISDOM nor the women's health initiative found an effect of combined HRT on depression measured by CES-D. It is possible that any antidepressant effect of oestrogen seen in women at or near the menopause might be related to reduction of menopausal symptoms.

Weaknesses of study

Loss to follow-up and considerable discontinuation of study medication, particularly in the combined HRT group, might have introduced selection bias. Because of premature closure of the trial around 36% of women in both treatment groups had not reached 40 weeks of treatment at closure and were excluded from all analyses in this paper. One year data were not available for 12% of women randomised to combined HRT and 9% of women randomised to placebo at least 40 weeks before trial closure. Most participants who did not attend a one year interview had stopped study treatment, so it is likely that their inclusion in an intention to treat analysis would have reduced the treatment effects we observed. Non-attenders at one year, however, might have had a different symptom profile and overall quality of life than attenders, and therefore some degree of selection bias is possible.

Participants who attended a one year interview but were no longer taking treatment in the combined HRT

WHAT IS ALREADY KNOWN ON THIS TOPIC

Combined HRT has a small but significant benefit in health related quality of life related to sleep disturbance, physical functioning, and bodily pain

Menopausal symptoms increase the effect of combined HRT on health related quality of life: women with flushing experienced improvements in health related quality of life related to emotional measures

WHAT THIS STUDY ADDS

Combined HRT started many years after menopause is associated with improvements in vasomotor symptoms, sexual function, sleep disturbance, aching joints and muscles, insomnia, and vaginal dryness but more women experience breast tenderness and vaginal discharge

Aching joints and muscles, insomnia, and vaginal dryness improve independently of whether participants experience vasomotor symptoms at baseline

Combined HRT improves condition specific but not overall generic measures of health related quality of life at one year

group experienced more side effects early in the trial than those who stayed on treatment, specifically bleeding and breast tenderness. Many similar combined HRT regimens are associated with early bleeding that mostly disappears over the first months of treatment. Overall, the effect of early bleeding and breast tenderness with combined HRT, causing women to preferentially discontinue treatment, might largely explain the reduction in quality of life as assessed by the visual analogue scale score at 4 and 14 weeks of treatment. Even in those women who kept taking treatment, however, there was a small, non-significant drop in quality of life at four weeks in the combined HRT group compared with placebo, suggesting a small true early adverse effect. Our study lacked power to show whether the effect differs in those who keep taking treatment and those who stop. In the placebo group some of those who stopped study medication might have started HRT outside the trial, although of the 89 patients on placebo who stopped taking trial treatment permanently, only five did so because they wanted to take HRT. See bmj.com for fuller discussion.

Relevance of findings

When women start combined HRT many years after the menopause they must balance the risk of increased cardiac events, venous thromboembolism, and breast cancer against possible benefits on health related quality of life.[1 7] They must also consider possible early side effects of combined HRT such as breast tenderness and uterine bleeding, which usually resolve with time or dose titration.[7]

Our results should be interpreted with caution, as the presence of statistical significance does not imply clinical significance. There is much background literature and guidelines that support the premise that women with debilitating menopausal symptoms will have the most benefit in health related quality of life from treatment with combined HRT.[10 11] This is an important message to convey to women with severe menopausal symptoms. Additionally, for younger women, recent data suggest a more favourable risk profile for combined HRT when it is started within a few years of menopause compared with many years after.[12-14]

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Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial

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ABSTRACT

Objective To determine the effects of low dose aspirin on cognitive function in middle aged to elderly men and women at moderately increased cardiovascular risk.

Design Randomised double blind placebo controlled trial.

Setting Central Scotland.

Participants 3350 men and women aged over 50 participating in the aspirin for asymptomatic atherosclerosis trial.

Intervention Low dose aspirin (100 mg daily) or placebo for five years.

Main outcome measures Tests of memory, executive function, non-verbal reasoning, mental flexibility, and information processing five years after randomisation, with test scores used to create a summary cognitive score (general factor).

Results At baseline, mean vocabulary scores (an indicator of previous cognitive ability) were similar in the aspirin (30.9, SD 4.7) and placebo (31.1, SD 4.7) groups. In the primary intention to treat analysis, there was no significant difference at follow-up between the groups in the proportion achieving over the median general factor cognitive score (32.7% and 34.8% respectively, odds ratio 0.91, 95% confidence interval 0.79 to 1.05, P=0.20) or in mean scores on the individual cognitive tests. There were also no significant differences in change in cognitive ability over the five years in a subset of 504 who underwent detailed cognitive testing at baseline.

Conclusion Low dose aspirin does not affect cognitive function in middle aged to elderly people at moderately increased cardiovascular risk.

Trial registration ISRCTN 66587262.

INTRODUCTION

Reduced levels of cognitive performance in older age have been associated with the presence of cardiovascular disease.[1 2] Antithrombotic medication such as aspirin might have a role in the preservation of cognitive function, particularly in individuals at increased risk of atherosclerotic vascular disease. Conversely, if aspirin promotes microhaemorrhages in the brain, this might exacerbate cognitive decline. Observational studies have reported either no association between regular use of aspirin or other non-steroidal anti-inflammatory drugs and cognitive decline in older age[3 4] or a modest trend towards protection of cognitive function.[5-8] A recent randomised controlled trial indicated that long term low dose aspirin had no effect on memory in healthy women aged over 64, with inconclusive findings for executive function.[9] A smaller trial in men aged over 55 without dementia and at risk of cardiovascular disease, suggested a beneficial effect of low dose aspirin on verbal fluency and mental flexibility.[10]

We determined the effects of long term low dose aspirin on a wide range of cognitive functions that are known to decline with age in a relatively young population of men and women. We included two cognitive assessments, one at baseline and one after five years, in an ongoing randomised controlled trial of daily aspirin in people aged over 50, in which the primary end points were cardiovascular events and death (the aspirin for asymptomatic atherosclerosis (AAA) trial). At randomisation, all participants in this trial were at moderately increased cardiovascular risk because of a low ankle brachial index (the ratio of systolic blood pressure in the ankle to that in the arm).

