The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database

Susan S. Jick & Katrina Wilcox Hagberg

Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA, USA

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Testosterone products are indicated for primary or secondary hypogonadism and can be delivered through various routes including oral and intramuscular injection.
- While many clinical trials have evaluated the effectiveness of testosterone therapy, there is little information on safety particularly in different formulations.
- Hypertension, polycythemia and prostatic abnormalities (prostatism, benign prostatic hypertrophy or prostate cancer) have been identified as potential adverse effects of testosterone replacement therapy, but data are limited.

WHAT THIS STUDY ADDS

- Risks of prostate cancer and prostatism were similar in users of the oral and injectable testosterone preparations, but risks were higher for hypertension and polycythemia in the injectable compared with the oral testosterone users.
- Risk of benign prostatic hypertrophy was slightly higher in the oral users, but the difference was small and could have been due to bias.

Correspondence

Dr Susan S Jick DSc, Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA 02421, USA.
Tel.: +1 781 862 6660
Fax: +1 781 862 1680
E-mail: sjick@bu.edu

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AIMS

To study the relative safety of the intramuscular injection formulation of testosterone with oral testosterone undecanoate in relation to the risks for hypertension, polycythemia, prostate cancer, benign prostatic hypertrophy (BPH) and prostatism.

METHODS

We conducted a cohort study of men in the UK based General Practice Research Database who were users of the oral undecanoate and injectable forms of testosterone and calculated rates and relative risks of hypertension, polycythemia and prostate conditions (cancer, BPH and prostatism).

RESULTS

We identified 5841 men who received at least one study testosterone preparation. There were 202 cases of hypertension (crude incidence rates (IRs) for oral and injectable testosterone respectively 12.3/1000 person-years (PY) and 14.4/1000 PY). There were 146 cases of polycythemia (IRs 1.2/1000 PY and 10.1/1000 PY), 46 cases of prostate cancer (IRs 2.5/1000 PY and 1.8/1000 PY), 106 cases of BPH (IRs 4.1/1000 PY and 2.1/1000 PY), and 251 cases of prostatism (IRs 8.4/1000 PY and 6.1/1000 PY respectively). Adjusted relative risks for oral compared with injectable testosterone were 0.8 (95% CI 0.6, 1.2) for hypertension, 0.13 (0.05, 0.35) for polycythemia, 1.1 (0.7, 1.7) for prostate cancer, 1.5 (1.1, 2.2) for BPH and 1.1 (0.8, 1.4) for prostatism.

CONCLUSIONS

Risks of prostate cancer and prostatism were similar in users of the two preparations, but risks were higher for hypertension and polycythemia in the injectable compared with the oral testosterone users. Risk of BPH was slightly higher in the oral users, but the difference was small and could have been due to bias.

Introduction

Testosterone products are indicated for primary or secondary hypogonadism [1] and can be delivered through various routes including oral, transdermal, subdermal or intramuscular injection. While many clinical trials have evaluated the effectiveness of testosterone therapy, there is little information on safety, particularly in long term testosterone users. Currently most of the available information on the safety of testosterone therapy comes from small clinical trials or spontaneous reports, as well as from a small number of observational studies [2–9]. Polycythemia has been described in men exposed to testosterone and raised haematocrit in testosterone users has been well documented [3–5]. The results of trials and small studies in relation to risk of hypertension have been inconclusive [5–8]. These trials have been small and of short duration resulting in small numbers of subjects and events and limited ability to draw useful inferences from the results. Investigations of the association between testosterone use and prostate cancer are subject to similar limitations [5, 8, 9]. While hypertension, polycythemia including increased haemoglobin/haematocrit, and prostatic abnormalities [prostatism, benign prostatic hypertrophy (BPH) or prostate cancer] have been identified as potential adverse effects of testosterone replacement therapy, there is no information on risk according to route of administration. Intramuscular testosterone injection results in variable serum testosterone concentrations over the course of the injection interval while oral testosterone use leads to more stable concentrations though the clinical response is variable [1]. Choice of testosterone formulation is based on personal preference, tolerance of testosterone concentrations and fluctuations, and age [1]. In order to compare risks in these two formulations of testosterone, oral testosterone undecanoate and intramuscular (i.m.) injectable testosterone therapy which account for around two thirds of non-topical testosterone use in the GPRD, we estimated incidence rates and relative risks of various adverse outcomes [hypertension, polycythemia and prostatic abnormalities (prostate cancer, BPH or prostatism)] using a cohort study in the United Kingdom (UK) based General Practice Research Database (GPRD).

Methods

Data resource

This study was conducted using data from the GPRD. The UK provides a unique medical environment to create an optimum computerized medical data resource, where the information on all relevant medical care is located in the offices of the general practitioners. The GPRD, currently owned and maintained by the UK's Medicines and Healthcare Products Regulatory Agency, comprises over 7 million Britons. The data are recorded using multiple data files

including the registration, drug and event (diagnoses, procedures) files, and additional files with information on laboratory test results, and patient details (such as height, weight smoking, etc). The Drug File contains detailed information on all drugs prescribed by the GP. Validation studies have been conducted to assess the quality and completeness of the information recorded in the GPRD [10–12] and have found the GPRD to be of high quality.

