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RESEARCH

Mortality in British military participants in human experimental research into chemical warfare agents at Porton Down: cohort study

K M Venables,[1] C Brooks,[1] L Linsell,[1] T J Keegan,[1] T Langdon,[1] T Fletcher,[2] M J Nieuwenhuijsen,[3,4] N E S Maconochie,[5] P Doyle,[5] V Beral,[6] L M Carpenter[1]

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[1]Department of Public Health, University of Oxford, Oxford OX3 7LF
[2]Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London
[3]Centre for Research in Environmental Epidemiology, IMIM and CIBERESP, 08003 Barcelona, Spain
[4]Division of Epidemiology, Public Health and Primary Care, Imperial College, London
[5]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London
[6]Cancer Epidemiology Unit, University of Oxford, Oxford
Correspondence to: K M Venables kate.venables@dphpc.ox.ac.uk; L M Carpenter lucy.carpenter@dphpc.ox.ac.uk

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ABSTRACT

Objective To investigate any long term effects on mortality in participants in experimental research related to chemical warfare agents from 1941 to 1989.

Design Historical cohort study.

Data source Archive of UK government research facility at Porton Down, UK military personnel records, and national death and cancer records.

Participants 18 276 male members of the UK armed forces who had spent one or more short periods (median 4 days between first and last test) at Porton Down and a comparison group of 17 600 non-Porton Down veterans followed to 31 December 2004.

Main outcome measures Mortality rate ratio of Porton Down compared with non-Porton Down veterans and standardised mortality ratio of each veteran group compared with the general population. Both ratios adjusted for age group and calendar period.

Results Porton Down veterans were similar to non-Porton Down veterans in year of enlistment (median 1951) but had longer military service (median 6.2 *v* 5.0 years). After a median follow-up of 43 years, 40% (7306) of Porton Down and 39% (6900) of non-Porton Down veterans had died. All cause mortality was slightly greater in Porton Down veterans (rate ratio 1.06, 95% confidence interval 1.03 to 1.10, P<0.001), more so for deaths outside the UK (1.26, 1.09 to 1.46). Of 12 cause specific groups examined, rate ratios in Porton Down veterans were increased for deaths attributed to infectious and parasitic (1.57, 1.07 to 2.29), genitourinary (1.46, 1.04 to 2.04), circulatory (1.07, 1.01 to 1.12), and external (non-medical) (1.17, 1.00 to 1.37) causes and decreased for deaths attributed to in situ, benign, and unspecified neoplasms (0.60, 0.37 to 0.99). There was no clear relation between type of chemical exposure and cause specific mortality. The mortality in both groups of veterans was lower than that in the general population (standardised mortality ratio 0.88, 0.85 to 0.90; 0.82, 0.80 to 0.84).

Conclusions Mortality was slightly higher in Porton Down than non-Porton Down veterans. With lack of information on other important factors, such as smoking or service overseas, it is not possible to attribute the small excess mortality to chemical exposures at Porton Down.

INTRODUCTION

After the use of chemical warfare agents in the first world war, the UK government initiated research at Porton Down to study their impact on military capability and the effectiveness of protective measures.[1-5] This included a "human volunteer programme" in which, since 1916, 30 000 people, mainly servicemen, are thought to have taken part.[3] After ex-servicemen expressed concern about whether participation might have damaged their health in the long term, the UK government commissioned this epidemiological study in 2002. There have been few studies of participants in such human experimental programmes[6-9] and results from mortality studies in American servicemen have been inconclusive.[7-10] A recent survey of members of a UK veterans' support group found them to report poorer quality of life than the general population.[11] This is the first report of mortality and cancer morbidity[12] in the cohort of British participants in the chemical tests at Porton Down.

METHODS

The Porton Down veteran cohort—Our cohort comprised all male members of the UK armed forces recorded as having participated in the "human volunteer programme" from 1 April 1941 to 31 December 1989 and for whom military personnel files had been retrieved (18 276) Porton Down veterans).

The comparison cohort—We identified a comparison group of veterans who did not visit Porton Down. A sample of veterans with adjacent military service numbers to Porton Down veterans had similar distributions of important characteristics, such as date of birth. Within each branch of the military, we generated a service number adjacent to that of each Porton Down veteran and requested the corresponding personnel file. The group comprised 17 600 non-Porton Down veterans.

Follow-up—We submitted identification details to the National Health Service central register which

Table 1 | Characteristics of 18 276 Porton Down veterans and 17 600 non-Porton Down veterans. Figures are numbers (percentages) of veterans

Characteristic	Porton Down veterans	Non-Porton Down veterans
Service at enlistment:		
Army	11 407 (62.4)	10 872 (61.8)
Air force	4026 (22.0)	3987 (22.7)
Navy (and marines)	2843 (15.6)	2741 (15.6)
Decade of birth:		
Before 1920	3742 (20.5)	3794 (21.6)
1920s	3515 (19.2)	3211 (18.2)
1930s	6088 (33.3)	5977 (34.0)
1940s or later	4931 (27.0)	4618 (26.2)
Place of birth:		
England	14 295 (79.2)	13 761 (78.9)
Wales	931 (5.2)	919 (5.3)
Scotland	1785 (9.9)	1803 (10.3)
Northern Ireland	307 (1.7)	248 (1.4)
Republic of Ireland	265 (1.5)	261 (1.5)
Overseas	458 (2.5)	444 (2.5)
Missing	235	164
Age (years) at enlistment:		
<16	1237 (6.8)	1220 (6.9)
16-<18	4987 (27.4)	4290 (24.4)
18-<20	6495 (35.7)	6211 (35.3)
20-<22	2270 (12.5)	2354 (13.4)
≥22	3226 (17.7)	3517 (20.0)
Missing	61	8
Period at enlistment*:		
Before second world war	975 (5.4)	884 (5.0)
During second world war	5275 (29.0)	5048 (28.7)
After second world war	7814 (42.9)	7667 (43.6)
After national service	4151 (22.8)	3993 (22.7)
Missing	61	8
Rank at enlistment:		
Private (or equivalent)	18 094 (99.3)	17 438 (99.4)
Other	122 (0.7)	112 (0.6)
Missing	60	50
Duration of service at first visit to Porton Down (years):		
<2	8160 (44.8)	NA
2-<3	3087 (17.0)	NA
3-<5	3572 (19.6)	NA
5-<10	2341 (12.9)	NA
≥10	1055 (5.8)	NA
Missing	61	
Total duration of service (years)†:		
<2	438 (2.4)	2771 (15.8)
2-<3	2830 (15.6)	3406 (19.4)
3-<5	2823 (15.6)	2728 (15.5)
5-<10	7011 (38.6)	5565 (31.6)
≥10	5043 (27.8)	3117 (17.7)
Missing	131	13
Vital status at 31 December 2004:		
Alive	10 409 (57.0)	10 222 (58.1)
Deceased	7306 (40.0)	6900 (39.2)
Follow-up censored at:		
Discharge from services	438 (2.4)	346 (2.0)
Emigration	68 (0.4)	69 (0.4)
Other	55 (0.3)	63 (0.4)

NA=not applicable.
*Second world war dates taken as 1 September 1939 to 30 April 1945; national service dates taken as 1 May 1945 to 31 December 1960.
†Includes 148 Porton Down veterans, and 132 non-Porton Down veterans still serving at time of data abstraction.

traced deaths, and, when available, emigrations. Untraced veterans were checked with the Commonwealth War Graves Commission, and the Department for Work and Pensions.

Exposures of Porton Down veterans—To assess exposure we used contemporaneous experimental records in the Porton Down historical archive. Each chemical test was classified as involving vesicant(s) (blistering agents), nerve agent(s), or other chemical(s). We grouped Porton Down veterans as ever or never exposed at least once to any chemical, vesicant, nerve agent, or other chemical, and to specific chemicals to which at least 1000 veterans had been exposed.