METHODS

Participants

This double blind, placebo controlled randomised clinical trial took place in Scotland in 1998-2006. Volunteers aged 50-75 were recruited by direct mailing of people registered with participating general practices.

At a screening clinic, researchers recorded right and left brachial, posterior tibial, and dorsalis pedis systolic pressures with a standard sphygmomanometer and a Doppler probe. The ankle brachial index was calculated as the ratio of the lowest pressure in either ankle to the higher of the measurements in the left or right arm. Exclusion criteria included an ankle brachial index >0.95 in both legs. See bmj.com for other exclusion criteria.

Participants were randomised to daily aspirin (100 mg enteric coated) or identical placebo. Staff working on the trial, the investigators, and participants remained blinded to treatment allocation.

Participants were contacted annually, in between which they were encouraged to report admission to hospital or cessation of study medication. If they started taking aspirin or another antiplatelet drug, their study medication was discontinued. Participants recorded their compliance in a diary. A research nurse assessed self reported compliance annually, after which study tablets were renewed by post.

Cognitive function testing

At baseline participants completed a version of the Mill Hill vocabulary scale, used to compare baseline characteristics and to assess the impact of any difference in previous cognitive ability on loss to follow-up and on change in cognitive performance over time.

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At five years, participants underwent a battery of tests in a predetermined order to assess a broad range of cognitive functions. The mini-mental state examination was included as a general mental assessment and is often used as a "screen" for dementia. Executive function was assessed with the verbal fluency test. As a measure of non-verbal reasoning, we used Raven's progressive matrices. Immediate and delayed memory was assessed with the auditory verbal learning test. The trail making test was used to measure mental flexibility and the digit symbol test as a measure of speed of information processing. The hospital anxiety and depression scale was used for the assessment of mood states. At follow-up the national adult reading test measured premorbid cognitive ability.

In addition, we undertook a highly sensitive assessment of cognitive change over time in a "cognitive change subset" of recruits who underwent the same detailed battery of tests as above at baseline. Baseline and follow-up cognitive test scores were available on 399 participants in this subset.

Data analysis

Our primary analysis was on an intention to treat basis, using both individual test scores and the proportion of participants achieving over an aggregate cognitive score. For the latter, those not achieving the aggregate score would include those failing to complete cognitive testing at follow-up, thereby reducing bias from death or unwillingness to complete the tests (likely to be associated with greater cognitive decline). From our power calculation we estimated that 3300 participants (including 480 for the cognitive change subset) would provide adequate power. Principal components analysis was carried out to determine a summary cognitive score (the general factor) for the cognitive function variables (auditory verbal learning, Raven's matrices, digit symbol, verbal fluency, and trail making) with scree slope analysis to determine the number of factors. Where one or two of the test results were missing for an individual, we performed multiple imputation. This analysis resulted in a single component (the general factor, reflecting general cognitive ability), which explained 58% of the total variance. The median general factor score for the trial population was used as the cut-point for the aggregate cognitive score used to assign participants into two groups in the primary analysis. We also determined differences in mean cognitive test scores between the aspirin and placebo groups at follow-up. See bmj.com for full details of statistical analysis.

RESULTS

Primary analyses

A total of 28 980 participants were screened. After exclusions (including 24 066 because they had an ankle brachial index >0.95 in both legs), 3350 were randomly assigned to aspirin or placebo. Baseline characteristics of the two groups at randomisation were similar. See bmj.com.

A total of 1025 participants were lost to cognitive follow-up. Compared with those who completed at least one cognitive test at follow-up, those not tested were slightly older, more likely to be men, and more socially deprived, with a poorer vascular risk factor profile. Differences between the tested and untested groups in prior cognitive ability were small (vocabulary score 31.1 (SD 4.7) *v* 30.6 (SD 4.6), P=0.03).

Of the 2325 participants cognitively tested, 1984 completed the full test battery. Using imputation, a general factor score was calculated for 2262 participants (1109 in aspirin group and 1153 in placebo group). For the purposes of the primary end point analysis, all 1088 participants without a general factor score at follow-up were included in the group who did not achieve the aggregate score.