Study population and design

The cohort study was conducted using data updated through October 2009. The base cohort was composed of all males who received at least one prescription for oral testosterone undecanoate or i.m. injectable testosterone in the GPRD between January 1 1991 and October 2009. Within this base cohort, sub-cohorts were identified to estimate the incidence rates of each outcome of interest (i.e. treated hypertension, polycythemia, prostate cancer, BPH and prostatism). In each sub-cohort, patients entered the cohort upon first receipt of a prescription for a study testosterone medication and were followed until the end of the study period, end of registration with the practice, death or until they developed the respective outcome of interest. Incidence rates (IRs) and incidence rate ratios (IRRs) for each outcome of interest during the person-time under risk were calculated separately for oral testosterone undecanoate and injectable testosterone users.

Sub-cohorts

To ensure that only incident cases of the different outcomes of interest were identified within this study, patients with a prior diagnosis of the respective outcome of interest at the time of cohort entry were excluded from the respective sub-cohorts.

Hypertension sub-cohort All potential new cases of treated primary hypertension (defined as at least one diagnosis code for hypertension plus at least one prescription for antihypertensive medication), that occurred during exposed person-time and at least 1 year after the start of the patient's record were identified. Patients who developed secondary hypertension were not considered as cases and their person-time was censored at the date of the first hypertension diagnosis.

Polycythemia/elevated haemoglobin or haematocrit sub-cohort All potential new cases of polycythemia, including those with a first haemoglobin value greater than 17.3 gm/dl or a first haematocrit greater than 52%, that occurred during exposed person-time and at least 1 year after the start of the patient's record were identified. Note that laboratory values were not available in the GPRD records until after 2000 so cases identified through laboratory test findings for haemoglobin or haematocrit were limited to the later years of the study. Patients who had

polycythemia diagnosed less than 1 year after the start of their record were not considered as cases and their person-time was not included.

Prostate cancer sub-cohort All potential new cases of prostate cancer that occurred after first study testosterone prescription and at least 2 years after the start of the patient's record were identified. To account for the induction period for prostate cancer, all potential cases were required to have at least 1 year from the day of first study testosterone prescription to the first prostate cancer diagnosis. Anyone with an indication of pre-existing prostate cancer (i.e. prior to cohort entry) or who developed prostate cancer less than 2 years after the start of their record was not considered a case and their person-time was censored at the date of the first prostate cancer diagnosis.

Benign prostatic hypertrophy sub-cohort All potential new cases of BPH that occurred after first study testosterone prescription and at least 2 years after the start of the patient's record were identified. Anyone with an indication of pre-existing BPH (i.e. prior to cohort entry), who developed BPH less than 2 years after the start of their record or who had a prostate cancer diagnosis prior to the first BPH diagnosis was not considered a case and their person-time was censored at the date of the first BPH diagnosis.

Prostatism sub-cohort All potential new cases of prostatism that occurred after first study testosterone prescription and at least 2 years after the start of the patient's record were identified and their records reviewed. Anyone with an indication of pre-existing prostatism (i.e. prior to cohort entry) or who had a prostate cancer or BPH diagnosis prior to the first prostatism diagnosis was not considered a case. Patients who developed prostatism less than 2 years after the start of their record were not counted as cases and their person-time was censored at the date of the first prostatism diagnosis.

Exposure

Exposed person-time was defined as the period of filled use plus an appropriate exposure time window. Filled use for each oral testosterone undecanoate prescription was estimated by dividing the number of tablets by the prescribed daily dose. Prescriptions for injectable testosterone were assumed, after a review of prescription records, to cover 30 days of filled use. The period of exposure differed according to the outcome under investigation. For *Hypertension and polycythemia*, a person was considered exposed from the day of a study testosterone prescription until the end of the prescriptions' filled use plus 90 days. If a person switched to the other study testosterone then person-time started accumulating on the new testosterone. We did not separately estimate person-time for concomitant exposure to both testosterone formulations (this represented less than 1% of all exposed time). At the end of

Table 1

Characteristics of men in the GPRD who received a prescription for oral testosterone undecanoate or injectable testosterone

Characteristic	Full cohort (n = 5841)		
	Injectable* n = 4190 (%)	Oral* n = 1329 (%)	Both* n = 322 (%)
Age at first use (years)			
<20	745 (18)	151 (11)	44 (14)
20–39	765 (18)	113 (9)	63 (20)
40–59	1577 (38)	605 (46)	143 (44)
60–79	1058 (25)	441 (33)	72 (22)
80+	45 (1)	19 (1)	0 (0)
Year of first use			
1988–1993	777 (19)	274 (21)	94 (29)
1994–1997	720 (17)	413 (31)	90 (28)
1998–2001	862 (21)	325 (24)	76 (24)
2002–2005	930 (22)	195 (15)	36 (11)
2006–2009	901 (22)	122 (9)	26 (8)
New user	3116 (74)	232 (17)	233 (72)
Prevalent user	1074 (26)	1097 (83)	89 (28)
BMI (kg m ⁻²)			
<20	118 (3)	24 (2)	6 (2)
20–25	610 (15)	224 (17)	47 (15)
26–30	970 (23)	361 (27)	75 (23)
30+	740 (18)	169 (13)	32 (10)
Unknown	1752 (42)	551 (41)	162 (50)
Smoking			
Never	1467 (35)	471 (35)	107 (33)
Current	647 (15)	245 (18)	44 (14)
Past	648 (15)	169 (13)	44 (14)
Unknown	1428 (34)	444 (33)	127 (39)
Klinefelter's syndrome	162 (4)	22 (2)	16 (5)
Hypogonadism	398 (10)	39 (3)	29 (9)
Erectile dysfunction	527 (13)	174 (13)	30 (9)
CVD	433 (10)	150 (11)	19 (6)
Hypertension	681 (16)	228 (17)	37 (11)
Diabetes	459 (11)	106 (8)	20 (6)
Asthma/COPD	591 (14)	166 (12)	38 (12)
Alcohol abuse	260 (6)	75 (6)	12 (4)