Mortality analysis—Analyses reported relate to underlying cause of death. Person years of follow-up for Porton Down veterans started from the earliest date (after 1 April 1941) they were recorded as included in a test at Porton Down. Person years for non-Porton Down veterans started from enlistment date plus the interval between the corresponding Porton Down veteran's enlistment and first visit to Porton Down. Person years stopped at the earliest of date of death, loss to follow-up, or 31 December 2004. We calculated expected deaths based on corresponding national rates for England, Wales, and Scotland and estimated standardised mortality ratios from the ratio of observed to expected deaths. We adjusted rate ratios for age group and calendar period. We compared mortality rates in specific exposure groups of Porton Down veterans with that of all non-Porton Down veterans. For groups of causes where there was either a prior hypothesis of association, or the data suggested an association, we calculated rate ratios for subgroups with "high" exposure.[13]

RESULTS

Of the Porton Down veterans, 62% (11 407/18 276) had joined the army, 22% (4026) the air force, and 16% (2843) the navy, including the marines. The distribution of service at enlistment of the 17 600 non-Porton Down veterans was virtually identical (table 1). The median year of enlistment was 1951 for both groups. Other important military and demographic characteristics were similar except that Porton Down veterans had a longer duration of military service. The median duration of military service was 6.2 years (interquartile range 4.2-11.4) for Porton Down veterans and 5.0 (2.1-7.5) for non-Porton Down veterans.

The median interval between first and last test carried out at Porton Down was four days (interquartile range 1-8 days), and median number of days on which tests were performed was two (1-4).[14] For 69% (12 601/18 276) of the Porton Down veterans, the first recorded visit to Porton Down was in the 1940s or 1950s. The type of test could be determined for 95% (17 303) of veterans and, of these, 91% (16 686) were in at least one test involving a chemical. Fifty eight per cent of veterans (10 539) were in at least one test involving a vesicant, 20% (3597) a nerve agent, and 65% (11 925) another chemical group. There were eight specific chemicals for which there were records of at least

1000 Porton Down veterans having been tested: three vesicants (sulphur mustard, Lewisite, and nitrogen mustard), one nerve agent (sarin), two lachrymators (CS and CR), and two anti-nerve agent pharmaceutical chemicals (pralidoxime and atropine). The median number of tests per veteran was five for vesicants, one for nerve agents, and three for other chemicals.[13]

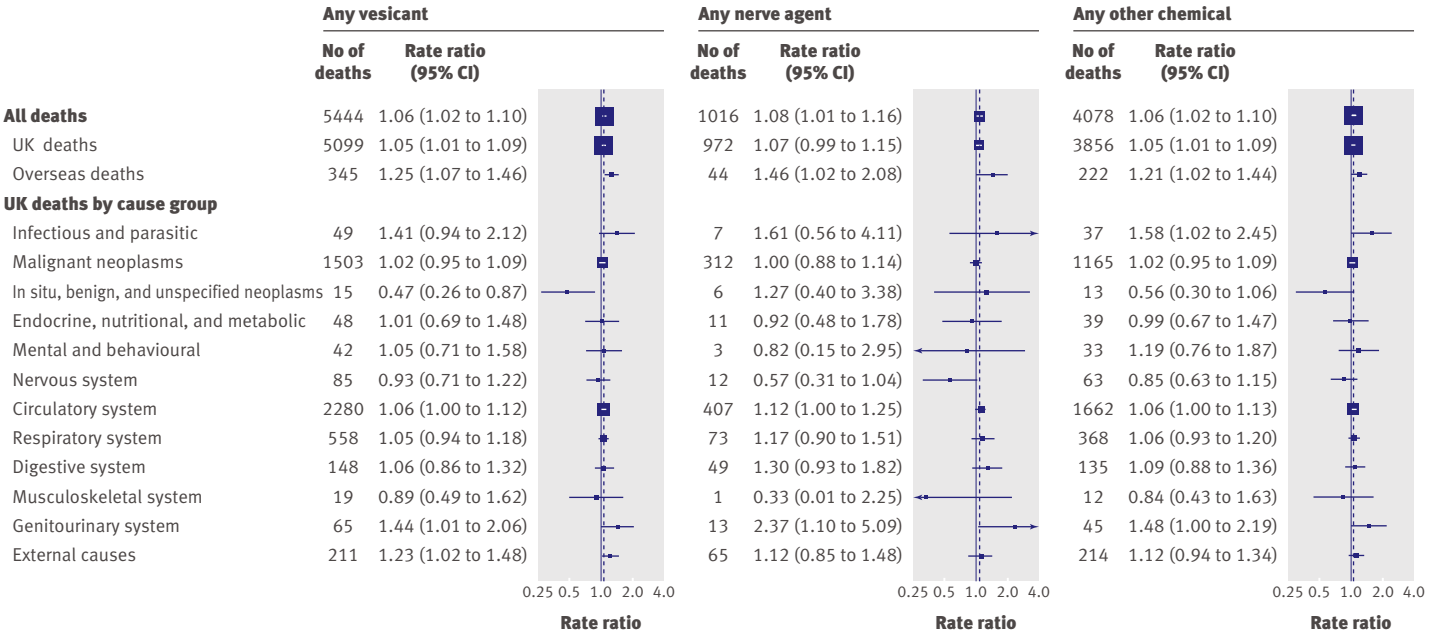
After a median follow-up of over 40 years (median 43.2 (interquartile range 31.4-51.0) for Porton Down and 43.7 (31.9-51.1) for non-Porton Down veterans), 40% (n=7306) of Porton Down and 39% (6900) of non-Porton Down veterans were notified as dead. All cause mortality in both groups was less than in the general population.

All cause mortality in the Porton Down veterans was higher than that of the comparison group (rate ratio 1.06, 95% confidence interval 1.03 to 1.10, table 2), particularly in deaths not registered in the UK (1.26, 1.09 to 1.46). For UK deaths, in four groups of underlying causes, there was a significant excess: infectious

Table 2 | Cause specific mortality in Porton Down veterans compared with non-Porton Down veterans. Rate ratios (95% confidence intervals) with and without adjustment for age group and calendar period

	Observed deaths		Rate ratio	
	Porton Down veterans	Non-Porton Down veterans	Unadjusted	Adjusted (95% CI)
All causes (ICD-10 code)				
Total	7306	6900	1.03	1.06*** (1.03 to 1.10)
All deaths registered in UK (A00-Z99)	6885	6582	1.02	1.06** (1.02 to 1.09)
All deaths not registered in UK	421	318	1.29***	1.26** (1.09 to 1.46)
Cause specific mortality in UK (ICD-10 code)				
Infectious and parasitic (A00-B99)	66	43	1.49	1.57* (1.07 to 2.29)
Malignant neoplasms:				
All (C00-97)	2093	2041	1.00	1.03 (0.97 to 1.10)
Upper aerodigestive (C00-14, C30-32)	59	57	1.01	1.03 (0.71 to 1.48)
Oesophagus (C15)	86	99	0.85	0.87 (0.65 to 1.16)
Stomach (C16)	152	137	1.08	1.13 (0.89 to 1.42)
Intestine and rectum (C17-20)	198	188	1.02	1.06 (0.87 to 1.30)
Pancreas (C25)	83	89	0.91	0.94 (0.70 to 1.27)
Trachea, bronchus, and lung (C33, C34)	785	726	1.05	1.09 (0.98 to 1.21)
Melanoma and other skin (C43, C44)	26	31	0.82	0.83 (0.49 to 1.40)
Prostate (C61)	146	149	0.95	1.01 (0.80 to 1.27)
Urinary tract (C64-68)	122	126	0.94	0.98 (0.76 to 1.26)
Brain and other central nervous system (C71, C72)	46	58	0.77	0.78 (0.53 to 1.15)
All lymphatic and haematopoietic (C81-96)	128	132	0.94	0.96 (0.76 to 1.23)
All other malignant neoplasms†	262	249	1.02	1.06 (0.89 to 1.26)
In situ, benign, and unspecified neoplasms (D10-48)	25	42	0.58*	0.60* (0.37 to 0.99)
Endocrine, nutritional, and metabolic (E00-90)	65	70	0.90	0.94 (0.67 to 1.31)
Mental and behavioural (F00-99)	53	51	1.01	1.08 (0.73 to 1.59)
Nervous system (G00-99)	104	132	0.77	0.80 (0.62 to 1.03)
Circulatory system:				
All (I00-99)	3007	2851	1.03	1.07* (1.01 to 1.12)
Ischaemic heart diseases (I20-25)	2021	1884	1.04	1.08* (1.01 to 1.15)
Cerebrovascular diseases (I60-69)	504	501	0.98	1.03 (0.91 to 1.17)
All other circulatory (I00-19, I26-59, I70-99)	482	466	1.01	1.05 (0.93 to 1.20)
Respiratory system:				
All (J00-99)	694	662	1.02	1.07 (0.96 to 1.19)
Chronic lower respiratory tract (J40-47)	426	417	0.99	1.04 (0.91 to 1.19)
All other respiratory (J00-39, J48-99)	268	245	1.06	1.12 (0.94 to 1.33)
Digestive system (K00-93)	218	206	1.03	1.05 (0.87 to 1.27)
Musculoskeletal system and connective tissue (M00-99)	23	27	0.83	0.87 (0.50 to 1.51)
Genitourinary system (N00-99)	81	57	1.38	1.46* (1.04 to 2.04)
All external causes (S00-T98, V01-Y98)	341	284	1.17	1.17* (1.00 to 1.37)
All other UK deaths with ICD code‡	44	39	1.10	1.12 (0.73 to 1.73)
All other UK deaths with no ICD code	71	77	0.90	0.92 (0.67 to 1.27)

