

# An evidence-based approach to understanding the pharmacological class effect in the management of prostatic diseases

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## INTRODUCTION

Ever more alternative products are available for each drug type commonly used to treat prostatic diseases, i.e.  $\alpha$ -blockers, 5 $\alpha$ -reductase inhibitors, antiandrogens and LHRH agonists. Once a urologist has decided which type of drug to use, their decision about which specific agent to prescribe will depend on several factors, including dosing regimen, delivery mechanism, speed of onset, treatment costs, local prescribing habits, marketing, patient choice, personal experience and published reports. Ideally, evidence-based medicine (EBM) should be the main factor in treatment choice. This review sets out the principles of EBM and examines the best available evidence for drugs that are commonly prescribed to treat BPH or prostate cancer. We consider whether a class effect can be shown for any of these groups of drugs and if class effects should be accepted in clinical practice. We focus on efficacy, but tolerability can also be an important factor when choosing between drugs of the same class, and will be discussed where relevant.

## PRINCIPLES OF EBM

EBM has been described as the 'conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients' [1]. For the clinician, this means identifying the best available evidence from a vast number of published medical reports, assessing whether it is applicable to the individual patient and then using it in clinical practice [2]. Of the types of published evidence available, systematic

reviews or meta-analyses of well-designed randomized controlled trials (RCTs), followed by individual RCTs and well-designed non-randomized studies are considered the most robust, reliable and therefore valuable [3]. Less robust evidence from case reports, clinical examples, or consensus meetings may also be considered.

Systematic reviews integrate otherwise unmanageable amounts of information from primary investigations in a way that limits bias and random error; meta-analyses allow an evaluation of consistency of findings and, if quantitative, may increase the accuracy of estimates of treatment effects [4]. As such, both should be useful tools in clinical decision-making. However, systematic reviews and meta-analyses are not always possible. For trials to be combined in a systematic review or meta-analysis, there needs to be a sufficient number of similar studies, i.e. with analogous study designs in patients with similar disease states and assessing comparable clinically relevant outcomes.

Whether trials are combined in a systematic review or meta-analysis, or examined for their individual merit, their design, endpoints and reporting quality need careful examination to determine the most appropriate and robust data. Trials must be of a high quality to avoid bias, sufficiently large enough to give a reliable answer, of good validity, and the population studied should allow the results to be clinically applicable.

One of the most important factors is randomization to exclude selection bias; it has been estimated that not randomizing can lead to an overestimation of treatment effect by 40% [5]. Other factors (and their percentage overestimation) include small trials (30%), poor reporting quality (25%), duplicate reporting (20%), and lack of blinding (17%).

Questions have been raised as to whether study sponsorship may also introduce bias and there are concerns that the process of publication itself can lead to bias in favour of positive results.

Although many clinical trials are conducted 'blind' to minimize observer bias, this is not always a realistic option. For example, in prostate cancer trials, it would not be reasonable to carry out sham orchidectomy or radiotherapy, and characteristic treatment effects, such as hot flushes with LHRH agonists, can effectively 'un-blind' a study. The more patients in a trial, the more accurately the size of a clinical effect can be assessed and the less likely the result is to be a result of random chance. The amount of information needed to avoid an incorrect conclusion depends on the size of the effect being studied and the level of certainty required. To be valid, a trial must be of an appropriate design to answer the question addressed; validity is based on criteria such as use of clinically important outcomes and duration of intervention and observation.

## IS THE CLASS EFFECT EVIDENCE-BASED?

Drugs are generally considered to be in the same class if they have a similar chemical structure and mechanism of action, and if they confer similar pharmacological effects. However, compounds with very similar structures can have different properties. For example, dihydrotestosterone differs from testosterone by only one hydrogen atom, but has a much greater binding affinity for the androgen receptor, resulting in different effects on gene expression. Consequently, the notion of a pharmacological 'class effect' should be considered with caution. Indeed, there is no universally accepted definition. A class effect is usually taken to mean that drugs in a class have similar therapeutic

effects and similar safety and tolerability, both in nature and extent [3]. If such a class effect exists, it would be likely that the least costly agent in each class would be the first choice. However, it is clear that no matter how strong the pathophysiological rationale or indirect evidence, the efficacy and safety of a new drug must be established in clinical outcome studies, and the equivalency of untested drugs even in a well-established 'class' should be considered unconfirmed.