Performance on cognitive function tests at follow-up*

	Aspirin group (n=1139)		Placebo group (n=1186)		
Test of cognition	No of participants	Mean (SD) score; 95% CI	No of participants	Mean (SD) score; 95% CI	P value
General cognitive factor score (summary cognitive score)†	1109	0.00 (1.01); −0.06 to 0.06	1153	−0.01 (0.99); −0.06 to 0.05	0.83
Raven's progressive matrices (5 sets of 12 item tests; maximum possible score 60)	1110	34.3 (9.5); 33.8 to 34.9	1153	34.4 (9.3); 33.9 to 35.0	0.83
Auditory verbal learning, trials I-V (sum of five trials with same list; maximum possible 75 words)	1118	63.0 (16.7); 62.1 to 64.0	1159	63.0 (16.9); 62.0 to 64.0	0.93
Digit symbol (total No of symbols matched correctly in 90 second test; maximum possible score 93)	1126	40.0 (11.7); 39.3 to 40.7	1170	40.0 (11.7); 39.4 to 40.7	0.92
Verbal fluency (total No of words generated in three 1 minute tests)	1117	37.6 (12.8); 36.9 to 38.4	1156	37.1 (12.7); 36.3 to 37.8	0.27
Trail making (seconds to completion)‡	1122	4.6 (0.4); 4.6 to 4.6	1167	4.6 (0.4); 4.6 to 4.6	0.90
Mini-mental state examination (total score, maximum possible 30)	1131	28.6 (1.7); 28.5 to 28.7	1178	28.5 (1.8); 28.4 to 28.6	0.20

*In all tests except trail making, higher scores indicate better function. Imputed test scores were used for individuals with ≤2 scores missing for Raven's progressive matrices (162 scores imputed), auditory verbal learning (95), digit symbol (10), verbal fluency (45), and trail making (37).
†Calculated from factor analysis with unrotated principal component analysis with current cognitive function measures excluding mini-mental state.
‡Natural log of time in seconds to complete trail making test (untransformed means 102 seconds for aspirin group and 101 seconds for placebo group).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Atherosclerotic cardiovascular disease might accelerate age related cognitive decline

Aspirin has a protective role in the secondary prevention of cardiovascular disease and might also reduce age related cognitive decline

WHAT THIS STUDY ADDS

Low dose aspirin over five years did not produce any cognitive benefit in men and women aged over 50 years without dementia and at moderately increased risk of cardiovascular disease

Overall, 32.7% (n=548) of participants in the aspirin group and 34.8% (n=583) in the placebo group achieved over the median general factor score (odds ratio 0.91, 95% confidence interval 0.79 to 1.05, P=0.20). There was little change in the odds ratio after adjustment for age, sex, ankle brachial index, deprivation category, smoking status, and total plasma cholesterol (0.93, 0.80 to 1.08, P=0.35). These results did not alter greatly when we repeated analyses excluding participants without a general factor score.

At follow-up there was no significant difference in the mean test scores between the two groups for any of the individual tests or for the general factor (table). The proportion of participants scoring below 24 on the mini-mental state examination was similar (2.4% (27) *v* 2.5% (29), P=0.91). There was also no significant difference in mean scores on the hospital anxiety scale (5.2 (SD 3.6) *v* 5.4 (SD 3.6), P=0.12) or the hospital depression scale (2.9 (SD 2.5) *v* 3.0 (SD 2.7), P=0.82).

Analysis of cognitive change subset

In the cognitive change subset there were no significant differences in the change in cognitive ability over the five years for any of the individual tests or for the general factor between the treatment groups. Overall, scores for speed of processing information and mental flexibility in the cognitive change subset declined over the five years, though the change in mental flexibility scores was not significant (mean digit symbol 45.0 at baseline, 42.4 at follow-up, P<0.001: mean trail making 94.2 seconds at baseline, 97.4 seconds at follow-up, P=0.2). There was no significant difference over time in verbal fluency or non-verbal reasoning and scores on the memory test improved (mean auditory verbal learning 63.8 at baseline, 68.5 at follow-up, P<0.001). Changes observed over time are probably underestimates of the true age related declines[11] because the effects of age can be ameliorated by familiarity with the test.

To examine whether compliance might have affected our results, we performed an on treatment analysis for 1708 participants who reported that they had taken their study medication for at least two thirds of the year before follow-up (850 were in the aspirin group and 858 were in the placebo group). There were no significant differences in baseline characteristics between these two groups. Of the 2325 participants cognitively tested at follow-up, 1505 (64.7%) were still taking treatment (743 and 762, respectively). The characteristics at randomisation of these two groups were also similar as were the mean cognitive scores at follow-up. See bmj.com.

DISCUSSION

In this large double blind, placebo controlled randomised clinical trial we found no significant difference in measures of cognitive function between people randomised to 100 mg aspirin daily compared with placebo over a five year period. In post hoc analysis, we found the same result for both younger (50-64 years) and older (≥65 years) participants and for both men and women. Our findings are consistent with those from a recent randomised controlled trial of aspirin in women, in which long term low dose aspirin had no effect on memory.[9] Our findings that aspirin also had no effect on cognitive functions other than memory were in contrast with those from a single older and much smaller trial.[10]

Limitations and strengths

A high proportion of participants (30%) failed to complete the cognitive tests at follow-up, consistent with previous studies of a similar design.[9] Relatively high levels of non-testing could have biased our findings. However, there was only a small difference in Mill Hill vocabulary scores at baseline between those who did and did not undergo cognitive testing at follow-up. The potential effect of cognitive decline over the period of the study on test completion was further addressed by use of the aggregate cognitive score in our primary analysis.

Despite efforts to maintain participants' compliance with study medication, this fell throughout the duration of the trial and could have affected our results. The on treatment analysis, however, failed to show any difference in the aggregate or mean cognitive scores between those taking aspirin and those taking placebo, or indeed any shift in the overall results that might have indicated an effect of aspirin.

