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Preliminary study with bicalutamide in heterosexual and homosexual patients with prostate cancer: a possible implication of androgens in male homosexual arousal

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What's known on the subject? and What does the study add?
A recent published paper regarding sexual and cognitive duality presents that androgens act synergic with female sexual pheromones while estrogens would act synergic with male sexual pheromones in normal potent men.

The same authors found in this study that bicalutamide disfavours sexual function predominantly in homosexual rather than heterosexual men suffering with prostate cancer. The results of this study are interpreted alone in this article, the similarities and differences with results corresponding to younger and normal potent men following to be discussed recently in a review regarding psychosexual dualism.

OBJECTIVE

- Not only has a precise characterization of libido and sexual arousal in men as a central neural process been lacking, but the interactive role of gonadal hormones and sexual orientation in such processes has never been investigated. We investigate the relationships among sexual hormones, sexual arousal, and sexual orientation in men by comparing the self-reported sexual response of heterosexual and homosexual men with locally advanced prostate neoplasm, receiving the non-steroidal anti-androgen bicalutamide as monotherapy.

PATIENTS AND METHODS

- 29 Romanian men participated in this study: 17 heterosexual and 12 homosexual. Patients were undergoing treatment for prostate cancer consisting of a standard daily dose of 50 mg bicalutamide, a fast acting non-steroidal anti-androgen with action comparable to other anti-androgen drugs but with reportedly fewer sexual side effects.
- Patients retrospectively provided information regarding their sexual functioning measured by the IIEF *prior to* commencing bicalutamide treatment.
- Then, about five weeks later, patients were asked to prospectively provide information regarding their *current* sexual functioning while undergoing bicalutamide treatment.

RESULTS

- Overall IIEF scores as well as the Erectile Function, Orgasmic Function, Sexual Desire, and Overall Satisfaction subscales showed group, treatment, and group by treatment effects.
- The Intercourse Satisfaction subscale showed group and group by treatment effects.
- On most subscales, homosexual men showed lower functioning than heterosexual men, primarily in response to treatment with bicalutamide.

CONCLUSIONS

- Treatment with an anti-androgen in a clinical population of men undergoing therapy for prostate cancer affected homosexual men more than heterosexual men, although not all heterosexual men were *un*affected.
- These results are discussed in the context of dual sexual natures, a concept recently developed in the sexual literature.
- Furthermore, these findings reiterate the importance of incorporating such variables as sexual orientation into studies investigating medical treatments on sexual response.

KEYWORDS

androgens, bicalutamide, homosexual, heterosexual, estrogens, duality

INTRODUCTION

Sexuality is a topic of interest from many perspectives, from a scientific, medical, humanistic, religious and legal perspective, to name a few. A comprehensive understanding of this complex phenomenon therefore requires a multidisciplinary approach capable of integrating, into a single model, perspectives and findings from neurophysiological, endocrinological, sexological, urological, psychological and socio-cultural research [1].
Such integration is essential to the understanding of all aspects of sexual

response, including those addressed in this paper: sexual physiology, desire (libido), arousal and the varying types of stimulation that induce it, and the resulting sexual behavior.

To give an example of the need for a multidisciplinary approach, the physiology of sexual reflexes has been quite well described at the spinal cord level, yet through evolution it is presumed that these reflexes have ascended to the brain level and that their function has been assumed by the cerebral mechanisms of sexuality [2]. Yet, the physiological processes that prepare the organism for sexual intercourse (lubrication, erection, tachycardia, tachypnoea, etc.) correspond strongly with the subjective state of sexual arousal, a phenomenon that is viewed primarily as a cerebral autonomic process [3]. Nevertheless, the cognitive-affective processes that intersect with the cerebral systems controlling sexual desire, the 'when, where, and how', are poorly understood and, therefore, continue to provoke discussion. For example, it has not yet been established whether libido corresponds to cerebral mechanisms which are solely psychological, solely autonomous, or a combination of both [4]. It has been almost impossible to distinguish between the somatic, autonomous and psychological processes of sexual response using today's investigative tools, and therefore the precise role and span of mental involvement in sexuality has not been well established.