For some products routinely used in prostate medicine, comparative data are limited, but prescription is still widespread based on the assumption of a class effect. To take an evidence-based approach to establishing a class effect, RCTs of direct comparisons of drugs within the class are needed [3]. However, this level of evidence is rarely available.

The next best level of evidence includes indirect comparisons across two or more placebo-controlled trials. In this case, only proportional effects such as the relative risk reduction can be compared. A class effect is considered to be present when drugs with similar mechanisms of action generate relative risk reductions (or odds ratios) that are similar in direction and magnitude [3]. However, such comparisons are less useful in determining whether one drug is more effective than another, because the comparison is between different cohorts of patients and the advantages of randomization are lost [3]. Decisions about the level of evidence necessary to establish a class effect are, necessarily, individual choices, which take into account local circumstances and personal comfort levels [3].

## BPH

In BPH, relief from symptoms is the key aim, with medical therapy being the first-line treatment for most men with symptomatic BPH. The two drug classes commonly used are  $\alpha$ -blockers and 5 $\alpha$ -reductase inhibitors, which aim to reduce LUTS by decreasing smooth muscle tone in the prostate and bladder, or by reducing prostate size, respectively.

### $\alpha$ -BLOCKERS

The  $\alpha$ -blockers are the most frequently used prescription medication for BPH; the class

includes tamsulosin, terazosin, alfuzosin, doxazosin and prazosin, which have different selectivity for the  $\alpha$ 1-adrenoceptor subtypes. Systematic reviews have been published for tamsulosin and terazosin, and a pooled analysis for alfuzosin (Table 1) [6–8]. These reports, in agreement with an earlier meta-analysis by Djavan and Marberger [9], conclude that the  $\alpha$ -blockers are effective and consistently improve LUTS and urinary flow compared with placebo.

$\alpha$ -Blockers have been directly compared in a few small trials (involving 50–256 patients) [9–12]. A review of trials directly comparing tamsulosin with terazosin found that these agents are equally effective in improving symptoms [7,8]. No definitive conclusions about differences in efficacy can be made from these studies; all  $\alpha$ -blockers, whether selective or not, seem to have similar efficacy in short-term trials [9]. The data suggest that  $\alpha$ 1-blockers, such as terazosin or doxazosin, give similar improvements as subtype-selective  $\alpha$ 1<sub>a</sub>-blockers, like tamsulosin, in peak urinary flow rates and symptom scores after 4 weeks of treatment. From these studies it might be concluded, on the basis of efficacy, that there possibly is a class effect. However, there are differences in tolerability, with tamsulosin better tolerated than doxazosin, prazosin and terazosin, as measured by withdrawals from treatment [9]. These may be related to different pharmacokinetic properties and adrenoceptor subtype selectivity, and contradict the concept of a class effect.

### 5 $\alpha$ -REDUCTASE INHIBITORS

For the last decade, finasteride, which acts on the type-2 isoenzyme of 5 $\alpha$ -reductase, has been the only available 5 $\alpha$ -reductase inhibitor. A recent systematic review of finasteride included 19 placebo-controlled trials of 3–48 months' duration (14 729 patients) [13]. The studies were of high quality, most were  $\geq 1$  year in duration, and most of the larger trials showed benefits in symptom score, maximum urinary flow rate and prostate volume for finasteride over placebo ( $P < 0.01$ ; Table 1) [13,14].