We cannot exclude the possibility that higher doses or longer duration of aspirin treatment, would have led to different results. Longer follow-up into older age might also be necessary to show any "delayed" effect of aspirin from the time of altered cerebral pathology to development of observable changes in cognitive decrements.

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Contributors: See bmj.com

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Effect of illicit direct to consumer advertising on use of etanercept, mometasone, and tegaserod in Canada: controlled longitudinal study

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ABSTRACT

Objective To assess the impact of direct to consumer advertising of prescription drugs in the United States on Canadian prescribing rates for three heavily marketed drugs—etanercept, mometasone, and tegaserod.

Design Controlled quasi-experimental study using interrupted time series analysis.

Population Representative sample of 2700 Canadian pharmacies and prescription data from 50 US Medicaid programmes.

Main outcome measures Differences in number of filled prescriptions per 10 000 population per month between English speaking and French speaking (control) Canadian provinces before and after the start of direct to consumer advertising in the United States.

Results Spending on direct to consumer advertising for study drugs ranged from $194m to $314m (£104m-£169m; €131m-€212m) over the study period. Prescription rates for etanercept and mometasone did not increase in English speaking provinces relative to French speaking controls after the start of direct to consumer advertising. In contrast, tegaserod prescriptions increased 42% (0.56 prescriptions/10 000 residents, 95% confidence interval 0.37 to 0.76) in English speaking provinces immediately after the start of US direct to consumer advertising. Uncontrolled analysis of US Medicaid data showed a larger 56% increase in tegaserod prescriptions. However, this increase did not persist over time in either country, despite continued advertising.

Conclusions Exposure to US direct to consumer advertising transiently influenced both Canadian and US prescribing rates for tegaserod, a drug later withdrawn owing to safety concerns. The impact of direct to consumer advertising on drug use seems to be highly variable and probably depends on the characteristics of the advertised drug, the level of exposure to direct to consumer advertising, and the cultural context.

INTRODUCTION

The merits of direct to consumer advertising have been extensively debated, which has led to differing regulations across countries.[1 2] Proponents argue that it increases use of effective treatments for undertreated conditions, such as depression.[1] Opponents, however, suggest that it drives up demand for newer drugs with higher costs, marginal benefits, and unknown safety profiles.[2] Both sides of the argument assume that direct to consumer advertising increases use. However, the effectiveness of drug advertising campaigns is unclear.[3 4] We studied the impact of US direct to consumer advertising campaigns on Canadian prescribing rates for three heavily marketed drugs by using a controlled longitudinal study design.

METHODS

Study setting—We examined the impact of US direct to consumer advertising campaigns on Canadian patterns of drug use in provinces with and without substantial exposure to such advertising—that is, in predominantly English speaking provinces compared with predominantly French speaking Quebec. For drugs for which we found an impact on Canadian prescribing rates, we used data from nationwide US Medicaid programmes to assess whether a dose-response relation might exist between greater exposure to direct to consumer advertising in the United States and more marked increases in drug use. Although Canada prohibits direct to consumer advertising that includes both a brand name and indications, substantial cross border exposure to US advertising occurs through cable and satellite television, radio, print media, and internet advertising.[5]

Data sources—Our primary analysis used monthly drug use data from the nationally representative CompuScript audit from IMS Health Canada, an independent health information company, from

January 2002 to December 2006. This audit uses a panel of approximately 2700 pharmacies (roughly 34% of all community pharmacies in Canada) to estimate total Canadian use of each drug. The major outcome of interest was the number of dispensed prescriptions of each drug per 10 000 residents per month. Our analysis in the United States used quarterly data from 50 US Medicaid programmes.[6] Using state level enrolment numbers, we calculated dispensed prescription rates per 10 000 Medicaid enrolees per quarter.[7] The start month and total spending on US direct to consumer advertising campaigns came from TNS Media Intelligence (see bmj.com).

Study drugs—We sought out drugs that were included in US marketing campaigns started between January 2003 and December 2005; approved for use in Canada before US advertising; and not advertised on Canadian television with a brand name. On the basis of these characteristics, we identified three study drugs. The first eligible drug was etanercept (Enbrel), a biological agent approved in Canada for the treatment of symptom refractory rheumatoid arthritis. The second eligible drug was mometasone (Nasonex), an inhaled nasal steroid spray for symptoms of allergy. Thirdly, tegaserod (Zelnorm) is a serotonin receptor agonist approved for the treatment of constipation predominant irritable bowel syndrome in women. The latter drug was eventually withdrawn in both Canada and the United States owing to concern about cardiac side effects.[8 9]

Analysis—We analysed the difference in prescribing rates between predominantly English speaking provinces (n=8) and Quebec, where French is the mother tongue for more than 80% of the population.[10] We used interrupted time series analysis to examine longitudinal changes in Canadian prescribing rates.[11] Firstly, we calculated the difference in the prescribing rate per 10 000 population by subtracting the rate in French speaking provinces from that in English speaking provinces. We then fitted time series models to test whether a statistically significant change occurred in the level or trend of the difference after the start of US advertising or US national network news advertising, controlling for the pre-direct to consumer advertising level and trend (see bmj.com).

RESULTS

All three drugs had large direct to consumer advertising expenditures, ranging from US$194 million to $314 million during the study period (see bmj.com). Pre-advertising trends in use for each of the study drugs were generally comparable between English speaking and French speaking provinces (figs 1, 2 and 3).