†C21-24, C26-29, C37-41, C45-50, C60, C62, C63, C69, C70, C73-80, C97.
‡D50-89, H00-95, L00-99, Q00-99, R00-99, U00-89, Z00-99.
*P<0.05; **P<0.01; ***P<0.001.



Rate ratios for cause specific mortality in Porton Down veterans included in test(s) involving vesicant(s), nerve agent(s), and any other chemical(s) compared with non-Porton Down veterans, adjusted for age group and calendar period. Rate ratio estimates are represented by boxes with size inversely proportional to variance. Vertical dotted line shows estimates for all deaths. For clarity, only rows for major ICD chapter headings are presented

and parasitic (1.57, 1.07 to 2.29), genitourinary (1.46, 1.04 to 2.04), circulatory (1.07, 1.01 to 1.12), and external (non-medical) (1.17, 1.00 to 1.37) causes (table 2). There was a significant deficit for in situ, benign, and unspecified neoplasms (0.60, 0.37 to 0.99).

When we restricted analysis to veterans with two or more years of service, the all cause mortality rate ratio was similar (1.07, 1.03 to 1.10).

In analyses according to chemical exposure group, the excess all cause mortality seen in the whole cohort was seen in most groups, as were several associations with cause specific mortality (figure). Lewisite exposure was associated with cancers of the trachea, bronchus, and lung (1.19, 1.00 to 1.43) (see bmj.com). In none of the rate ratios for selected causes of death in subgroups of "high" exposure was the estimate higher than the upper bound of the 95% confidence interval for the rate ratio for the exposure group as a whole.

DISCUSSION

Mortality in men in the armed forces who took part in tests at Porton Down from 1941 to 1989 was slightly higher than that of similar veterans who did not take part (rate ratio 1.06). This excess was particularly evident in deaths from infectious and parasitic, circulatory, genitourinary, and external (non-medical) causes, as well as in deaths overseas for which no underlying cause was available. Mortality from cancer was not increased, a similar finding to that for cancer morbidity.[12] Overall mortality in Porton Down veterans was 12% lower than that of the general population. This is perhaps not surprising because these men had all met the selection criteria for military service; similarly low mortality has been found in other UK military cohorts.[14 15]

Strengths and weaknesses

Our large cohort included over 17 000 exposed veterans compared with 6720 and 1545 veterans studied in the United States.[7-10] As well as collecting detailed exposure information[13 16] we assembled a comparison group of similar veterans who did not attend Porton Down. The median duration of follow-up was over 40 years and should be sufficient for major long term risks to emerge.

Previous research

One possible explanation for the excess mortality is the chemical exposures received by the veterans or other aspects of the experience of visiting Porton Down. Increased mortality from respiratory cancer was noted in US and UK service personnel from sulphur mustard in the first world war,[17-19] and UK and Japanese workers who manufactured sulphur mustard in the second world war had raised mortality from malignant and non-malignant respiratory disease.[20 21] In Porton Down veterans with exposure to sulphur mustard, there was an 8% excess mortality from respiratory cancers and a 2% excess from non-malignant respiratory diseases, but these were not statistically significant and the findings in the "high" exposure subgroups were inconsistent. The probable explanation is that, whereas manufacturing workers accumulated months or years of exposure, servicemen spent only days or weeks in experimental programmes with few instances of exposure.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Since the first world war, research programmes into chemical warfare agents and defences against them have involved experiments on members of the armed forces

Few studies have looked at the long term effects on their health

WHAT THIS STUDY ADDS

Mortality was slightly higher than expected in UK veterans of the programme at Porton Down

It was not possible to attribute the higher mortality to these chemicals in the absence of data on other risk factors, such as smoking

There have been few previous studies on the long term effects of these chemicals other than sulphur mustard.[6-9] Although nitrogen mustard has been associated with leukaemias,[22] mortality from lymphatic and haematopoietic cancers was not increased in this study. Our findings suggest that Lewisite exposure in Porton Down veterans might be associated with mortality from cancers of the trachea, bronchus, and lung.[12]

Interpretation

The associations we found between chemical exposure group and cause specific mortality are difficult to interpret. It is possible that Porton Down and non-Porton Down veterans differed in ways that relate to mortality, leading to confounding. We did not collect information about lifestyle factors, most importantly smoking. This limits interpretation.

The large number of outcomes and exposures mean that some significant associations might have occurred by chance.

Summary

This large cohort study with detailed information on chemical exposure provides insights into the long term health of Porton Down veterans. Mortality was slightly higher than in non-Porton Down veterans but with the lack of information about other factors, such as smoking or service overseas, we cannot attribute this small excess to chemical exposures at Porton Down.

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Competing interests: None declared.

Ethical approval: The study was approved by the south east multicentre research ethics committee, the Defence Medical Services clinical research committee, and the Patient Information Advisory Group.

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Cancer morbidity in British military veterans included in chemical warfare agent experiments at Porton Down: cohort study

L M Carpenter,[1] L Linsell,[1] C Brooks,[1] T J Keegan,[1] T Langdon,[1] P Doyle,[2] N E S Maconochie,[2] T Fletcher,[3] M J Nieuwenhuijsen,[4,5] V Beral,[6] K M Venables[1]

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[1]Department of Public Health, University of Oxford, Oxford OX3 7LF
[2]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London
[3]Department of Public Health and Policy, London School of Hygiene and Tropical Medicine
[4]Center for Research in Environmental Epidemiology, IMIM and CIBERESP, 08003 Barcelona, Spain
[5]Division of Epidemiology, Public Health and Primary Care, Imperial College, London
[6]Cancer Epidemiology Unit, University of Oxford
Correspondence to: L M Carpenter lucy.carpenter@dphpc.ox.ac.uk; K M Venables kate.venables@dphpc.ox.ac.uk

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ABSTRACT

Objective To determine cancer morbidity in members of the armed forces who took part in tests of chemical warfare agents from 1941 to 1989.

Design Historical cohort study, with cohort members followed up to December 2004.

Data source Archive of UK government research facility at Porton Down, UK military personnel records, and national death and cancer records.

Participants All veterans included in the cohort study of mortality, excluding those known to have died or been lost to follow-up before 1 January 1971 when the UK cancer registration system commenced: 17 013 male members of the UK armed forces who took part in tests (Porton Down veterans) and a similar group of 16 520 men who did not (non-Porton Down veterans).

Main outcome measures Cancer morbidity in each group of veterans; rate ratios, with 95% confidence intervals, adjusted for age group and calendar period.

Results 3457 cancers were reported in the Porton Down veterans compared with 3380 cancers in the non-Porton Down veterans. While overall cancer morbidity was the same in both groups (rate ratio 1.00, 95% confidence interval 0.95 to 1.05), Porton Down veterans had higher rates of ill defined malignant neoplasms (1.12, 1.02 to 1.22), in situ neoplasms (1.45, 1.06 to 2.00), and those of uncertain or unknown behaviour (1.32, 1.01 to 1.73).

Conclusion Overall cancer morbidity in Porton Down veterans was no different from that in non-Porton Down veterans.