*These are mutually exclusive exposure categories.

filled use plus 90 days person-time stopped accumulating. All other time was considered non-exposed time. For each case exposure was assigned to the last testosterone formulation received prior to the index date. For *Prostate cancer, prostatism, and benign prostatic hypertrophy*, a person was considered exposed to either oral testosterone undecanoate or injectable testosterone from the day of first study testosterone prescription until the end of follow-up (i.e. the earliest of the respective prostate diagnosis, death, transferred out of the practice or end of record). This definition of person-time at risk was used to take into consideration the fact that testosterone exposure may influence the future risk of developing a prostate outcome even after intake was discontinued. If a person switched to the other study testosterone then person-time started accumulating on the new testosterone preparation. Cases were considered exposed to the last testosterone formulation received before the index date.

Table 2

Distribution of testosterone exposure among cases of hypertension and polycythemia (displayed as %)

Characteristic	Full cohort (n = 5841)			Hypertension cases (n = 202)		Polycythemia cases (n = 146)	
	Injectable* n = 4190 %	Oral* n = 1329 %	Both* n = 322 %	Injectable n = 168 %	Oral n = 34 %	Injectable n = 142 %	Oral n = 4 %
Age at first use (years)							
<20	18	11	14	0	0	0	0
20–39	18	9	20	8	9	10	0
40–59	38	46	44	49	53	37	100
60–79	25	33	22	41	38	51	0
80+	1	1	0	2	0	2	0
Year of first use							
1988–1993	19	21	29	6	15	1	0
1994–1997	17	31	28	10	12	4	0
1998–2001	21	24	24	26	20	16	0
2002–2005	22	15	11	34	47	28	50
2006–2009	22	9	8	24	6	51	50
New user	74	17	72	67	68	74	75
Prevalent user	26	83	28	33	33	26	25
BMI (kg m ⁻²)							
<20	3	2	2	1	0	1	0
20–25	15	17	15	15	18	11	0
26–30	23	27	23	20	24	24	50
30+	18	13	10	19	12	35	25
Unknown	42	41	50	45	47	29	25
Smoking							
Never	35	35	33	31	44	42	0
Current	15	18	14	19	6	15	50
Past	5	13	14	13	12	20	50
Unknown	34	33	39	38	38	23	0
Klinefelter's syndrome	4	2	5	4	0	8	25
Hypogonadism	10	3	9	10	9	11	0
Erectile dysfunction	13	3	9	8	15	19	25
CVD	10	11	6	2	6	12	0
Hypertension	16	17	11	–	–	21	25
Diabetes	11	8	6	10	6	11	0
Asthma/COPD	14	12	2	11	9	7	0
Alcohol abuse	6	6	4	6	9	4	25

*Exposure categories are mutually exclusive.

Covariates

Age, calendar year and new use vs. prevalent use of testosterone were important covariates. Patients who received a first study testosterone prescription 6 or more months after the start of the computer record were considered 'new users' and prevalent users were patients who received their first study testosterone prescription less than 6 months after the start of their computer record.

We also evaluated the effects of other covariates including body mass index (BMI), smoking (current, never, past or unknown) and presence of one of the following comorbidities: Klinefelter's syndrome, hypogonadism, erectile dysfunction, cardiovascular disease (CVD), hypertension, diabetes, asthma or COPD or alcohol abuse.

Statistical analyses

We described all men in the study population according to whether they had ever received injectable, oral or both

formulations of testosterone. We estimated crude IRs and 95% confidence intervals (CIs) for each of the study outcomes for oral testosterone undecanoate and injectable testosterone use and calculated IRRs and corresponding 95% CIs. All IRs and IRRs are reported per 1000 person-years (PY) at risk. Analyses were adjusted for age and calendar year using Mantel Haenszel multivariate regression for each of the five sub-cohorts.

The list of potential confounders evaluated in the final analysis was derived from the baseline characteristics that differed between users of the two study testosterone formulations. All covariates were evaluated as potential confounders, by testing to see if they changed the main effect by more than 10%, but none met this level of effect. All analyses were stratified by age, calendar year; and additionally by new vs. prevalent use of the study testosterone to account for bias related to prevalent use at cohort entry. We also conducted analyses restricted to men who had no