Etanercept and mometasone

Figure 1 shows that the times series of monthly prescribing rates of etanercept in Canada were very similar in both language regions. We found that advertising had no statistically significant impact on the level or trend of differences in prescribing rate between English speaking and French speaking provinces (level change −0.18 prescriptions per 10 000 population, 95% confidence interval −0.39 to 0.04, P=0.10; trend change −0.03 prescriptions per 10 000 population per month, −0.06 to 0.003, P=0.07). Similarly, we saw no differences for momentasone (level change −3.61 prescriptions per 10 000 population, −10.51 to 3.29, P=0.30; trend change −0.08 prescriptions per 10 000 population per month, −0.57 to 0.40, P=0.73) (fig 2).

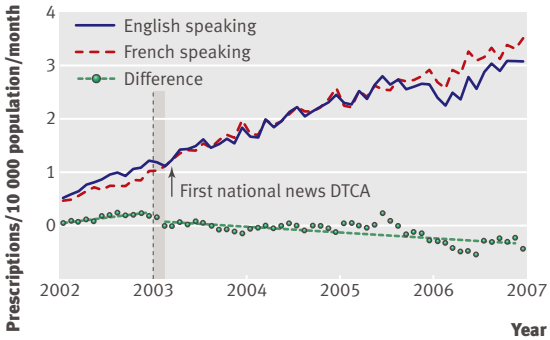

Fig 1 | Number of etanercept prescriptions per 10 000 population per month in Canadian provinces that are predominantly English speaking (n=8) or French speaking (n=1). Vertical line indicates start of US advertising in January 2003. Difference between rates shown at bottom of chart; fitted trend line shows predicted differences from interrupted time series regression. DTCA=direct to consumer advertising

Tegaserod

Figure 3 shows the monthly prescribing rates for tegaserod. The February 2003 campaign, which contained no US network news advertising, had no significant impact on prescribing rates and was incorporated into the pre-advertising period. In contrast, a level increase of 0.56 prescriptions per 10 000 population (0.37 to 0.76, P<0.001) in the difference in prescribing rate between English speaking and French speaking provinces occurred immediately after the

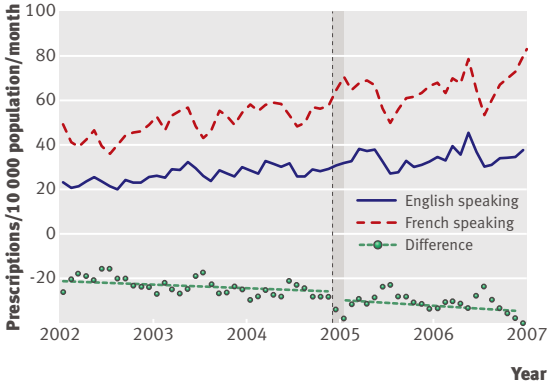

Fig 2 | Number of mometasone prescriptions per 10 000 population per month in Canadian provinces that are predominantly English speaking (n=8) or French speaking (n=1). Vertical line indicates start of US advertising in December 2004. Difference between rates shown at bottom of chart; fitted trend line shows predicted differences from interrupted time series regression

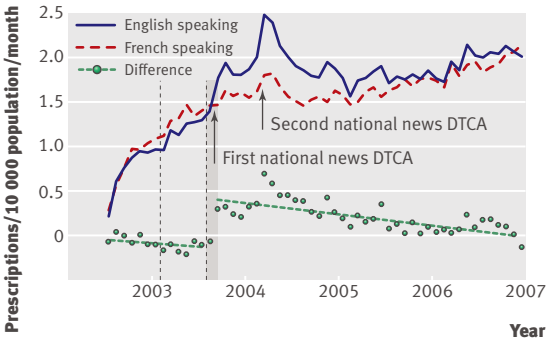

Fig 3 | Number of tegaserod prescriptions per 10 000 population per month in Canadian provinces that are predominantly English speaking (n=8) or French speaking (n=1). Vertical lines indicate start of US advertising in February 2003 and start of new TV advertising campaign in August 2003. Difference between rates shown at bottom of chart; fitted trend line shows predicted differences from interrupted time series regression. DTCA=direct to consumer advertising

August 2003 campaign. The estimated 42% increase in the first month after direct to consumer advertising did not persist despite continued advertising throughout the study period. Within two years of direct to consumer advertising, prescribing rates were again virtually identical between English speaking and French speaking regions.

Figure 4 shows that the pre-advertising upward trend in tegaserod use was substantially higher in US Medicaid than in Canada. After direct to consumer advertising on national network news, we saw an increase in the level of prescribing in the United States; the number of prescriptions per 10 000 enrolees increased by 5.70 (3.65 to 7.75, P<0.001). The estimated increase in prescribing in the first quarter of direct to consumer advertising was 56% higher than would have been expected.

DISCUSSION

To our knowledge, this study is the first analysis that uses a concurrent control group to evaluate the impact of direct to consumer advertising on use of specific drugs. We found that for two of three drugs the US direct to consumer advertising had no apparent impact on Canadian prescribing rates, and for one drug (tegaserod) we saw a short lived effect. These mixed findings are surprising, as we included several expensive advertising campaigns that were highly recalled by consumers.[12 13] Our empirical results raise important questions about whether and how prescribing trends for specific drugs respond to advertising directed at consumers. For a discussion of possible explanations for these findings see bmj.com.