INTRODUCTION

After the first world war, research conducted at the chemical defence establishment at Porton Down included a "human volunteer programme" and members of the armed forces took part in experiments studying the potential impact of chemical agents on military capability and the effectiveness of protective measures.[1 2] Between 1941 and 1989, over 18 000 members of the armed forces were recorded as having taken part in this programme. Over 50% of these veterans took part in tests involving chemicals that are known or probable human carcinogens.[3] While their overall cancer mortality was similar to that of veterans who did not take part in tests at Porton Down,[4] past exposure to these chemicals might have affected their risk of developing common cancers with relatively good survival. We report here on cancer morbidity in Porton Down veterans.

METHODS

Study population

Porton Down veterans were all male members of the British armed forces recorded as having participated in tests between 1 April 1941 and 31 December 1989, while non-Porton Down veterans were other similar members of the armed forces not recorded as having taken part in tests at Porton Down.[4] We excluded veterans known to have died or been lost to follow-up before 1 January 1971.

Follow-up

We obtained death certificates, notifications of emigrations, and data on all cancers registered since 1 January 1971, when the UK cancer registration system commenced, from the National Health Service central registers.[4]

Classification of chemical exposures

We used contemporaneous experimental records from the Porton Down historical archive to retrospectively assess exposure.[3 5] The type of chemical was coded as being a vesicant (blistering agent), a nerve agent, or other chemical. There were eight specific chemicals for which there were records of at least 1000 Porton Down veterans having been tested: three vesicants (sulphur mustard, Lewisite, and nitrogen mustard), one nerve agent (sarin), two lachrymators (CS and CR), and two anti-nerve agent pharmaceutical chemicals (pralidoxime and atropine). Two of these chemicals have been classified by the International Agency for Research on Cancer (IARC) as either a known (sulphur mustard and cancer of the upper and lower respiratory tract) or probable (nitrogen mustard and squamous cell carcinoma of the skin) human carcinogen.[6] We also considered benzene, a chemical classified by IARC as a leukaemogen[6] and used as a diluent in tests in 994 veterans.[3]

Where possible we classified veterans according to cumulative exposure. For vesicants, we classed "high" exposures as ≥10.63 mg of sulphur mustard, ≥13.69 mg of Lewisite, and ≥23.73 mg of nitrogen mustard.[3] At

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least one dermal vesicle or necrosed area after tests was considered a "high" biological effect. For chemicals other than vesicants or nerve agents, we collected information on the number of tests recorded.

Statistical analysis

All veterans included in the previously reported mortality analysis as alive and under follow-up on or after 1 January 1971 contributed to the analysis. We compared cancer registration rates in Porton Down veterans with those of non-Porton Down veterans by calculating rate ratios. For each Porton Down veteran, we counted person years of follow-up from 1 January 1971 or the earliest subsequent date that they were first recorded as being included in a test. For non-Porton Down veterans, we counted person years from their enlistment date plus the interval between the corresponding Porton Down veteran's enlistment and first visit to Porton Down. For each specific cancer site or type, person years stopped at the earliest of date of registration of the first cancer, death, loss to follow-up, or 31 December 2004.

Rate ratios were estimated for all neoplasms combined and according to type (malignant, in situ, benign, uncertain or unknown behaviour). For malignant neoplasms, we also estimated rate ratios separately for 16 predetermined cancer sites or types. Veterans with more than one cancer of the same site or type had only the first cancer counted while those with cancers registered for two or more different types (such as primary cancers of skin and bladder) contributed a cancer to each. All rate ratios were adjusted for age group and calendar period.

We also compared rates of cancer in each group of veterans with rates in England and Wales. Standardised registration ratios were estimated from the ratio of observed to expected registrations.

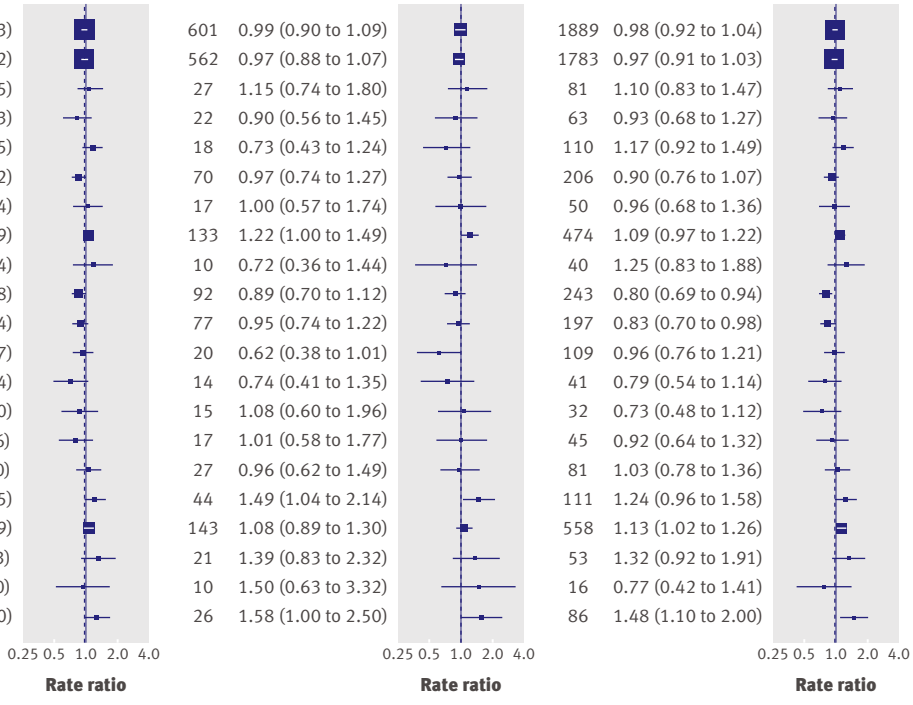
Analyses reported here relate to 17 013 Porton Down veterans, and 16 520 non-Porton Down veterans.

RESULTS

Of the veterans included in the mortality analysis, 93% (17 013/18 276) of Porton Down veterans and 94% (16 520/17 600) of non-Porton veterans contributed data to analyses on cancer morbidity. Service at enlistment and other characteristics were similar to that of non-Porton Down veterans. Porton Down veterans had a longer total duration of military service.

The number of men with one or more cancer registrations was 3029 in Porton Down veterans and 3015 in non-Porton Down veterans. We identified a further 530 veterans with cancer from death certificates (259

	Any vesicant		Any nerve agent		Any other chemical	
	No of cases	Rate ratio (95% CI)	No of cases	Rate ratio (95% CI)	No of cases	Rate ratio (95% CI)
Any neoplasm	2173	0.97 (0.92 to 1.03)	601	0.99 (0.90 to 1.09)	1889	0.98 (0.92 to 1.04)
Any malignant neoplasm	2076	0.97 (0.91 to 1.02)	562	0.97 (0.88 to 1.07)	1783	0.97 (0.91 to 1.03)
Upper aerodigestive	85	1.09 (0.83 to 1.45)	27	1.15 (0.74 to 1.80)	81	1.10 (0.83 to 1.47)
Oesophagus	63	0.82 (0.60 to 1.13)	22	0.90 (0.56 to 1.45)	63	0.93 (0.68 to 1.27)
Stomach	145	1.15 (0.92 to 1.45)	18	0.73 (0.43 to 1.24)	110	1.17 (0.92 to 1.49)
Intestine and rectum	230	0.86 (0.73 to 1.02)	70	0.97 (0.74 to 1.27)	206	0.90 (0.76 to 1.07)
Pancreas	64	1.04 (0.75 to 1.44)	17	1.00 (0.57 to 1.74)	50	0.96 (0.68 to 1.36)
Trachea, bronchus, and lung	618	1.07 (0.96 to 1.19)	133	1.22 (1.00 to 1.49)	474	1.09 (0.97 to 1.22)
Melanoma of skin	33	1.17 (0.75 to 1.84)	10	0.72 (0.36 to 1.44)	40	1.25 (0.83 to 1.88)
Other skin	269	0.84 (0.73 to 0.98)	92	0.89 (0.70 to 1.12)	243	0.80 (0.69 to 0.94)
Prostate	254	0.89 (0.75 to 1.04)	77	0.95 (0.74 to 1.22)	197	0.83 (0.70 to 0.98)
Bladder	134	0.94 (0.75 to 1.17)	20	0.62 (0.38 to 1.01)	109	0.96 (0.76 to 1.21)
Other urinary tract	37	0.71 (0.49 to 1.04)	14	0.74 (0.41 to 1.35)	41	0.79 (0.54 to 1.14)
Brain and other central nervous system	36	0.87 (0.58 to 1.30)	15	1.08 (0.60 to 1.96)	32	0.73 (0.48 to 1.12)
All leukaemias	43	0.80 (0.55 to 1.16)	17	1.01 (0.58 to 1.77)	45	0.92 (0.64 to 1.32)
Other lymphatic and haematopoietic	82	1.06 (0.80 to 1.40)	27	0.96 (0.62 to 1.49)	81	1.03 (0.78 to 1.36)
All other primary	113	1.21 (0.94 to 1.55)	44	1.49 (1.04 to 2.14)	111	1.24 (0.96 to 1.58)
Ill defined, secondary, or unspecified	683	1.07 (0.97 to 1.19)	143	1.08 (0.89 to 1.30)	558	1.13 (1.02 to 1.26)
Any in situ neoplasm	49	1.32 (0.90 to 1.93)	21	1.39 (0.83 to 2.32)	53	1.32 (0.92 to 1.91)
Any benign neoplasm	18	0.93 (0.51 to 1.70)	10	1.50 (0.63 to 3.32)	16	0.77 (0.42 to 1.41)
Any neoplasm of uncertain or unknown behaviour	78	1.26 (0.93 to 1.70)	26	1.58 (1.00 to 2.50)	86	1.48 (1.10 to 2.00)