Dutasteride, which inhibits both isoenzymes of 5 $\alpha$ -reductase, was launched in the USA in 2003. The results of three large, double-blind RCTs of dutasteride including 4325 men were recently reported (Table 1) [14]. Dutasteride and finasteride have not been formally

compared and no definitive conclusions can currently be drawn about any differences between them. While dutasteride is said to inhibit serum 5 $\alpha$ -reductase to a greater extent than finasteride, the significance of this may be limited, as it is prostatic stromal intracellular 5 $\alpha$ -reductase that mediates gene transcription for growth factor genes. Therefore, although the data support the efficacy of both finasteride and dutasteride in BPH, there is as yet insufficient evidence to address the question of whether a class effect exists for the 5 $\alpha$ -reductase inhibitors.

### $\alpha$ -BLOCKERS COMBINED WITH 5 $\alpha$ -REDUCTASE INHIBITORS

The long-term efficacy of the  $\alpha$ -blocker doxazosin and the 5 $\alpha$ -reductase inhibitor finasteride, as monotherapy or combined, was evaluated in a randomized, long-term, double-blind placebo-controlled trial [15]. While each agent reduced the risk of overall clinical progression, combined therapy was significantly more effective than either monotherapy. This trial was of excellent design, yet raises several interesting issues about the class effect. For example, is it appropriate to extrapolate the role of doxazosin to other  $\alpha$ -blockers? The trial was designed for an intent-to-treat analysis, which in theory mimics 'real-world clinical medicine', but 27% of patients in the doxazosin arm could not tolerate even 4 mg and were withdrawn from therapy. In clinical practice these patients would probably have been switched to an  $\alpha$ 1<sub>a</sub>-subtype-selective drug such as tamsulosin. Examining the number of side-effects that occurred statistically significantly more often than with placebo, there were five with doxazosin, three with finasteride and nine with combined therapy. However, only 18% of patients in the combined arm discontinued treatment. Potential explanations for this include the possibility that the better efficacy resulted in patients tolerating an increase in side-effects, or it may have been the case that patients had to discontinue both drugs to be counted as 'off treatment'. Thus, the intent-to-treat concept, drug tolerability and definition of discontinuation are potentially contributing to the outcomes reported. Assuming a class effect, a clinician may deduce that tamsulosin, with lower discontinuation rates than doxazosin, would be better for combined therapy. This reasoning, while deductive, is not actually evidence-based.

TABLE 1 Systematic reviews and pooled analyses of  $\alpha$ -blockers and 5 $\alpha$ -reductase inhibitors in the treatment of patients with LUTS suggestive of BPH

Ref	Treatment(s)	Study (N men)	Duration of study	Efficacy
<b><math>\alpha</math>-blockers</b>				
[8]	Tamsulosin vs placebo	SR including 6 RCTs (2758)	6–17 weeks	USS significantly improved vs placebo in 5/6 studies: % decreases in USS 20–48% for tamsulosin vs 18–28% for placebo. Significant improvement in peak urine flow in 5/6 studies: mean change 1.2–4 mL/s for tamsulosin and –0.1–1.4 mL/s for placebo
[7]	Terazosin vs placebo	SR including 10 RCTs (3941)	8–52 weeks	USS significantly improved vs placebo in 6/10 studies: % decreases in USS 31–69% for terazosin vs 10–58% for placebo. Significant improvement in peak urine flow in 8/9 studies: mean improvement 2.2 mL/s for terazosin and 1.1 mL/s for placebo
[6]	Alfuzosin vs placebo	PA including 11 RCTs (1470)	1–6 months	Significant reduction in PVR: at 6 months, 36.8 mL (28%) for alfuzosin vs 22.6 mL (16%) for placebo ( $P=0.01$ )
[7,8]	Tamsulosin vs terazosin	SR including 4 trials (492)	4–9 weeks	Mean IPSS improvement from baseline 41% for tamsulosin vs 40% for terazosin. Peak urine flow increased by 29% for tamsulosin vs 25% for terazosin
[9]	Alfuzosin, terazosin, doxazosin, tamsulosin	Meta-analysis of data from 21 placebo-controlled studies and 4 comparative studies	1–12 months	Total USS improved 30–40% and maximum urinary flow rate by 16–25% with $\alpha$ -blocker treatment. No efficacy comparisons between the different agents
<b>5<math>\alpha</math>-reductase inhibitors</b>				
[13]	Finasteride vs placebo	SR including 19 RCTs (14 729)	3–48 months	Most large trials* showed that finasteride was better than placebo for USS (3.7 points less for finasteride vs 2.3 for placebo at 1 year), maximum urinary flow rate (+1.3 mL/s finasteride vs 0.8 mL/s placebo at 2 years) and prostate volume (25% less for finasteride vs 4% less for placebo at 2 years)
[14]	Dutasteride vs placebo	Combined results of three double-blind RCTs of identical design (4325)	24 months	Statistically significantly better vs placebo at 2 years in: USS (4.5 points less for dutasteride vs 2.3 for placebo, $P<0.001$ ); maximum urinary flow (+2.2 mL/s dutasteride vs 0.6 mL/s placebo, $P<0.001$ ); and prostate volume (26% less dutasteride vs 2% more placebo, $P<0.001$ )