Table 3

Hypertension incidence rates per 1000 person-years (PY) and rate ratios

		Oral	Injectable (reference)						
Cases		PY	Rate	Cases	PY	Rate	IRR	95% CI	
Incidence rates and IRR by age group									
<20 years	0	300	0.0	0	1074	0.0	NA		
20–39 years	3	339	8.9	13	2771	4.7	1.89	0.43, 6.17	
40–59 years	18	1161	15.5	82	4695	17.5	0.89	0.52, 1.45	
60–79 years	13	909	14.3	70	3006	23.3	0.61	0.33, 1.08	
80+ years	0	58	0.0	3	147	20.4	0	0.00, 4.35	
Cases		Oral	Rate	Cases	Injectable	Rate	IRR	95% CI	
		PY			PY				
Incidence rates and IRR by year category									
1988–1993	5	347	14.4	10	1237	8.1	1.78	0.55, 5.18	
1994–1997	4	631	6.3	16	1845	8.6	0.73	0.21, 2.07	
1998–2001	7	739	9.5	44	2508	17.5	0.54	0.22, 1.15	
2002–2005	16	595	26.9	57	3063	18.6	1.45	0.81, 2.48	
2006–2009	2	455	4.4	41	3040	13.5	0.33	0.05, 1.14	
Cases		Oral	Rate	Cases	Injectable	Rate	IRR	95% CI	Adjusted IRR* (95% CI)
		PY			PY				
Incidence rates and IRR									
Total	34	2767	12.3	168	11 693	14.4	0.86	0.58, 1.23	0.81 (0.56, 1.17)
New	23	1841	12.5	112	7450	15.0	0.83	0.52, 1.28	0.79 (0.51, 1.23)
Prevalent	11	926	11.9	56	4243	13.2	0.90	0.45, 1.67	0.88 (0.46, 1.68)
Incidence rates and IRR restricted to those with no prior testosterone use before cohort entry									
Total	33	2587	12.7	156	10 952	14.2	0.90	0.61, 1.29	0.85 (0.59, 1.25)
New	22	1680	13.1	100	6807	14.7	0.89	0.55, 1.40	0.85 (0.54, 1.35)
Prevalent	11	907	12.1	56	4145	13.5	0.90	0.45, 1.67	0.87 (0.46, 1.66)

*Adjusted for age and calendar time.

prior history of receiving prescriptions for a non-study testosterone preparation before entering the cohort. Finally, we conducted several sensitivity analyses to evaluate whether the results were influenced by our outcome definitions and our exposure windows. We conducted analyses using a shorter exposure window for the two acute outcomes. We also assessed the possibility that the time window assigned to each acute outcome was too short by re-analyzing the data using an extended time window. The analysis of BPH was stratified by whether there was treatment for the BPH or not.

All statistical analyses were carried out using SAS Release 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

There were 5841 men who received at least one study testosterone preparation and who had an average of 7.3 years of follow-up after entry into the cohort. Seventy-two percent of men had received prescriptions for injectable testosterone, 23% had received prescriptions for oral testosterone and 5% had received both. Because a small proportion of men received both formulations of testosterone,

and only one case (prostatism) received both concomitantly at the index date, we were not able to evaluate separately the effects of exposure to both. Seventy-one percent of all men had 1 or more years between the start of their GPRD record and their first study testosterone prescription (mean 5.4 years). Characteristics of all men who used a study drug are provided in Table 1. Users of oral testosterone undecanoate were similar to users of the injectable forms of testosterone with respect to smoking history, BMI, and history of CVD, hypertension, asthma/COPD and alcohol abuse. Users of injectable testosterone were younger, more likely to have been new users (compared with prevalent users), more likely to have had their first prescription later in the study period, slightly more likely to have a history of diabetes than users of oral testosterone undecanoate, three times as likely to have hypogonadism and twice as likely to have Klinefelter's syndrome. Eight percent of men in the cohort had received a non-study testosterone prior to their first study testosterone prescription.

There were 4895 people in the *Hypertension* sub-cohort (946 people had hypertension prior to testosterone use) from which we identified 202 cases with newly diagnosed hypertension. Table 2 provides the characteristics of the

Table 4

Polycythemia incidence rates per 1000 person-years (PY) and rate ratios

		Oral	Injectable (reference)						
	Cases	PY	Rate	Cases	PY	Rate	IRR	95% CI	
Incidence rates and IRR by age group									
<20 years	0	300	0.0	0	1079	0.0	NA		
20–39 years	0	354	0.0	14	2846	4.9	0.0	0.00, 1.92	
40–59 years	4	1371	2.9	52	5500	9.5	0.31	0.09, 0.78	
60–79 years	0	1349	0.0	73	4346	16.8	0.0	0.00, 0.14	
80+ years	0	72	0.0	3	263	11.4	0.0	0.00, 6.35	
	Cases	Oral PY	Rate	Cases	Injectable PY	Rate	IRR	95% CI	
Incidence rates and IRR by year category									
1988–1993	0	409	0.0	1	1365	0.7	0.0	0.00, 63.4	
1994–1997	0	756	0.0	5	2106	2.7	0.0	0.00, 2.29	
1998–2001	0	901	0.0	23	2977	7.7	0.0	0.00, 0.46	
2002–2005	2	784	2.6	40	3714	10.8	0.24	0.04, 0.83	
2006–2009	2	596	3.6	73	3872	18.9	0.18	0.03, 0.61	
	Cases	Oral PY	Rate	Cases	Injectable PY	Rate	IRR	95% CI	Adjusted IRR* (95% CI)
Incidence rates and IRR									
Total	4	3446	1.2	142	14 034	10.1	0.11	0.04, 0.28	0.13 (0.05, 0.35)
New	3	2365	1.3	105	9254	11.4	0.11	0.03, 0.31	0.14 (0.04, 0.41)
Prevalent	1	1081	0.9	37	4780	7.7	0.12	0.01, 0.62	0.13 (0.02, 0.90)
Incidence rates and IRR restricted to those who received a study testosterone after 1/1/2000 and who had a laboratory test noted									
Total	3	1452	2.1	71	7181	9.9	0.21	0.05, 0.59	0.23 (0.07, 0.72)
New	2	1310	1.2	62	6147	10.1	0.15	0.02, 0.52	0.17 (0.04, 0.68)
Prevalent	1	142	7.0	9	1034	8.7	0.81	0.04, 4.93	0.69 (0.08, 5.75)
Incidence rates and IRR restricted to those with no prior testosterone use before cohort entry									
Total	4	3202	1.3	126	13 704	9.2	0.14	0.04, 0.33	0.15 (0.06, 0.39)
New	3	2142	1.4	89	8391	10.6	0.13	0.03, 0.37	0.15 (0.05, 0.48)
Prevalent	1	1060	0.9	37	4683	7.9	0.12	0.01, 0.62	0.13 (0.02, 0.89)