Rate ratios for selected cancer sites or types in Porton Down veterans included in tests involving vesicants, nerve agents, and any other chemical relative to all non-Porton Down veterans, adjusted for age group and calendar period. Rate ratio estimates are represented by box with size inversely proportional to variance. Vertical dotted line shows the estimate for any neoplasm

Rate ratios (95% confidence intervals) for selected cancer sites and types in Porton Down veterans relative to non-Porton Down veterans, unadjusted and adjusted for age group and calendar period

Cancer site/type (ICD-10 code)	No of cases		Rate ratio	
	Porton Down veterans	Non-Porton Down veterans	Unadjusted	Adjusted (95%CI)
Any malignant neoplasm (C00-C97)	3114	3140	0.96	0.99 (0.94 to 1.04)
Upper aerodigestive (C00-C14, C30-C32)	132	117	1.10	1.11 (0.87 to 1.43)
Oesophagus (C15)	103	115	0.87	0.89 (0.68 to 1.16)
Stomach (C16)	189	170	1.08	1.12 (0.91 to 1.38)
Intestine and rectum (C17-C20)	364	392	0.90	0.93 (0.81 to 1.07)
Pancreas (C25)	89	91	0.95	0.98 (0.73 to 1.31)
Trachea, bronchus, and lung (C33, C34)	851	782	1.06	1.09 (0.99 to 1.20)
Melanoma of skin (C43)	60	50	1.17	1.19 (0.82 to 1.74)
Other skin (C44)	436	496	0.86	0.87* (0.77 to 0.99)
Prostate (C61)	381	422	0.88	0.92 (0.80 to 1.05)
Bladder (C67)	193	202	0.93	0.97 (0.79 to 1.18)
Other urinary tract (C64-C66, C68)	65	85	0.75	0.76 (0.55 to 1.04)
Brain and other central nervous system (C71, C72)	56	66	0.83	0.83 (0.58 to 1.19)
All leukaemias (C91-C95)	74	84	0.86	0.89 (0.65 to 1.21)
Other lymphatic and haematopoietic (C81-C90, C96)	139	126	1.08	1.09 (0.86 to 1.39)
All other primary malignant neoplasms†	182	148	1.20	1.22 (0.99 to 1.52)
Ill defined, secondary, or unspecified malignant neoplasms (C76-C80)	975	878	1.08	1.12* (1.02 to 1.22)
Any in situ neoplasm (D00-D09)	93	64	1.42	1.45* (1.06 to 2.00)
Any benign neoplasm (D10-D36)	31	31	0.98	0.99 (0.60 to 1.63)
Any neoplasm of uncertain or unknown behaviour (D37-D48)	126	95	1.29	1.32* (1.01 to 1.73)
Any neoplasm (C00-C97, D00-D48)	3288	3282‡	0.97	1.00 (0.95 to 1.05)

*P<0.05.
†C21-24, C26-C29, C37-C41, C45-C50, C60, C62, C63, C69, C70, C73-C75, C97.
‡Excludes neoplasms for four veterans for whom person years could not be calculated.

and 271). The total number of cancers recorded in each group was 3457 and 3380, respectively.

Overall, rates for all neoplasms were the same in both groups of veterans (rate ratio 1.00, 95% confidence interval 0.95 to 1.05) as were those for all malignant neoplasms (0.99, 0.94 to 1.04) (table). Porton Down veterans had higher rates of ill defined, secondary, or unspecified malignant neoplasms (1.12, 1.02 to 1.22), in situ neoplasms (1.45, 1.06 to 2.00), and those of uncertain or unknown behaviour (1.32, 1.01 to 1.73) and lower rates of skin cancer other than melanoma (0.87, 0.77 to 0.99).

Rate ratios for all neoplasms and all malignant neoplasms were just below unity for veterans exposed to tests involving any vesicant (figure), sulphur mustard, or nitrogen mustard and just above unity for Lewisite (see bmj.com). Veterans exposed to Lewisite had rates of cancer of the trachea, bronchus, and lung 25% higher than non-Porton Down veterans (1.25, 1.05 to 1.48, P=0.01). Porton Down veterans exposed to tests involving any nerve agent, sarin, or any chemical other than nerve agents or vesicants had rate ratios for all neoplasms and all malignant neoplasms just below unity (figure and see bmj.com). The rate of cancer of the oesophagus was raised in veterans exposed to CS (2.17, 1.04 to 4.52, P=0.03).

We estimated rate ratios in veterans classified as having had high levels of exposure or biological effect either for chemicals with previous evidence of carcinogenicity or where rate ratios were raised in Porton Down veterans (see bmj.com). The only instance where the estimate for the high exposure group was above the upper limit of the 95% confidence interval for all veterans was for skin cancers other than melanoma in relation to high dermal exposure to nitrogen mustard (1.59, 0.97 to 2.61, *v* 1.13, 0.82 to 1.57). For veterans with a dermal vesicle recorded (high biological effect), however, the rate ratio estimate was lower than that of all exposed veterans (1.05, 0.59 to 1.87).

When compared with cancer registration rates in England and Wales, rates in Porton Down veterans were 10% lower for all neoplasms (standardised registration ratio 0.90, 0.87 to 0.93) and 6% lower for all malignant neoplasms (0.94, 0.91 to 0.98). Corresponding results for non-Porton Down veterans were 0.87 (0.85 to 0.90) and 0.94 (0.90 to 0.97), respectively.

DISCUSSION

Overall occurrence of cancer in veterans who took part in tests at Porton Down was similar to that of other veterans and lower than in the general population. These findings are in accord with their cancer

mortality.[4] We also found no evidence of an excess of any specific, clearly defined, cancer type or site in all Porton Down veterans combined. In the current study, we were particularly interested in cancers with a relatively good survival. There was no evidence to suggest rates of one of the commonest of these—malignant skin cancers other than melanoma—were higher in Porton Down veterans. Porton Down veterans did, however, experience increased rates of ill defined, secondary or unspecified malignant neoplasms, in situ neoplasms, and neoplasms of uncertain or unknown behaviour. Such findings are difficult to interpret in the absence of information on smoking habits and other risk factors for cancer.