SR, systematic review; USS, urinary symptom score; PA, pooled analysis; PVR, postvoid residual; IPSS, International Prostate Symptom Score; \*Except a study that included men with small prostates.

## PROSTATE CANCER

Survival is recognized as a key endpoint in trials of anticancer agents, and in contrast to endpoints in trials in other fields, differences in outcome of just 2–3% may be of considerable clinical importance. However, detecting statistically significant differences at this level requires clinical trials involving many patients and, commonly, studies are not powered well enough to detect such small differences. In the case of a highly prevalent disease such as prostate cancer, differences in the 2–3% range can result in a large gain in life across the population. If such differences are observed between agents within the same class this could be sufficient to suggest that a class effect should not be assumed, but that agents should be assessed on individual merits.

## LHRH AGONISTS

There have been few direct comparisons of LHRH agonists, and from which no definitive conclusions can be made. One randomized study of reasonable size ( $\geq 40$  patients per arm) was conducted, comparing the efficacy, safety and testosterone pharmacodynamics of 1-month formulations of triptorelin (3.75 mg) and leuprorelin (7.5 mg) [16]. Men with advanced prostate cancer (stage C or D) in the intent-to-treat population received either triptorelin (137 men) or leuprorelin (140 men) for 9 months. Triptorelin induced castrate levels of testosterone at a slower rate than leuprorelin, but maintained castration as effectively [16]. There was no evidence that the slower onset of castration with triptorelin was deleterious, indeed the 9-month survival

rate showed a small difference favouring triptorelin (97.0% vs 90.5%,  $P=0.033$ ), but a longer follow-up is required. This study highlights that similar levels of testosterone suppression do not necessarily indicate similar levels of clinical efficacy, and that use of castrate levels of testosterone as a surrogate marker for survival may not be appropriate. A further point is that the monthly dose of leuprorelin licensed for use in most countries is 3.75 mg, in contrast to the dose of 7.5 mg used in that study; therefore, conclusions made on the basis of that study may not reflect true clinical practice in many parts of the world.