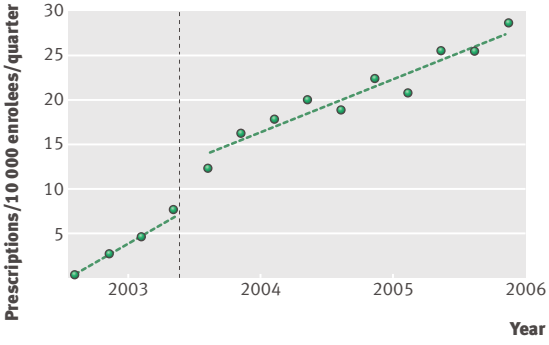

Fig 4 | Number of tegaserod prescriptions per 10 000 enrolees per quarter in US Medicaid programmes. Vertical line indicates start of new TV advertising campaign in third quarter of 2003. Fitted trend line represents fitted interrupted time series analysis for rate of use in Medicaid

Limitations

Differences such as variation in provincial drug reimbursement plans would bias our results only if they coincidentally changed when the individual direct to consumer advertising campaigns started. We could find no evidence that this occurred for any of the drugs studied. None the less, exclusion from provincial formularies might constrain the effects of successful advertising campaigns. However, most private insurance plans in Canada do not have formularies and cover most of the population.[14] Moreover, although Ontario and Alberta both excluded tegaserod from their public drug programmes, the effect of direct to consumer advertising was apparent in both provinces (data not shown).

The study has other limitations. Firstly, generalising beyond the three drugs that met our inclusion criteria is difficult. Secondly, we do not have information on whether these drugs were subject to disease awareness advertising by companies that did not mention the brand name. However, this would bias our results only if it was similarly timed, and we found no indication for mometasone or etanercept of increased use coincident with branded direct to consumer advertising, thus making it unlikely. Thirdly, variation in drug coverage, the overall health system, culture, levels of exposure to advertising, or television viewing patterns might result in the effect of direct to consumer advertising differing between drugs and between countries. However, the percentage increase in and duration of effect for tegaserod was similar in both countries.

Implications

Our analysis indicates that illicit cross border exposure to direct to consumer advertising has the potential to modify drug use, even where such advertising is technically prohibited. Secondly, to our knowledge, these results are the strongest evidence that direct to consumer advertising can increase use of a drug that was removed from the market as a result of concerns about safety. Finally, our findings suggest that the impact of direct to consumer advertising campaigns is mixed, as they seem to work for some drugs and not others. If the overall impact of direct to consumer advertising is limited or variable, then a substantial portion of expenditure on such advertising—borne by governments, insurers, and patients in the form of higher costs or by companies as reduced profits—may be better spent elsewhere. Previous commentary may

WHAT IS ALREADY KNOWN ON THIS TOPIC

Although direct to consumer advertising (DTCA) of prescription drugs remains controversial, no controlled studies have investigated its impact on prescribing

In the absence of such evidence, both opponents and proponents of DTCA have generally assumed it to be highly effective at increasing the use of advertised drugs

WHAT THIS STUDY ADDS

DTCA campaigns seem to have mixed effectiveness; drug use did not increase for two of three drugs studied

Despite prohibitions, DTCA can influence prescribing across national borders

The drug (tegaserod) for which use increased with DTCA was eventually withdrawn owing to safety concerns

have overemphasised the impact of direct to consumer advertising for many individual drugs for which evidence that it increases use is either weak or non-existent.[1] Until we better understand how direct to consumer advertising modifies prescribing for particular drugs, debates about its positive and negative consequences will continue to be based on conjecture rather than strong evidence.

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Competing interests: None declared.

Ethical approval: The research was appraised and granted an exemption from review by the Harvard Pilgrim Health Care Human Studies Committee.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Police violence and sexual risk among female and transvestite sex workers in Serbia: qualitative study

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ABSTRACT

Objective To explore female and transvestite sex workers' perceptions of risk in the sex work environment in Serbia.

Design Qualitative interview study.

Setting Street based locations for sex work in Belgrade and Pancevo, Serbia.

Participants 31 female and transvestite sex workers.

Results Violence, including police violence, was reported as a primary concern in relation to risk. Violence was linked to unprotected sex and the reduced capacity for avoiding sexual risk. Participants reported that coerced sex was routinely provided to the police in exchange for freedom from detainment, arrest, or fine, and was enforced by the perceived threat of violence, sometimes realised. Accounts contained multiple instances of physical and sexual assault, presented as abuses of police authority, and described policing as a form of moral punishment. This was largely through non-physical means but was also enforced through physical violence, especially towards transvestite and Roma sex workers, whose experience of police violence was reported as relentless and brutal and connected with broader social forces of discrimination in this setting, especially towards Roma.

Conclusion Preventing violence towards sex workers, which can link with vulnerability to sexually transmitted

infections, is a priority in Serbia. This requires monitoring perpetrators of violence, providing legal support to sex workers, and creating safer environments for sex work.

INTRODUCTION

Violence links with vulnerability to sexually transmitted infections through coerced unprotected sex and the reduced capacity to negotiate sexual risk.[1] Violence, which can be ubiquitous in street sex work,[2-4] can feature alongside other acts of social discrimination,[5] and sex work is highly stigmatised.[6] Policing practices, and police violence, can also impact adversely on health, especially among vulnerable people.[7] Street policing, for example, can displace sex work geographically and disrupt sex workers' networks of support, exacerbating the risk of sexually transmitted infections and violence from clients.[6 8 9] Preventing violence is a global public health and human rights priority.[10]

Serbia is characterised by social and economic uncertainty, which links to illegal economies (including sex work), corruption, and ethnic and gender inequalities.[11] Roma populations especially are subject to pervasive social and health inequalities.[12] We report findings from a qualitative study of risk perception in two sex work environments in Serbia.