Given the large number of outcomes and exposure groups in the study, some of the associations found might be due to chance. Of the nine specific chemicals we focused on, over half of Porton Down veterans were included in tests involving the carcinogen sulphur mustard but they experienced no increased cancer morbidity, either overall or for any specific cancer. This probably reflects the low cumulative exposures received, especially compared with those of manufacturing workers in whom excesses of upper and lower respiratory cancer have been reported.[7 8]

Despite it being a known human carcinogen, there was no evidence of an overall excess of cancer in veterans exposed to benzene. Previous epidemiological evidence indicates an association between occupational exposure to benzene and leukaemia.[6] The increased strength of association with skin cancer other than melanoma in veterans recorded to have high exposure to nitrogen mustard is noteworthy, given previous evidence that this chemical is a human carcinogen.[6] This needs to be qualified, however, by the absence of an increase in those in whom the biological effect was high.

While there was no evidence of an overall excess of cancer in Porton Down veterans exposed to Lewisite (an organic arsenic compound), there was an excess of lung cancer morbidity. The lack of association with increasing exposure or effect levels for this chemical, together with the lack of data on a known key confounding factor (smoking), make it difficult to attribute this excess to tests at Porton Down.

For the other chemicals examined, there were no clear associations between any specific defined cancer type or site with sarin, pralidoxime, or atropine. For CS, while the overall cancer occurrence was lower than in non-Porton Down veterans, it was raised for cancer of the oesophagus, particularly in those who had two or more tests. A similar excess was seen in veterans exposed to CR, the other lachrymator included in our analyses.

In summary, the overall rates of cancer morbidity in Porton Down veterans were not raised relative to other veterans or the general population. The excesses of ill defined, secondary or unspecified malignant neoplasms, in situ neoplasms, and neoplasms of uncertain or unknown behaviour were seen across several of the chemical exposure groups analysed and are difficult to interpret.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many tests in the Porton Down research programme into chemical warfare agents involved known carcinogens

WHAT THIS STUDY ADDS

Overall cancer morbidity was no higher in military personnel who had been included in tests at Porton Down than in those who had not been included or in the general population

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Competing interests: None declared.

Ethical approval: The study was approved by the south east multicentre research ethics Committee, the Defence Medical Services clinical research committee, and the Patient Information Advisory Group.

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Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study

Roel de Heus,[1] Ben Willem Mol,[2,3] Jan-Jaap H M Erwich,[4] Herman P van Geijn,[5] Wilfried J Gyselaers,[9] Myriam Hanssens,[10] Linda Härmark,[7] Caroline D van Holsbeke,[9] Johannes J Duvekot,[6] Fred F A M Schobben,[8] Hans Wolf,[3] Gerard H A Visser[1]

EDITORIAL by Smith and colleagues

[1]Department of Perinatology and Gynaecology, University Medical Centre Utrecht, KJ.02.507.0/ PO Box 85090, Utrecht, Netherlands
[2]Department of Perinatology and Gynaecology, Maxima Medical Centre, Veldhoven, Netherlands
[3]Department of Perinatology and Gynaecology, Academic Medical Centre, University of Amsterdam, Netherlands
[4]Department of Perinatology and Gynaecology, University Medical Centre Groningen, Netherlands
[5]Department of Obstetrics and Gynaecology, Free University Medical Centre, University of Amsterdam
[6]Department of Perinatology and Gynaecology, Erasmus University Medical Centre, Rotterdam
[7]Pharmacovigilance Centre Lareb, Hertogenbosch, Netherlands
[8]Department of Clinical Pharmacy, University Medical Centre, Utrecht
[9]Department of Perinatology and Gynaecology, Hospital Oost-Limburg, Genk, Belgium
[10]Department of Perinatology and Gynaecology, University Hospital of Leuven, Belgium

Correspondence to: R de Heus
R.deHeus-2@umcutrecht.nl

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ABSTRACT

Objective To evaluate the incidence of serious maternal complications after the use of various tocolytic drugs for the treatment of preterm labour in routine clinical situations.

Design Prospective cohort study.

Setting 28 hospitals in the Netherlands and Belgium.

Participants 1920 consecutive women treated with tocolytics for threatened preterm labour.

Main outcome measures Maternal adverse events (those suspected of being causally related to treatment were considered adverse drug reactions) leading to cessation of treatment.

Results An independent panel evaluated the recorded adverse events, without knowledge of the type of tocolytic used. Of the 1920 women treated with tocolytics, 1327 received a single course of treatment (69.1%), 282 sequential courses (14.7%), and 311 combined courses (16.2%). Adverse drug reactions were categorised as serious or mild in 14 cases each. The overall incidence of serious adverse drug reaction was 0.7%. Compared with atosiban, the relative risk of an adverse drug reaction for single treatment with a β adrenoceptor agonist was 22.0 (95% confidence interval 3.6 to 138.0) and for single treatment with a calcium antagonist was 12 (1.9 to 69). Multiple drug tocolysis led to five serious adverse drug reactions (1.6%). Multiple gestation, preterm rupture of membranes, and comorbidity were not independent risk factors for adverse drug reactions.

Conclusions The use of β adrenoceptor agonists or multiple tocolytics for preventing preterm birth is associated with a high incidence of serious adverse drug reactions. Indometacin and atosiban were the only drugs not associated with serious adverse drug reactions. A direct comparison of the effectiveness of nifedipine and atosiban in postponing preterm delivery is needed.

INTRODUCTION

Preterm labour is the most reported cause of perinatal morbidity and mortality in the Western world.[1 2] Tocolytic drugs have not been shown to improve fetal outcome but are used to postpone delivery for 48 hours to allow for maximal effect of parenteral steroids in the mother and to enable the mother to be transferred to a centre with a neonatal intensive care unit.[3] Drugs registered for tocolysis include the β adrenoceptor agonist ritodrine and the oxytocin receptor antagonist atosiban. Cyclo-oxygenase inhibitors and calcium channel blockers are also used,[4 5] although they are not registered for tocolysis.

The choice of first line tocolytics for the treatment of preterm labour is controversial because of inconclusive information on the relative safety of the agents.[6 7] We carried out a prospective cohort study to evaluate the incidence of serious maternal complications with the use of various tocolytics to treat preterm labour in routine clinical situations.

METHODS

We carried out an open label, prospective, cohort study of consecutive women treated with tocolytics according to local protocol in 28 hospitals in the Netherlands and Belgium during January 2006 to July 2007. Potential participants were identified by the attending doctor or a study nurse and registered through a study website. We recorded the personal and obstetrical characteristics of each woman, including the date of birth, gestational age, parity, cervical dilation, blood loss, intact versus ruptured membranes, number of fetuses, and any comorbidities such as cardiopulmonary disease, hypertension, and diabetes. We also recorded the type of tocolytic treatment and any maternal adverse event that required cessation of treatment. In cases of possible adverse events the principal investigator completed a standard case report.

Three obstetricians (J-JHME, HW, MH) and two pharmacologists (LH, FFAMS) established whether the adverse events occurred during tocolysis and required discontinuation of treatment in the opinion of the attending obstetrician, and then classified them for severity (serious or mild). The reviewers individually considered all adverse events, blind to the tocolytic used. A serious adverse event was any of the following: severe hypotension (systolic blood pressure <100 mm Hg and >20% drop compared with baseline values), severe dyspnoea, lung oedema, myocardial infarction, anaphylactic shock, admittance to intensive care, or maternal death.[8] A mild adverse event was one leading to cessation of treatment but not meeting the criteria for a serious adverse event.

Each reviewer subsequently received the list of adverse events and tocolytics to assess whether the adverse events were related to each drug, using the causality categories of the World Health Organization: certain, probable, possible, unlikely, conditional, and non-assessable (see bmj.com).[9] We defined all adverse

events causally related to tocolytic treatment as adverse drug reactions.

Analysis

We classified the administration of tocolytics as single treatment (one tocolytic), sequential treatment (multiple tocolytics given separately in sequence), or combined treatment (multiple tocolytics given simultaneously). The primary outcome of the study was the incidence of serious adverse drug reactions to tocolytics. In each of the three treatment categories we calculated the incidence of a tocolytic related adverse drug reaction. For single treatments, we carried out a separate analysis for each type of tocolytic. We then calculated the relative risk, the associated 95% confidence interval, and the number needed to harm, using the single course tocolytic with the lowest incidence as a reference category. Using logistic regression we carried out a subgroup analysis of possible contributing factors to the incidence of tocolytic related adverse drug reactions, such as multiple gestation, medical history, or any obstetric comorbidity.