As there are few direct comparative data, indirect evidence from RCTs comparing the various LHRH agonists with other

TABLE 2 RCTs comparing LHRH agonists vs orchidectomy or DES or CPA in the treatment of prostate cancer

Ref	LHRH agonist	N men randomized, vs orchidectomy or other	LHRH agonist dosing interval	Follow-up, years	Survival, % (P)
<b>vs orchidectomy</b>					
[17]	Goserelin	148 vs 144	Monthly	2 (median)	42 vs 36 (NS, 0.23)
[18]		138 vs 145	Monthly	4 (minimum)	29 vs 33 (NS, 0.42)
[19]	Buserelin	113 vs 118 vs plus CPA 111	Daily	5.7 (median)	13 vs 10 vs 14 (NS, not available)
[20]		72 vs 46 vs oestrogens 22	Daily	1	(NS, 0.40)
[21]	Triptorelin	55 vs 49	Monthly	2	Mean 16 vs 13 months ( <i>P</i> not given)
	Leuprorelin	No comparative studies			
<b>vs DES</b>					
[27]	Goserelin	124 vs DES 126	Monthly	>3	32 vs 36 (0.88)
[22]	Buserelin	111 vs DES/orch 56 or MTX + DES/orch (98)	Daily	>2	No difference among groups by log-rank analysis
[23]		105 vs DES 41/orch 14	Daily	>2	No difference among groups by log-rank analysis
[25]	Leuprorelin*	92 vs DES 94	Daily	1	87 vs 78 (0.17)
	Triptorelin	No comparative studies vs DES			
<b>vs CPA</b>					
[26]	Goserelin	175 vs CPA 175	Monthly	4 (maximum)	Not reported. Median TTP (days) 346 vs 225 (0.016)
[24]		152 vs CPA 71	Monthly	2	Median 132 vs 130 weeks (NS)
	Buserelin	No comparative studies with CPA			
	Triptorelin				
	Leuprorelin				

\*The dose was 1.0 mg daily, compared with the currently licensed doses of 3.75 mg or 7.5 mg per month. NS, not significant; MTX, methotrexate; orch, orchidectomy; TTP, time to progression.

treatments need to be considered. Historically, orchidectomy has been the 'gold standard', with the synthetic oestrogen diethylstilbestrol (DES) and the steroidal antiandrogen cyproterone acetate (CPA) providing treatment alternatives. Although DES and CPA have not become well established treatments because of tolerability problems and a lack of benefit in terms of overall survival, LHRH agonists have been compared with all three of these treatments in RCTs. Studies that compare LHRH agonists with orchidectomy are shown in Table 2 [17–21]; in each there was no significant survival difference between treatments.

RCTs with  $\geq 40$  patients per arm that compared LHRH agonists with DES or CPA are also shown in Table 2 [22–27]. In comparisons with DES, none of the studies showed a significant survival difference between treatments. Studies of LHRH agonists vs CPA have only been conducted with goserelin and, while no survival data were reported, Thorpe *et al.* [26] reported a benefit in time to progression favouring goserelin over CPA ( $P = 0.016$ ; Table 2).

In a meta-analysis that included 12 trials comparing LHRH agonist monotherapy

with orchidectomy or DES, the overall hazard ratio (HR) for survival with LHRH agonists relative to orchidectomy suggested that LHRH agonists are essentially equivalent to orchidectomy in terms of survival [4]. Although none of these trials directly compared the three LHRH agonists, indirect comparison of seven goserelin studies (1137 men), four buserelin studies (308 men), and one leuprorelin study (94 men) found that HRs for survival with the individual agents relative to orchidectomy were similar.

#### Adjuvant therapy

There have been no systematic reviews of LHRH agonists as adjuvant therapy. A recent analysis of published studies suggested that differences in drug regimen, duration and timing of treatment in trials of adjuvant or neoadjuvant LHRH agonist therapy mean that pooling these trials for meta-analysis would not be possible [28]. However, in individual studies one LHRH agonist, goserelin, has shown a consistent benefit in terms of delaying progression and improving survival, as summarized below.

Goserelin is the only LHRH agonist studied as monotherapy in large ( $\geq 40$  patients per arm)

RCTs of adjuvant hormonal therapy after radiotherapy or radical prostatectomy (Table 3) [29–35]. Adjuvant hormonal therapy with goserelin significantly improved survival in the radiotherapy setting and in node-positive men after radical prostatectomy, and this is good evidence on which to base treatment decisions. However, the optimum timing and duration of therapy remain to be clarified.