METHODS

We undertook 31 qualitative semistructured interviews with female and transvestite sex workers in two street based locations in Belgrade and Pancevo, Serbia. We recruited through outreach projects at five discrete sex work "hotspots" and supplemented through snowballing and chain referral within networks of sex workers.

Interviews focused on perceptions of risk linked to sex work, were tape recorded and then transcribed verbatim. Coding of data was descriptive and thematic.[13] Data were collected in two waves to enable provisional coding to inform ongoing recruitment, purposive sampling, and refinement of topics for interview. Findings and codes therefore emerged iteratively.[13 14] At the interim analysis, violence emerged as a key theme. Coding of data was undertaken in two phases, with first level codes identifying key topics and concepts on the basis of participants' accounts and a priori defined topics of interest (for example, "violence"), and second level codes breaking these into units for analysis (for example, "client violence," "police violence").

The sample comprised 24 women and seven transvestites (average age 28). Most (n=25) were street based sex workers or solicited sex through advertising. Half were Roma (n=15), all of whom worked the streets and among whom were the transvestites. All street based sex workers reported some kind of violence linked to their work. Sex work is illegal in Serbia.

RESULTS

Violence, by police in particular, was identified as a primary concern of sex workers in their descriptions of the risks involved in street sex work in Serbia.

The risk environment of sex work

As elsewhere,[3 4] sex workers placed emphasis on condom use in transactional encounters: "Not using condoms with a client, God forbid!" Condom use, and hygiene more generally, was linked with presentations of personal integrity and responsibility: "I take good care of myself. All that [HIV] comes from the lack of hygiene, to those who don't take good care." "Client sorting" was a core strategy to reduce perceived risk, whereby the "messy", "dirty," and "dangerous" were avoided in favour of the "married," "normal," and "clean." Judgments about hygiene seemed to influence condom use: "It happened, even without a condom, but he was married, clean, neat, spotless."

The risk of violence seemed to be ubiquitous. Violence was reported as being linked to mishaps related to condom use as well as condom breakages from rough or coerced sex: "If they push it in violently, then it [condom] breaks." Violence was linked directly to unprotected sex through coercion: "I had to accept everything he asked for . . . without the rubber." The perceived threat of physical violence also had indirect effects on sex workers' capacity for reducing risk by feeding a sense of pervasive insecurity and loss of control in transactions: "I get scared every time I get in [a car] with someone I don't know, so that I am consumed with fear." Violence by clients was common, but it was violence by police that was perceived as the greater threat and as less open to risk management: "You can manage your clients somehow, but to be honest, the greatest threat to us is the police."

Police violence

Although some participants had not experienced physical violence by the police—"I perhaps got two slaps one time, that's all," deception and coercion, extortion, and discrimination by the police seemed normative (boxes 1-3).

Sexual services were described as being commonly provided to police without payment or secured by them through deception and coercion (box 1). Sex workers reported being presented with the option of providing services without payment as a means of avoiding arrest, detainment, or fine. In cases of deception, policemen would usually reveal their identity once services had been negotiated and exchanged, demanding their

Box 1 Sex by deception and coercion

And at the end of the job he shows me his badge, and says like "Give me my money back now." That's what he does. And he's not on duty. But he's some cop. *What do you do?* Give the money back (case 14, female)

They want blowjobs, fucking, if you want them to let you go. You've got to. The police like fucking us more than anyone. They don't pay. It's like this: they fuck us, and so they let us go (case 5 transvestite)

He wants me to blow him for free. I don't want to. Later, when he gets me on my shift, he beats me silly. Beats me silly (case 20, transvestite)

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Box 2 Extortion of money or information

Yesterday, or the day before, the patrol, they wanted money from us. First he says, "C'mon, get in the car." Nothing to it, I get in the car. Then he says, "Why don't you treat us?" And he says, "C'mon, sort it out among yourselves," how much money we are to give him (case 14, female)

The first time they beat me because I didn't want to admit who I worked for. They slapped me around. Like, "Gypsy, motherfucker, why don't you start talking?" I was pregnant, and he started beating me. Like, "You ain't going to say you're pregnant any more, now you're going to get beaten up at the station, and nobody's going to believe you, and if you report me, I beat you up" (case 8, female)

money back (box 1). This was described as a no choice situation, which for some had become routine: "They're in power, and we are not, what can I do?" Although there were exceptions ("I don't do cops"), sex would normatively be provided in exchange for freedom from detainment or arrest (box 1).

The risk of detainment, arrest, or fine or the threat of physical violence were given as the reasons why sex workers acquiesced to police demands for sex without payment. Sex coerced through violence perpetrated by those presumed to be police was reported to usually involve condoms: "Leave off mate, not only am I doing you for free, but you're not jacking me up without a rubber." Attempts to resist demands for sex without payment might incite violence (box 1). Accounts also indicated routine extortion of money as unofficial fines or as "negotiated" payments to secure freedom from detainment, arrest, or registration as a prostitute (box 2). Extortion of money or information (particularly about pimps) was also described as being enforced by the threat of violence (box 2).