Some authors argue that sexual behaviour in men follows a biological imperative, ensuring copulation, ejaculation/orgasm, and ultimately procreation. For some people, however, libido and sexual arousal are not derived from activities that lead to procreation. Such activities are represented by autoeroticism, masturbation, cybersex, sexual relations involving other orifices (oral/anal), individuals of the same sex, with different species, with objects etc. which, although non-procreative, may nevertheless become powerful activators of sexual drive and arousal. In such instances, the stimuli responsible for libido and arousal interfere with the presumed (procreative) objects of desire and attraction, and these may differ depending on the person's sexual orientation, past sexual experiences, objects of gratification, and various internal (e.g. hormones) and external (e.g. pheromones) modulators [5].

To understand the relationship between the psychological factors and sexuality (desire, arousal, behaviour), the physiological mechanisms involved in sexual and mental processes of the brain need to be examined as a unified psycho-physiological model that takes into consideration not only the process of arousal, but the sexual orientation of the individual. This latter element plays a critical role in the motivation, desire and activation of sexual behaviour. Furthermore, as sexual hormones are known to both influence prenatal and activate post-pubertal sexual systems in the brain [6], the understanding of the relationships between such hormones on the one hand, and arousal, desire and sexual orientation on the other, could provide insight into this process. It was recently posited that sexual desire and sexual arousal might correspond to relatively similar or symmetrical neurophysiological mechanisms, the first representing sexual perceptions (perhaps modulated by such factors as sexual pheromones) and the second corresponding with sexual sensations (perhaps under sexual hormonal control) [7]. If sexual arousal and libido indeed represent two symmetrical mechanisms, then two questions arise that require clarification, one related to sexual arousal and the other to libido. First, is there a relationship between sexual arousal, the nature of sexual hormones, and sexual orientation? Second, is sexual desire primarily a psychological process, primarily a reflexive autonomic process, or an autonomic process requiring cerebral involvement (though not necessarily psychological in nature)?

In this study, we address the first question regarding the relationships among sexual hormones, sexual arousal and sexual orientation in men, an idea that may be tested using one pure sex hormone antagonist known to bind to androgen receptors. Specifically, we compared the self-reported sexual response of heterosexual and homosexual men with locally advanced prostate neoplasm, who were receiving the non-steroidal anti-androgen bicalutamide as monotherapy.

SUBJECTS AND METHODS

A total of 29 Romanian men participated in this study. Of these, 17 were self-identified as heterosexual and 12 were self-identified as homosexual through an interview with one of the investigators. Although external verification of sexual orientation was not possible, we observed that men undergoing treatment for a life-threatening disease are generally more motivated to be forthright in their disclosure of sexual orientation. Mean ± SD ages for the two groups did not differ (60.4 ± 4.8 vs. 62.2 ± 5.9 years, $F[1,28] = 0.52$, $P = 0.88$).

All subjects had been suspected within the past 2 months of having prostate cancer through PSA and or palpitation, and the diagnosis was confirmed using at least two or more of the following: TRUS; biopsy; bone scintigraphy; CT; and NMR. Their cancer was characterized as locally advanced prostate cancer with no detectable metastases. The subjects for this study either were patients undergoing treatment at a local hospital or had been referred by a GP.

The participants entered the study at the point when the prostate cancer diagnosis was completely documented, and treatment with bicalutamide was started less than a week after this. The treatment consisted of a standard daily dose of 50 mg bicalutamide, a fast-acting non-steroidal anti-androgen with action comparable with other anti-androgen drugs, but with reportedly fewer sexual side effects. The selection criteria for the subjects were as follows: they were free from other major diseases and were not undergoing therapy for chronic disease; they had not undergone any other treatment for their prostate cancer before treatment in this study; and they had a stable female partner, in the case of the heterosexual group, or a stable male anal-receptive partner, in the case of the homosexual group.

Prospective subjects were contacted by the urologist who explained the nature of the study without revealing its full purpose (as this might have biased the results). A brief interview, designed to collect basic demographic and biographical information from the subject, was conducted. After providing informed consent as approved by the Medical Ethics Committee of St. Pantelimon Hospital in Bucharest, the urologist asked the patient to provide retrospectively information regarding his sexual functioning *before* starting bicalutamide treatment, using the International Index of Erectile Function (IIEF) either in oral or written form (items were translated into Romanian). After starting treatment with bicalutamide, ≈ 1 month later,

the patient was asked to provide prospectively information regarding his *current* sexual functioning, an assessment that lasted ≈ 4–6 weeks, again using the translated IIEF.