*Adjusted for age and calendar time.

cases. Of these men 83% were exposed to injectable testosterone while the remaining 17% were exposed to oral testosterone at the onset of hypertension. The crude rates of hypertension were lower in those taking oral compared with injectable testosterone (IR 12.3/1000 PY and 14.4/1000 PY, respectively). The adjusted IRR for oral compared with injectable testosterone was 0.8 (95% CI 0.6, 1.2) (Table 3). The IRs were similar in new and prevalent users. The rates of hypertension did not materially change when we restricted the analysis to men who had not received another testosterone preparation prior to entering the cohort, or when we conducted sensitivity analyses to evaluate alternate exposure windows.

There were 5813 men in the *Polycythemia* sub-cohort (28 men had polycythemia before receipt of their first testosterone prescription) and 146 men had a diagnosis of polycythemia or a high haemoglobin or haematocrit value. Of these, nearly all were exposed to an injectable form of testosterone (97%). Men with polycythemia tended to be older than all men in the sub-cohort, and were more likely to have a history of hypertension and erectile dysfunction. The number of cases also increased over the period of the

study, likely because of the increased recording of laboratory values starting around the year 2000 (see Table 2 for characteristics of the cases). The rates of polycythemia were lower in those taking oral compared with injectable testosterone (IRs 1.2/1000 PY and 10.1/1000 PY, respectively). The adjusted IRR for oral compared to injectable testosterone was 0.13 (95% CI 0.05, 0.35) (Table 4).

To evaluate the possibility that men taking injectable testosterone may have had more laboratory tests and therefore been more likely to be identified as a case, for the *polycythemia* sub-cohort we conducted an analysis restricted to those individuals who had received a study testosterone after January 1 2000 (when laboratory values began to be consistently recorded in the GPRD) and who had at least one laboratory test noted in their record. The rates of polycythemia were not significantly changed and continued to be lower in those taking oral compared with injectable testosterone. The adjusted IRR was 0.23, (95% CI 0.07, 0.7). The rates of polycythemia did not materially change when we restricted the analysis to men who had not received a non-study testosterone preparation prior to entering the cohort. The IRRs were also similar in the new

Table 5

Distribution of testosterone exposure among cases of prostate cancer, BPH and prostatism (displayed as %)

Characteristic	Full cohort (n = 5841)			Prostate cancer cases (n = 76)			BPH cases (n = 106)			Prostatism cases (n = 251)		
	Injectable* n = 4190 %	Oral* n = 1329 %	Both* n = 322 %	Injectable* n = 46 %	Oral* n = 26 %	Both* n = 4 %	Injectable* n = 56 %	Oral* n = 45 %	Both* n = 5 %	Injectable* n = 159 %	Oral* n = 81 %	Both* n = 11 %
Age at first use (years)												
<20	18	11	14	0	0	0	0	0	0	<1	0	0
20–39	18	9	20	0	0	0	0	0	0	0	0	0
40–59	38	46	44	11	19	0	14	11	40	22	35	18
60–79	25	33	22	83	65	100	72	84	60	71	56	64
80+	1	1	0	7	15	0	14	4	0	6	10	18
Year of first use												
1988–1993	19	21	29	2	4	0	4	2	0	4	7	0
1994–1997	17	31	28	7	8	0	14	4	20	16	17	18
1998–2001	21	24	24	17	15	25	25	24	0	16	20	36
2002–2005	22	15	11	41	42	50	34	40	60	32	25	9
2006–2009	22	9	8	33	31	25	23	29	20	33	31	36
New user	74	17	72	83	85	50	89	89	60	79	90	82
Prevalent user	26	83	28	17	15	50	11	11	40	21	10	18
BMI (kg m ⁻²)												
<20	3	2	2	0	0	0	0	2	0	0	0	0
20–25	15	17	15	28	23	50	14	27	0	17	20	18
26–30	23	27	23	30	35	0	36	27	0	28	31	36
30+	18	13	10	20	8	0	20	9	20	16	14	9
Unknown	42	41	50	22	34	50	30	36	80	38	36	36
Smoking												
Never	35	35	33	61	46	0	43	31	20	40	36	18
Current	15	18	14	11	19	75	16	20	20	16	17	18
Past	15	13	14	11	4	0	20	18	0	19	20	27
Unknown	34	33	39	17	31	25	21	31	60	25	27	36
Klinefelter's syndrome	4	2	5	0	0	0	0	0	0	3	0	0
Hypogonadism	10	3	9	2	0	0	2	2	0	6	3	9
Erectile dysfunction	13	13	9	17	8	25	16	11	0	11	15	18
CVD	10	11	6	17	15	25	18	13	0	21	20	9
Hypertension	16	17	11	15	12	50	18	22	0	28	21	9
Diabetes	11	8	6	14	4	0	16	2	0	2	11	0
Asthma/COPD	14	12	12	13	19	25	14	9	0	10	9	9
Alcohol abuse	6	6	4	9	4	0	4	7	0	8	4	0

*Exposure categories are mutually exclusive.

and prevalent users (Table 4) and when we conducted sensitivity analyses to evaluate alternate exposure windows.