A common theme was a fatalist acceptance of the inevitability of police violence, borne out of the internalisation of police "rights" to victimise ("They have a right to beat us") and realisation that rights to police protection are unrealistic ("I can't complain to anybody"). A striking feature of the accounts was that police violence was presented as transgressing boundaries of legal acceptability or rationality, and thus was thought to be moral punishment (box 3). Enforced sex and coerced payments to police, although outside the law, were experienced as discipline as if for moral wrongdoing, to "bring sex workers to their senses," suggesting that they were matter out of place (box 3). A common tactic was humiliation. This involved unwanted disclosure of a sex worker's identity to friends and family (box 3). Public shaming included police collaborations with media, with crackdowns and arrests of sex workers being televised (box 3).

Moral punishments for selling sex overlapped with other forms of social discrimination, especially towards Roma and transvestites: "There is nothing [about me] that is normal for our people here, for our nation, here in Serbia." Police violence was especially brutal towards transvestites, all of whom in this study were Roma, and most Kosovo refugees (box 3). Extreme violence towards transvestites and Roma was generally interpreted as driven by contempt for being of minority or deviant status (box 3).

Taken together there was strong emphasis in sex workers' accounts on the need for greater protection from police violence and corruption, and for creating safer and regulated off-street environments for sex work, including through legislation: "If it was legal, we'd go to doctors, we'd have medical records, it'd be much better."

Box 3 Discrimination

Moral punishment

They [police] take us into their office, and one starts kicking you in the legs, the other one into kidney. Without any reason. They want to accomplish something, to prevent us from doing something. *From what?* From doing this work. "Why don't you find another job?" I say, "Come on, find me another job and I will do it" And he goes, "Why should I look for a job for you?" and so on. It's like that (case 2, female)

Public humiliation and shaming

A few times I went out with my boyfriend. I would sit down, drink coffee, and they [police] come in. "Hey, do you know . . .?" I mean, it's the first thing they say, "Do you know what she . . .?" And he [my boyfriend] goes, "Well, can I not have a drink with her?" "You know, well . . . Do you know what, do you know what she does?" (case 15, female)

Most of the women get arrested. The last time they arrested people it was on television. I saw it in person. Arrested, chased, and filmed on camera (case 1, transvestite)

Extreme violence driven by contempt

They [police] started going wild, only on us transvestites. They let the girls go. They just pick us up, and go to the woods, and go wild on us . . . First, they beat us in the woods, and then they take us to the station. And then they tell us at the station "Hey, freshen up," and they beat us up in the bathroom (case 5, transvestite)

The [police] kicked, kicked, kicked the hell out of us. Just transvestites . . . I said a million times, "Take me away . . . Arrest me . . . but, do not beat me up" (case 20, transvestite)

DISCUSSION

Violence was reported as a primary risk concern of sex workers in street based locations in Serbia, and was linked to coerced unprotected sex and rape, breakages of condoms, and reduced capacity to negotiate sexual safety. Moreover, sex workers described being coerced into providing sex to police in exchange for freedom from detainment, arrest, or fine, and this was reportedly enforced by perceived or realised risks of physical violence by police.

This study is exploratory and generalisability is inevitably limited to this sample and setting. The study is an interpretative analysis of accounts and reflects the themes of these. Counter narratives are possible, and we did not investigate accounts by the police.

Interviews contained multiple descriptions of physical and sexual assault, presented as abuses of police authority. Reported coerced sex by police usually involved condoms, but the pervasive risk of violence contributed to a reduced sense of control over the negotiation of sexual transactions. Sex workers largely adopted a fatalistic acceptance to reported police demands for money or sex without payment. This study extends concepts of sex in exchange for money or goods to include sex in exchange for freedom from police detainment, arrest, or fine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Violence can link with coerced unprotected sex and the risk of sexually transmitted infections, but little is known about police violence towards female and transvestite sex workers

WHAT THIS STUDY ADDS

In Serbia, coerced sex was reported to be routinely provided to police in exchange for freedom from detainment, arrest, or fine, and was enforced by the perceived threat of violence, sometimes realised

Policing acted as moral punishment through non-physical means but was also reportedly enforced through physical violence, especially towards transvestite and Roma sex workers

The policing practices identified here had little basis in legal rationality but acted as forms of moral punishment. These practices discipline and stigmatise, positioning sex workers as having waived rights to respect or protection on account of having transgressed. Such practices usually comprised bullying, such as humiliation and shaming involving the unwanted disclosure of a sex worker's identity to "normal others." But discriminatory practices were also embedded in physical violence, and much of it brutal, as in the relentless violence reported by transvestite sex workers, all of whom were Roma. Other studies have noted that the use of force can be excessive when policing street sex work.[7 15 16]

Violence linked to sex workers reflects institutionalised social inequalities and anxieties relating to gender, ethnicity, sexuality, and vulnerability.[17 18] In Serbia, Roma are subject to immense social discrimination and impoverishment.[19]

In conclusion, physical violence, enacted or threatened, can link with unprotected sex, vulnerability to sexually transmitted infections,[1 2 5 15 20] and sex workers' diminished sense of volitional control.[5 11 16 17] A need exists to "design out" violence from sex work.[21] This requires interventions to monitor perpetrators of violence and contraventions in police conduct, legal support protecting sex workers' health and human rights, and the creation of safer environments for sex work.

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