RESULTS

Overall, 1920 women were treated with tocolytic drugs in the study hospitals. The mean maternal age was 29.8 years (interquartile range 26.4-33.3 years), and the mean gestational age was 29 weeks (interquartile range 27-31 weeks). The tocolytics used were nifedipine (n=1022, 34.3%), atosiban (n=1248, 41.9%), the β adrenoceptor agonists ritodrine and fenoterol (n=411, 13.8%), the cyclo-oxygenase inhibitor indometacin (n=261, 8%), magnesium sulphate (n=18, 0.6%), and transdermal nitroglycerin (n=4).

Adverse events were recorded in 38 women. Of the remaining 31 cases after exclusions, 16 were categorised as serious adverse events and 15 as mild (see bmj.com). A causal relation to treatment was considered unlikely in two cases of serious adverse events and in one case of mild adverse events (see bmj.com). These cases were not included in further analyses, leaving 14 serious adverse drug reactions and 14 mild adverse drug reactions. Four women needed intensive care, all after multiple treatment with tocolytics. No fetal deaths were reported during treatment and none of the mild or serious adverse drug reactions was followed by fetal or neonatal death.

Adverse drug reactions associated with single tocolytic treatment. Values are numbers (percentages) of women unless stated otherwise

Tocolytic	No of patients	Severity of adverse drug reaction		Total	Relative risk* (95% CI)
		Serious	Mild		
β mimetics	175	3 (1.7)	4 (2.3)	7 (4.0)	3.8 (1.6 to 9.2)
Nifedipine	542	5 (0.9)	6 (1.1)	11 (2.0)	2.0 (0.8 to 4.8)
Atosiban	575	0	1 (0.2)	1 (0.2)	0.07 (0.01 to 0.4)
Cyclo-oxygenase inhibitors	35	0	0	0	NA

NA=Not applicable.
*For total adverse drug reactions.

Among 575 women treated with a single course of atosiban, none had a serious adverse drug reaction and one had a mild adverse drug reaction (0.2%; table). Among 542 women treated with nifedipine, five had a serious adverse drug reaction (0.9%) and six had a mild adverse drug reaction (1.1%). Among 175 women treated with β adrenoceptor agonists, three had a serious adverse drug reaction (1.7%) and four had a mild adverse drug reaction (2.3%). The number needed to treat to prevent a serious adverse drug reaction with atosiban compared with β adrenoceptor agonists was 59 (lower limit of 95% confidence interval 35) and compared with nifedipine was 108 (56). Compared with atosiban the relative risk of an adverse drug reaction (mild and serious) with β adrenoceptor agonists was 22.0 (95% confidence interval 3.6 to 138.0) and with nifedipine was 12 (1.9 to 69.0).

Ten different combinations of tocolytics were recorded in 311 instances. In patients who received these combinations, five serious (1.6%) and one mild (0.3%) adverse drug reactions were observed. No serious adverse drug reactions were reported in combinations using cyclo-oxygenase inhibitors (n=143). In 282 women who received sequential treatment, one serious and two mild (0.7%) adverse drug reactions were observed, all during administration of the second drug; a β mimetic and nifedipine.

The use of tocolytics was recorded in 414 women with a multiple pregnancy. Four of these women had a serious adverse drug reaction compared with women with a singleton pregnancy (relative risk 1.5, 95% confidence interval 0.39 to 5.0). Two of the women (2.0%) were treated with a single course of nifedipine (n=101) and two (2.4%) were treated with combined courses (n=84). Logistic regression showed that preterm rupture of membranes, blood loss, and other obstetric comorbidities were not independently related to an adverse event.

DISCUSSION

The use of β adrenoceptor agonists or multiple tocolytics, but not indometacin or atosiban, to prevent preterm labour is associated with a high incidence of serious adverse drug reactions.

Randomised studies on the efficiency of tocolytics and adverse events have generally been restricted to well defined (low risk) populations, excluding women with multiple pregnancies, preterm rupture of membranes, vaginal bleeding, diabetes, or a history of cardiovascular diseases; however, many of the case reports on adverse drug reactions to tocolytics have been associated with these conditions.[10-14] We assessed the occurrence of serious adverse drug reactions in women related to the use of different tocolytics in a routine clinical setting. Our results therefore apply to situations normally encountered in clinical practice, with low and high risk cases. We cannot exclude the possibility of under-reporting of adverse events as the intensity of monitoring—especially of blood pressure—may vary between hospitals.

In our study the overall incidence of serious adverse drug reactions was low (0.7%). The incidence of serious

WHAT IS ALREADY KNOWN ON THIS TOPIC

Preterm birth is the major cause of perinatal mortality and mobidity

Tocolytics are used to postpone delivery to allow for maximal effect of steroids given to the mother and transfer of the mother to a centre with a neonatal intensive care unit

The choice of first line tocolytic drug is controversial because of inconclusive information on the mother's safety with use of various tocolytic agents

WHAT THIS STUDY ADDS

β adrenoceptor agonists or multiple tocolytics for preventing preterm birth are associated with a high incidence of adverse drug reactions

Indometacin and atosiban are the only tocolytic drugs not associated with serious adverse drug reactions in women

A direct comparison of effectiveness between nifedipine and atosiban in postponing preterm delivery is needed

adverse drug reactions in women receiving combined courses of tocolytics (16.2% of all patients) was, however, high (1.6-2.5%). In women treated with a single tocolytic, the incidence of serious adverse drug reactions was 1.7% for β mimetics and 0.9% for nifedipine. No serious adverse drug reaction was observed after treatment with a single course of atosiban. Most of the adverse drug reactions reported in women treated with nifedipine were related to blood pressure. In six of the seven cases, hypotension developed within two to four hours after the start of tocolysis.

In most of the recent case reports that raised concerns about the safety of calcium antagonists in women, complicating factors such as multiple pregnancy, cardiovascular disease, diabetes, or infections were present.[10 13 15 16] We did not find any significant association between adverse drug reactions to nifedipine and these factors. We found four non-significant serious adverse drug reactions in women with multiple pregnancy—two women receiving nifedipine (2%) and two receiving combined treatment (2.4%).

β adrenoceptor agonists do not seem to be more effective than atosiban, nifedipine, or cyclo-oxygenase inhibitors in preventing preterm birth,[4 5 17-19] and our results confirm the high incidence of adverse drug reactions with these agents.[17 20] In our study only a few women were treated with cyclo-oxygenase inhibitors, most likely because in Belgium and the Netherlands these drugs are restricted to women in early gestation. Moreover, concerns about fetal side effects limit the use of cyclo-oxygenase inhibitors for tocolysis.[21 22] We found no adverse drug reactions, either with single treatment or with cyclo-oxygenase inhibitors combined with other tocolytics.

An ideal tocolytic should postpone delivery at low costs without maternal and fetal side effects. None of the tocolytics described in this study fulfils these criteria. We found that combined treatment or a single treatment using β adrenoceptor agonists led to a higher incidence of serious adverse drug reactions. The overall incidence of serious adverse drug reactions with a single course of nifedipine in a singleton pregnancy seems to be low, but not absent. Atosiban has the best maternal and fetal safety profile but at considerable cost. A direct comparison of effectiveness between oxytocin antagonists and calcium channel blockers is lacking.

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Competing interests: WJG did a retrospective cohort study on tocolysis in 2006 (not published) which was supported by an unconditional grant from Ferring Pharmaceuticals.
Ethical approval: This study was approved by the medical review ethics committee of University Medical Centre Utrecht.

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Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data

Tony Kendrick,[1] Christopher Dowrick,[2] Anita McBride,[1] Amanda Howe,[3] Pamela Clarke,[2] Sue Maisey,[3] Michael Moore,[1] Peter W Smith[4]

EDITORIAL by Van Weel and colleagues

[1]University of Southampton Primary Medical Care Group, Aldermoor Health Centre, Southampton SO16 5ST
[2]University of Liverpool School of Population, Community and Behavioural Sciences, University of Liverpool, Liverpool L69 3GB
[3]University of East Anglia School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ
[4]Southampton Statistical Sciences Research Institute, University of Southampton, Southampton SO17 1BJ
Correspondence to: T Kendrick A.R.Kendrick@Southampton.ac.uk

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STUDY QUESTION Do general practitioner rates of drug prescribing and referrals for depression vary in line with patients' scores on the depression severity questionnaires recommended in the UK quality and outcomes framework (QOF)?