There were 5253 men in the *Prostate cancer* sub-cohort after excluding 588 men who had cancer prior to first testosterone use. After exclusions there were 76 cases of newly diagnosed prostate cancer in the study population that occurred at least 1 year after receipt of the first study testosterone prescription and who had at least 2 years of history in their record prior to diagnosis. Of these 46 (60%) had taken injectable testosterone, 26 (34%) had taken oral testosterone undecanoate and four (5%) had received both forms at some time prior to the cancer diagnosis. Men with prostate cancer tended to be older than all men in the sub-cohort (there were no cases under age 40 years), but were otherwise similar (see Table 5 for details). The crude rates of prostate cancer were slightly higher in those taking oral compared with injectable testosterone (IR 2.5/1000 PY and 1.8/1000 PY, respectively), but the adjusted IRR for oral compared with injectable testosterone was 1.1

(95% CI 0.7, 1.7). The IRRs were similar in the strata of prevalent and new users. The rates of prostate cancer did not materially change when we restricted the analysis to men who had not received another testosterone preparation prior to entering the cohort; adjusted IRR was 1.2 (95% CI 0.7, 1.9) (Table 6).

There were 5766 men in the *BPH cohort* and 106 men who had a new diagnosis of BPH in their record after excluding 75 men who had BPH before first receiving testosterone. Of these, 45 men (42%) had been exposed to oral testosterone undecanoate, 56 (53%) to injectable testosterone and 5 (5%) had taken both forms at some time prior to the index date. Men with BPH tended to be older than all men in the sub-cohort (there were no cases less than age 40 years). They were also more likely to have CVD and be new vs. prevalent users of a study testosterone (Table 5). The rate of BPH was slightly higher in those taking oral compared with injectable testosterone (IR 4.1/1000 PY and 2.1/1000 PY, respectively). The adjusted IRR

Table 6

Prostate cancer incidence rates per 1000 person-years (PY) and rate ratios

		Oral		Injectable (reference)				
Cases	PY	Rate	Cases	PY	Rate	IRR	95% CI	
Incidence rates and IRR by age group								
<20 years	0	608	0.0	0	2 514	0.0	NA	
20–39 years	0	1 121	0.0	0	5 303	0.0	NA	
40–59 years	5	3 888	1.3	5	9 019	0.6	2.35	
60–79 years	19	5 327	3.6	40	9 486	4.2	0.85	
80+ years	4	468	8.6	3	730	4.1	2.08	
Cases	PY	Rate	Cases	PY	Rate	IRR	95% CI	
Incidence rates and IRR by year category								
1988–1993	1	625	1.6	1	1 839	0.5	2.94	
1994–1997	2	1 787	1.1	3	3 840	0.8	1.43	
1998–2001	5	3 074	1.6	8	5 973	1.3	1.21	
2002–2005	12	3 198	3.8	20	7 592	2.6	1.42	
2006–2009	8	2 728	2.9	16	7 808	2.1	1.43	
Cases	PY	Rate	Cases	PY	Rate	IRR	95% CI	Adjusted IRR* (95% CI)
Incidence rates and IRR								
Total	28	11 412	2.5	48	27 052	1.8	1.38	0.87, 2.20
New	23	9 257	2.5	39	20 878	1.9	1.33	0.79, 2.23
Prevalent	5	2 155	2.3	9	6 174	1.5	1.59	0.53, 4.75
Incidence rates and IRR restricted to those with no prior testosterone use before cohort entry								
Total	28	10 855	2.6	44	25 846	1.7	1.51	0.93, 2.43
New	23	8 729	2.6	35	19 711	1.8	1.48	0.87, 2.51
Prevalent	5	2 126	2.4	9	6 135	1.5	1.60	0.49, 4.79

*Adjusted for age and calendar time.

for BPH was 1.5 (95% CI 1.1–2.2) for users of oral testosterone undecanoate compared with users of injectable testosterone. Rates were higher in the stratum of new users compared with prevalent users for both oral and injectable testosterone users. Not all cases of BPH could be confirmed through their computer record as having symptoms or appropriate treatment, so in order to address the possibility that not all men with a BPH diagnosis code had true BPH we stratified the analysis by treated vs. untreated BPH. The stratified rates remained slightly higher among users of oral compared with injectable testosterone, though the adjusted IRR for the treated BPH cases (oral compared with injectable testosterone) was lowered to 1.3 (95% CI 0.9, 2.0) while the IRR for the untreated cases was 3.8 (95% CI 1.4, 10.6). The rates of benign prostatic hypertrophy did not materially change when we restricted the analysis to men who had not received another testosterone preparation prior to entering the cohort ($n = 5292$). Nor were there differences in the analyses stratified by new vs. prevalent use (Table 7).

There were 5422 men in the *Prostatism* cohort. We identified 251 cases of prostatism diagnosed at least 1 year after receiving testosterone. Of these cases, 159 (63%) were exposed to an injectable form of testosterone, 81 (32%) received oral testosterone undecanoate, and the remaining 11 (4%) received both forms. Men with prostatism

tended to be older than all men in the sub-cohort, only one case was younger than 40 years, and to have more CVD and hypertension. They were otherwise similar to the base cohort (Table 5). The rates of prostatism were similar for those taking oral and injectable testosterone (IRs 8.4/1000 PY and 6.1/1000 PY, respectively). The adjusted IRR for prostatism in oral compared with injectable testosterone was 1.1 (95% CI 0.8, 1.4). The rates did not materially change when we restricted the analysis to men who did not have a record for another testosterone preparation prior to entering the cohort (Table 8). Finally there were no notable differences between new and prevalent users.