The present study used a 2 × 2 design (orientation: heterosexual vs. homosexual x treatment: before treatment vs. during treatment), and a 2 × 2 factorial ANOVA was carried out using SPSS software. Overall IIEF scores were analysed first, followed by analysis of each of the IIEF subscales: erectile function; orgasmic function; sexual desire; intercourse satisfaction; and overall satisfaction. Analyses were carried out blind to the patient group.

RESULTS

On the overall scale, a significant group (orientation) effect was found ($F[1,27] = 23.2$; $P = 0.000$), with homosexual men scoring lower than heterosexual men. In addition, significant treatment and interaction (group x treatment) effects were found ($F1,27] = 23.7$, $P = 0.000$; and $F[1,27] = 38.6$, $P = 0.000$); overall IIEF scores were lower during treatment than before treatment, and homosexual men showed a greater decrease in IIEF during treatment than heterosexual men.

The erectile function, orgasmic function, sexual desire, and overall satisfaction subscales showed group, treatment, and group x treatment effects. The intercourse satisfaction subscale showed group and group x treatment effects (Table 1). On most subscales, homosexual men showed lower functioning than heterosexual men, primarily in response to treatment with bicalutamide.

TABLE 1 Overall and subscale IIEF scores for heterosexual and homosexual men before and during treatment with bicalutamide

	Subject group			
IIEF score	Heterosexual	Homosexual	Effect	
Overall				
			Group	$F(1,27) = 23.2, P < 0.001$
Before treatment	54.3	52.9	Tx	$F(1,27) = 23.7, P < 0.001$
During treatment	56.1	28.7	Gp x Tx	$F(1,27) = 38.6, P < 0.001$
Erectile function				
			Group	$F(1,27) = 19.2, P < 0.001$
Before treatment	25.1	24.5	Tx	$F(1,27) = 45.3, P < 0.001$
During treatment	24.1	12.1	Gp x Tx	$F(1,27) = 32.8, P < 0.001$
Orgasm function				
			Group	$F(1,27) = 14.5, P = 0.001$
Before treatment	7.1	7.2	Tx	$F(1,27) = 22.4, P < 0.001$
During treatment	7.1	3.3	Gp x Tx	$F(1,27) = 23.9, P < 0.001$
Sexual desire				
			Group	$F(1,27) = 7.2, P = 0.012$
Pre-treatment	6.5	7.6	Tx	$F(1,27) = 13.2, P = 0.001$
During treatment	7.5	3.7	Gp x Tx	$F(1,27) = 35.1, P < 0.001$
Intercourse satisfaction				
			Group	$F(1,27) = 6.7, P = 0.016$
Pre-treatment	7.1	8.0	Tx	$F(1,27) = 1.6, P = .214$
During treatment	10.3	6.2	Gp x Tx	$F(1,27) = 21.1, P < 0.001$
Overall satisfaction				
			Group	$F(1,27) = 20.1, P < 0.001$
Pre-treatment	7.2	7.1	Tx	$F(1,27) = 28.8, P < 0.001$
During treatment	7.1	3.4	Gp x Tx	$F(1,27) = 25.3, P < 0.001$

Tx, treatment; Gp, group.

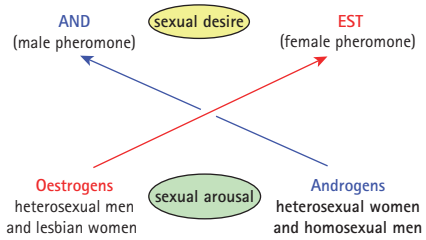
DISCUSSION

The findings of the present study suggest that the activational effects of androgens on sexual motivation, arousal and behaviour may be different for men with different sexual orientation. Specifically, treatment with an anti-androgen in a clinical population of men undergoing therapy for prostate cancer produced significant differences in the sexuality of heterosexual and homosexual men. In a retrospective assessment of sexual response before treatment, both groups were essentially equivalent on subscales measuring erectile function, orgasm function, sexual desire, intercourse satisfaction and overall sexual satisfaction. In contrast, effects of androgen withdrawal through bicalutamide significantly and adversely affected homosexual men's sexual arousal, orgasm function, sexual desire and overall sexual satisfaction, whereas heterosexual men's functioning largely remained unchanged.