#### Neoadjuvant therapy

The rationale for neoadjuvant hormonal therapy is to directly improve outcomes or enhance the primary therapy, e.g. by reducing the dose of radiation or field size, thereby minimizing the adverse effects of radiation. The only randomized study of an LHRH agonist neoadjuvant to radiotherapy is with goserelin, which, combined with flutamide, was associated with a significant improvement in overall survival compared with radiotherapy alone [36] (Table 3). Comparison of hormonal therapy (goserelin plus flutamide) neoadjuvant or adjuvant to radiotherapy, found no significant difference in progression-free or overall survival [37] (Table 3). Although neoadjuvant hormonal

TABLE 3 RCTs of adjuvant and neoadjuvant treatment with LHRH agonists in the treatment of prostate cancer

Ref	LHRH agonist, study	Treatment (N patients randomized)	Median follow-up, years	Survival, % (P)
<b>Adjuvant</b>				
[29,31]	Goserelin, EORTC 22863	RT + goserelin 3 years (207) vs RT alone + goserelin after relapse (208)	5.5	5-year, 78 vs 62 (<0.001)
[32]	Goserelin, RTOG 85-31	RT plus goserelin (488) vs RT alone + goserelin after relapse (489)	7.3	10-year, 53 vs 38 (<0.0043)
[33]	Goserelin, RTOG 92-02	Flutamide + goserelin for 2 months before and for 2 months during RT then randomized to 2 years of goserelin (753) or no further treatment (761)	5.8	5-year, 80 vs 79 (NS, 0.73) For patients with Gleason score of 8-10 (337), 5-year survival was 81 vs 71 (0.044)
[34,35]	Goserelin, ECOG 7887/EST3886	RP + immediate goserelin or orchidectomy (47) or RP alone (51)*	10	10-year, 72 vs 49 (0.025)
[30]	Goserelin/leuprorelin	RT + flutamide and either goserelin (10) or leuprorelin (88) for 6 months vs RT alone (104)	4.5	5-year, 88 vs 78 (0.04)
	Buserelin Triptorelin	No comparative studies		
<b>Neoadjuvant</b>				
[36]	Goserelin, RTOG 86-10	Goserelin + flutamide 2 months before and during RT (226) vs RT alone (230)	6.7	At 8 years, statistically significant improvement in local control (42 vs 30) (0.016), reduction in the incidence of distant metastases (34 vs 45) (0.04), PFS (33 vs 21) (0.004), PSA PFS (24 vs 10) (<0.001) and prostate cancer mortality (23 vs 31) (0.05)
[37]	Goserelin, RTOG 94-13	1295 randomized to 4 treatment arms: neoadjuvant goserelin + flutamide for 2 months before and during RT (whole pelvis [Arm 1] or prostate only [Arm 2]) or adjuvant goserelin + flutamide for 4 months after RT (whole pelvis [Arm 3] or prostate only [Arm 4])	5	No significant difference in 4-year PFS or overall survival in patients treated with neoadjuvant vs adjuvant therapy

\*An additional two patients were randomized but found to be ineligible. EORTC, European Organization for the Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; NS, not significant; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; RP, radical prostatectomy; PFS, progression-free survival; PSA, prostate-specific antigen.

therapy with radical prostatectomy significantly decreases the positive margin rate, randomized studies have shown no improvement in overall survival [38].

#### Summary: LHRH agonists

The prevailing data suggest equivalent survival between LHRH agonists and orchidectomy. It is apparent that within the LHRH agonist class, the vast majority of available data are for goserelin, which is associated with benefits in several settings. The amount and quality of evidence that compares goserelin with other members of the class, or that compares LHRH agonists with other treatments, is insufficient to establish a class effect.