Discussion

This study provides rates (IRs) and relative risks (IRRs) for five adverse outcomes among men exposed to either oral testosterone undecanoate or injectable testosterone. While men of all ages received testosterone most outcomes occurred in men aged 40 years or older. This is particularly true of the prostate outcomes (prostate cancer, BPH and prostatism). Many men in this study had Klinefelter's syndrome or erectile dysfunction, received testosterone for long periods of time and injectable testosterone was prescribed more often than oral testosterone undecanoate.

Table 7

BPH incidence rates per 1000 person-years (PY) and rate ratios

	Oral			Injectable (reference)			IRR	95% CI	
	Cases	PY	Rate	Cases	PY	Rate			
Incidence rates and IRR by age group									
<20 years	0	660	0.0	0	2 696	0.0	NA		
20–39 years	0	1 175	0.0	0	6 095	0.0	NA		
40–59 years	6	4 110	1.5	9	10 178	0.9	1.65	0.54, 4.69	
60–79 years	40	5 443	7.3	41	10 046	4.1	1.80	1.16, 2.79	
80+ years	2	464	4.3	8	685	11.7	0.37	0.05, 1.60	
	Cases	Oral PY	Rate	Cases	Injectable PY	Rate	IRR	95% CI	
Incidence rates and IRR by year category									
1988–1993	1	667	1.5	2	2 026	1.0	1.52	0.05, 20.0	
1994–1997	2	1 864	1.1	9	4 218	2.1	0.50	0.07, 2.11	
1998–2001	11	3 214	3.4	14	6 528	2.2	1.60	0.70, 3.54	
2002–2005	20	3 313	6.0	20	8 329	2.4	2.51	1.34, 4.71	
2006–2009	14	2 794	5.0	13	8 599	1.5	3.31	1.54, 7.19	
	Cases	Oral PY	Rate	Cases	Injectable PY	Rate	IRR	95% CI	Adjusted IRR* (95% CI)
Incidence rates and IRR									
Total	48	11 852	4.1	58	29 700	2.0	2.07	1.41, 3.04	1.53 (1.05, 2.24)
New	42	9 753	4.3	51	22 694	2.3	1.92	1.27, 2.88	1.45 (0.97, 2.18)
Prevalent	6	2 099	2.9	7	7 006	1.0	2.86	0.90, 8.83	2.23 (0.75, 6.63)
Treated BPH	37	11 852	3.1	53	29 700	1.8	1.75	1.14, 2.66	1.31 (0.86, 1.98)
Untreated BPH	11	11 852	0.9	5	29 700	0.2	5.51	1.94, 17.6	3.78 (1.36, 10.6)
Incidence rates and IRR restricted to those with no prior testosterone use before cohort entry									
Total	46	11 280	4.1	54	28 346	1.9	2.15	1.44, 3.18	1.57 (1.06, 2.32)
New	40	9 185	4.4	47	21 361	2.2	1.98	1.29, 3.02	1.49 (0.98, 2.27)
Prevalent	6	2 095	2.9	7	6 985	1.0	2.86	0.90, 8.82	2.19 (0.73, 6.57)
Treated BPH	35	11 280	3.1	49	28 436	1.7	1.80	1.16, 2.78	1.32 (0.86, 2.04)
Untreated BPH	11	11 280	1.0	5	28 436	0.2	5.55	1.96, 17.7	3.80 (1.37, 10.6)

*Adjusted for age and calendar time.

Rates of hypertension and polycythemia were lower among the oral testosterone users compared with the injectable testosterone users, particularly for polycythemia where there were only four cases among users of the oral therapy. The adjusted IRR for hypertension was 0.8 (95% CI 0.6, 1.2), and for polycythemia it was 0.14 (95% CI 0.05, 0.37). While the effect of any testosterone replacement therapy on haemoglobin production has been previously documented, to our knowledge, this difference in effect according to route of administration has not. It has been demonstrated, however, that higher testosterone dose is associated with erythrocytosis [1]. Thus it is possible that the difference in effect is related to the higher hormone concentrations produced by the i.m. testosterone formulation [1]. It is unlikely that this strong observed effect could be explained by detection bias or residual confounding since there was no previous suggestion of a differential effect between the oral and injectable testosterone formulations [3–5]. For the prostate outcomes there were proportionally more cases among users of oral testosterone undecanoate compared with injectable testosterone, but when adjusted the IRRs for oral testosterone undecanoate

use compared with injectable testosterone use were all around 1.0.

We conducted sensitivity analyses to evaluate whether the results would have differed materially if we had used different outcome inclusion criteria or different exposure windows. For prostate cancer we changed the case definition to require only 3 months from the day of first study testosterone prescription to the first prostate cancer diagnosis (compared with the 1 year to account for the induction period required in the main analysis) and the results did not materially change. The rates for oral testosterone undecanoate users were slightly higher (2.45/1000 PY compared with 1.25/1000 PY for injectable testosterone), but the adjusted IRR for oral compared with injectable was 1.0 (95% CI 0.6, 1.5) compared with 1.1 in the primary analysis. Further sensitivity analyses were conducted for hypertension and polycythemia where the exposure windows were changed to 180 and 45 days. The IRRs did not materially change in any of these analyses.