SUMMARY ANSWER Prescriptions and referrals were significantly associated with higher depression severity scores. Overall rates of treatment and referral were similar for patients assessed with the two most frequently used questionnaires, however, despite more than 80% of patients scoring as moderately to severely depressed on one questionnaire compared with just over half of patients on the other. Doctors' decisions on intervention are not based on the questionnaire scores alone. Questionnaires' threshold scores for intervention should be made more consistent with each other and with doctors' clinical judgment.

Participants and setting
Thirty eight general practices in three sites—Southampton, Liverpool, and Norwich—agreed to participate.

Design
Anonymised medical record data were collected on 2294 patients who had been assessed with depression severity questionnaires in April 2006 to March 2007.

Primary outcomes
Rates of prescribing of antidepressants and referrals to specialist mental health or social services.

Main results
A total of 1658 patients were assessed with the patient health questionnaire (PHQ-9), 584 with the hospital anxiety and depression scale (HADS), and 52 with the Beck depression inventory (BDI-II). Overall, 79.1% of patients assessed with either PHQ-9 or HADS received a prescription for an antidepressant, and 22.8% were referred to specialist services. The odds of receiving a prescription or referral were significantly higher where questionnaire scores indicated moderate to severe depression. Overall rates of intervention were similar for patients assessed with either measure despite PHQ-9 classifying 83.5% of patients as moderately to severely depressed, compared with only 55.6% of patients assessed with HADS. The odds of receiving intervention tended to be lower for older patients and those with physical comorbidity (see table) even though screening for depression among such patients is encouraged in the QOF.

Bias, confounding, and other reasons for caution
The sample included too few patients assessed with BDI-II for meaningful analysis of that measure. The sample assessed with HADS was only a third of the size of that assessed with PHQ-9 and included relatively fewer older patients, recurrent cases, and patients with physical illness, increasing the risk of missing associations with severity and the other factors in the HADS group (type II error).

Generalisability to other populations
This was not a random sample of practices but volunteers that probably included doctors with a particular interest in the study; they may not be representative of UK general practitioners. The odds of receiving antidepressants or referral varied between the three centres, possibly because of variation in the availability of psychological therapies as an alternative to drug treatment.

Study funding/potential competing interests
The study was funded by Lilly, Lundbeck, Servier, and Wyeth pharmaceuticals; Southampton City Primary Care Trust; and the Mental Health Research Network. None had any role in study design, execution, or publication. TK has received fees for presenting at meetings from pharmaceutical companies. TK and CD are members of the mental health expert panel for the QOF.

LOGISTIC REGRESSION ANALYSES OF FACTORS PREDICTING INTERVENTION FOR DEPRESSION

Intervention	Adjusted odds ratio (95% CI)			
	Moderate to severe depression score	Age ≥65 years	Diabetes	Coronary heart disease
Patients assessed with PHQ-9				
Prescription for an antidepressant	8.75 (4.97 to 15.44)***	0.79 (0.53 to 1.18)	0.57 (0.37 to 0.87)*	0.54 (0.35 to 0.83)**
Referral to mental health or social services	1.63 (0.81 to 3.30)	0.50 (0.31 to 0.80)**	0.51 (0.29 to 0.89)*	0.40 (0.23 to 0.71)**
Patients assessed with HADS				
Prescription for an antidepressant	6.55 (3.84 to 11.18)***	1.23 (0.55 to 2.74)	0.52 (0.22 to 1.24)	0.68 (0.26 to 1.78)
Referral to mental health or social services	2.35 (1.26 to 4.37)**	0.18 (0.05 to 0.60)**	0.69 (0.22 to 2.20)	1.98 (0.61 to 6.44)

*P<0.05; **P<0.01; ***P<0.001

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Patients' and doctors' views on depression severity questionnaires incentivised in UK quality and outcomes framework: qualitative study

Christopher Dowrick,[1] Geraldine M Leydon,[2] Anita McBride,[2] Amanda Howe,[3] Hana Burgess,[2] Pamela Clarke,[1] Sue Maisey,[3] Tony Kendrick[2]

EDITORIAL by Van Weel and colleagues

[1]University of Liverpool School of Population, Community and Behavioural Sciences, University of Liverpool, Liverpool L69 3GB
[2]University of Southampton Primary Medical Care Group, Aldermoor Health Centre, Southampton SO16 5ST
[3]University of East Anglia School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ
Correspondence to: C Dowrick
cfd@liverpool.ac.uk

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STUDY QUESTION What are general practitioners' and patients' views of the introduction of severity questionnaires for depression and their interpretation in practice?

SUMMARY ANSWER General practitioners were more cautious about the validity and utility of severity measures than were patients. Doctors favoured clinical judgment over questionnaires, whereas patients placed more weight on questionnaires as an objective adjunct to medical judgment and an indication of doctors' careful assessment.

Rationale, design, data collection method
Since April 2006 the UK quality and outcomes framework (QOF) has offered financial incentives to general practitioners to measure the severity of depression, using validated questionnaires, at the outset of treatment in all diagnosed cases. How doctors and patients view this is unclear. We did a semistructured qualitative interview study to examine their views.

Participants and setting
Thirty four general practitioners and 24 patients from Southampton, Liverpool, and Norfolk took part.

Recruitment/sampling strategy
The doctors were recruited from a parallel quantitative study. Potential patients for participation were identified by general practitioners during routine consultations, by written invitation, or by self referral.

Data analysis method
Semistructured interviews were done by researchers. Topic guides included views on intended and unintended consequences of the introduction of the depression severity indicator. Analysis of transcribed interviews followed the principles of constant comparison.

Main findings
Patients generally favoured the measures of severity for depression, whereas general practitioners were generally cautious about their validity and utility and sceptical about the motives behind their introduction. Both doctors and patients considered that assessments of severity should be seen as one aspect of holistic care. Doctors considered their clinical judgment to be more important than objective assessments and were concerned that the assessments reduced the human element of the consultation. Patients were more positive about the questionnaires, seeing them as an efficient and structured supplement to medical judgment and as evidence that doctors were taking their problems seriously. Doctors and patients were aware of the potential for manipulation of indicators: for economic reasons for doctors, and for patients to avoid stigma or achieve desired outcomes.

Implications
Patients' favourable responses suggest that the depression severity measures may have benefits for primary care consultations, by increasing patients' confidence that doctors are taking their mental health seriously. Education of primary care staff may be necessary to optimise the use of the measures. In future, quality indicators should be piloted before their introduction. The findings of both convergence and divergence between doctors' and patients' perspectives are likely to have relevance beyond the UK's indicators for depression care.

Bias, limitations, generalisability
Doctors who took part in this study may have expressed stronger opinions than the norm: we need to be aware of the complexity of doctors' narratives. Patients recruited through general practitioners may have been relatively sympathetic to general practice. We could not assess whether patients' responses may have varied according to current severity of depression.

Study funding/potential competing interests
Funding came from Lilly, Lundbeck, Servier, and Wyeth pharmaceuticals; Southampton City Primary Care Trust; and the Mental Health Research Network. The study sponsor was the University of Liverpool. None of the above bodies had any role in the conduct of the study or its publication. TK and CD are mental health expert advisors for the UK GP contract QOF.

PARTICIPANTS' COMMENTS

General practitioners
"Mental health, mental illness ... more than most other illnesses are so patient specific ... How it affects their lives depends on what they're doing in their lives, depends on what their background is, might depend on family history, and might depend on so many other factors, I think it's um ... (completely) impossible to, to mechanise the assessments"

"Yeah, I mean the threat, the threat is that people will rely on the HAD score as opposed to their own clinical judgment"

"So, whilst I do feel ... that kind of idea of recipe book medicine, or, or, um ... if you get this score you do that, you know, is a bit ... is a bit less human"

Patients
"It's probably something the doctor should have asked a long time ago, you know, 'cause blokes especially are never going to come in and say, 'Ooh I'm depressed': it's like, 'Come back with a proper illness,' you know"

"It can be perceived as you're being taken more seriously, I suppose"

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