#### ANTIANDROGENS

Steroidal and nonsteroidal antiandrogens are not members of the same class. These two groups of agents differ in structure and mechanism of action. Steroidal antiandrogens, e.g. CPA, chlormadinone acetate and megestrol acetate, have mixed agonistic and antagonistic activities, while nonsteroidal antiandrogens, e.g. bicalutamide, flutamide and nilutamide, have a pure anti-androgenic effect.

#### Monotherapy

There have been no direct RCTs comparing steroidal antiandrogens, and there are minimal clinical data with chlormadinone acetate and megestrol acetate from which to

draw conclusions about any class effect. Similarly, to date, no comparative monotherapy trials of nonsteroidal antiandrogens have been conducted. In the absence of direct comparative data, there are too few RCTs relating to antiandrogen monotherapy to draw any conclusions about a class effect in this setting.

#### Combined therapy

Despite numerous trials investigating combined therapy (medical or surgical castration plus an antiandrogen, otherwise known as maximal androgen blockade), only one randomized, double-blind trial compared combined therapies directly [39]. Of 813 patients, 404 were assigned to bicalutamide combined with an LHRH agonist, and 409 to

flutamide plus an LHRH agonist. There was no significant difference between groups in survival. Beyond this one comparative RCT, the currently available data relating to the efficacy of combined therapy shed no light on whether a class effect exists for antiandrogens.

#### Tolerability

The efficacy evidence is insufficient to show a class effect for the antiandrogens but there are differences between nonsteroidal antiandrogen monotherapies in terms of tolerability. Pharmacological effects associated with androgen receptor blockade, such as gynaecomastia and breast pain, have been reported with similar ranges of incidence for monotherapy with bicalutamide (38–66% and 13–73%, respectively), flutamide (21–80% and 22–69%, respectively) and nilutamide (gynaecomastia 50%, breast pain data not available) [40]. Gastrointestinal effects (e.g. diarrhoea) have also been reported with all three agents, but occur more often with flutamide than bicalutamide or nilutamide [40]. In contrast, visual disturbances and alcohol intolerance have been reported only with nilutamide [40]. There were also tolerability differences between treatments in the study by Schellhammer *et al.* [39]; e.g. the incidence of haematuria was significantly higher for the bicalutamide plus LHRH agonist group than for the flutamide plus LHRH agonist group (12% vs 6%,  $P=0.007$ ) and there was a significantly higher incidence of diarrhoea (26% vs 12%,  $P<0.001$ ) with flutamide than bicalutamide.

#### Summary: antiandrogens

Available efficacy data are insufficient to draw conclusions about the existence of a class effect for either steroidal or nonsteroidal antiandrogens. On the basis of tolerability data for nonsteroidal antiandrogens, it is clear that drugs in this class have different characteristics, suggesting that it is not appropriate to assume a class effect.

#### CONCLUSIONS

As outlined herein, there is a substantial amount of evidence that should be considered, together with clinical experience, so that urologists and their patients may make informed choices about the treatment of prostatic disease. It is clear that the issue is multifactorial and complex which, in addition

to efficacy considerations, also encompasses differences between agents in safety/ tolerability profiles. Although a class effect is commonly assumed in prostate medicine by some urologists, on the whole this is not supported by the evidence. For example, in the case of LHRH agonists, particularly for adjuvant therapy, the vast majority of data come from studies of goserelin. In contrast, there is less clinical evidence for other LHRH agonists in the adjuvant setting, because there are too few RCTs. This raises doubt as to whether a class effect for LHRH agonists is proven by existing clinical data across all stages of hormone-responsive prostate cancer. Similarly, a class effect has not been proven for other classes of agent that have been reviewed here. Urologists recognize the value of evidence-based practice, and on this basis, should not assume a class effect when making treatment choices for prostatic disease.

#### CONFLICT OF INTEREST

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**Abbreviations:** EBM, evidence-based medicine; RCT, randomized controlled trial; DES, diethylstilbestrol; CPA, cyproterone acetate.