Men who received injectable testosterone were, on average, younger than men on the oral therapy, and use of injectable testosterone increased over the length of the

Table 8

Prostatism incidence rates per 1000 person-years (PY) and rate ratios

Oral			Injectable (reference)			IRR	95% CI		
Cases	PY	Rate	Cases	PY	Rate				
Incidence rates and IRR by age group ^a									
<20 years	0	660	0.0	1	2 693	0.4	0.00	0.00, 62.7	
20–39 years	0	1 170	0.0	0	6 089	0.0	NA		
40–59 years	29	3 806	7.6	37	9 684	3.8	1.99	1.23, 3.24	
60–79 years	48	4 315	11.1	117	8 433	13.9	0.80	0.57, 1.12	
80+ years	9	345	26.1	11	505	21.8	1.20	0.50, 2.89	
Oral			Injectable			IRR	95% CI		
Cases	PY	Rate	Cases	PY	Rate				
Incidence rates and IRR by year category ^a									
1988–1993	6	595	10.1	6	1 935	3.1	3.25	1.05, 10.1	
1994–1997	15	1 642	9.1	26	3 909	6.7	1.37	0.73, 2.59	
1998–2001	18	2 793	6.5	28	6 004	4.7	1.38	0.76, 2.50	
2002–2005	21	2 841	7.4	51	7 620	6.7	1.10	0.66, 1.84	
2006–2009	26	2 425	10.7	55	7 936	6.9	1.55	0.97, 2.47	
Oral			Injectable			IRR	95% CI	Adjusted IRR* (95% CI)	
Cases	PY	Rate	Cases	PY	Rate				
Incidence rates and IRR ^a									
Total	86	10 296	8.4	166	27 404	6.1	1.38	1.06, 1.79	1.06 (0.82, 1.37)
New	77	8 398	9.2	132	20 835	6.3	1.45	1.09, 1.92	1.13 (0.85, 1.49)
Prevalent	9	1 898	4.7	34	6 569	5.2	0.92	0.44, 1.91	1.03 (0.67, 1.58)
Incidence rates and IRR restricted to those with no prior testosterone use before cohort entry									
Total	83	9 792	8.5	154	26 184	5.9	1.45	1.11, 1.89	1.10 (0.84, 1.43)
New	74	7 894	9.4	120	19 692	6.1	1.54	1.15, 2.05	1.19 (0.89, 1.58)
Prevalent	9	1 898	4.7	34	6 492	5.2	0.91	0.41, 1.84	0.68 (0.32, 1.42)

*Adjusted for age and calendar time.

^aOne patient received both oral and injectable testosterone simultaneously and counted in both oral and injectable group.

study period while use of oral testosterone declined. These factors were adjusted in all analyses to control for these differences. Other differences between the two groups of users were small and did not effect the study results.

Strengths and limitations

Given the quality of the data in the GPRD and our past research experience [2–6], we are confident that we identified virtually all cases of newly diagnosed, and clinically important hypertension and prostatic abnormalities, and we reviewed the computerized record of each potential case to verify that they met all study criteria. We performed several subgroup and/or sensitivity analyses to evaluate the robustness of the results and the overall results remained stable. Laboratory values for haematocrit and haemoglobin were not consistently recorded in the GPRD until around 2000. Therefore we could not use laboratory values to identify cases of increased haemoglobin or haematocrit until the latter part of the study period. This was evident in the tables where the rates of polycythemia increased greatly between the period 1994–1997 and 1998–2001. While polycythemia diagnoses were available throughout the entire study period most cases in this outcome category were identified through elevated haemoglobin and haematocrit values. Thus the overall rate of

polycythemia/elevated haemoglobin or haematocrit is an underestimate of the rate over the whole study period, though the rate in the later years is more likely to be closer to the true rate.

Not all cases of BPH could be confirmed through identification of symptoms or appropriate surgery or other treatment. We stratified the analyses by treated vs. untreated BPH, in order to address the possibility that some men with a BPH diagnosis code did not have true BPH. While the IRs of treated BPH were higher than the IRs of untreated BPH, the IRR for BPH was lower among those with treatment confirmed BPH compared with untreated BPH. This is possibly due to the small number of untreated BPH cases. It is also of note that we found no cases of prostate cancer or BPH in men younger than 40 years. This finding could have implications for prostate examinations and tests in younger men when looking for clinically relevant prostate abnormalities, cancer or symptoms of BPH. Only 5% of men in this study had received prescriptions for both formulations of testosterone at any time and less than 1% had used both formulations concomitantly. Further there was only one case (prostatism) in a man who had received both concomitantly. Thus we were not able to evaluate effects in this exposure group.

It is possible that some men stopped taking testosterone sooner than was assumed in our estimation of person-time. To evaluate whether misclassification of exposure could account for our results we used a shorter time window for each acute outcome (sensitivity analysis). In no instance did the results change with the shorter exposure window. We also assessed the possibility that the time window assigned to each outcome was too short by re-analyzing the data using an extended time window for each acute outcome. There were no material differences in the results of these analyses either.

In summary, detailed drug and diagnosis information in a population-based data resource enabled us to calculate rates of various adverse outcomes in users of oral and injectable testosterone formulations and to compare rates between the two routes of testosterone administration. Risks of prostate cancer and prostatism were similar in users of the two preparations, but risks were higher for hypertension and polycythemia in the injectable compared with the oral testosterone users. Risk of BPH was slightly higher in the oral users, but the difference was small and could have been due to bias.

Competing Interests

This study was supported by financing from Abbott Laboratories.

This study was approved by the Independent Scientific Advisory Committee (ISAC) of the General Practice Research Database (GPRD).

Both authors have seen and approved the final version of this manuscript.

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