Not known from this current assessment is whether various domains of the sexual response cycle (desire, arousal, orgasm) were independently affected, or whether one component, such as sexual arousal, might have produced a cascading effect on the others. Nevertheless, these data suggest that the overall sexual response of homosexual men may depend more heavily on androgens than that of heterosexual men. However, not all heterosexual men were unaffected by anti-androgen therapy; four men in the heterosexual group exhibited sexual side effects from bicalutamide, similar to those in the homosexual group. These four men present neurophysiological similarities to homosexual men but did not share their homosexual identity, exhibiting perhaps a 'behavioural' heterosexuality attributable to psycho-social rather than neuroendocrinological factors. Or, it is possible that these four men hid their true sexual identity or were bisexual, a category that was not included in the study. Whatever the case, these data identify sexual orientation as a potentially significant factor in understanding the biopsychological elements of sexual desire and arousal.

How might such findings be explained and integrated into the larger existing literature? One possibility draws on the idea of the existence of dual sexual natures which now seems to be confirmed by several studies. Sexual pheromones, for example, have been implicated in human sexuality and are presumably transmitted through the olfactory system [8]. These olfactory signals are transmitted to various sex centres in the brain, including the medial preoptic area or anterior hypothalamus, which in turn has an

FIG. 1. The two human sexual neuroendocrine axes.



effect on sexual behaviour (according to animal studies) [9]. Using positron emission tomography (PET), recent studies have demonstrated that in heterosexual women and homosexual men, only the progesterone derivate AND (4, 16- androstadien-3-one), primarily detected in male sweat, led to activation of the sexual medial preoptic area, whereas the signal induced by oestrogen-like steroid EST (1,3,5,10,16-tetraen-3-ol), detected in female urine, is transmitted in these subjects using common olfactory networks (represented by the amygdala, piriform, orbitofrontal and insular cortex) similar to other common odours [10]. In contrast, in lesbian women and heterosexual men, only EST led to activation of the sexual medial preoptic area, while the message induced by AND was transmitted through common olfactory networks [11].

In addition, some studies have used magnetic resonance volumetry to determine cerebral and cerebellar hemispheric asymmetry, or PET to measure cerebral blood flow, so as to elucidate functional connections between the right and left amygdala. The results have shown that in heterosexual men and lesbian women there is a rightward cerebral and no cerebellar asymmetry, while the connections were more widespread from the right amygdala to caudate, putamen and prefrontal cortex. In homosexual men and heterosexual women, no cerebral or cerebellar asymmetry was found, while the connections were more widespread from the left amygdala to anterior cingulate and the contralateral amygdala [12].

Such findings are in accordance with the new concept of sexual duality recently described in the literature [7,13], which hypothesizes the existence of two neuroendocrine sexual axes, one for heterosexual women and homosexual men, and the other for heterosexual men and lesbian women (Fig. 1). Presumably, only one axis would be functional in an individual, having perhaps a genetically related [14], though not hormonal [15], origin. The gender/sexual hormone activity of an individual is perhaps coded by another distinct genetic factor, such that male and female homosexuality results from asynchrony between the genes that codify the active sexual axis and the gene responsible for the gender of the person [7].

The two neuroendocrine axes would correspond to two cerebral poles responsible for libido and, perhaps, two cerebral poles responsible for sexual arousal. As suggested by the above findings, only one pole of libido and only one pheromone type would be sexually active in any individual; the other pole of libido and the other type of sexual pheromone are presumably inactive. With regard to sexual arousal we suggest that, just as with the libido centre, only one arousal centre would be active in an individual, namely, either the sympathetic arousal centre under androgenic control, or the parasympathetic arousal centre under oestrogenic control [2]. In such a scenario androgens would be responsible for sexual arousal in homosexual men, while oestrogens would be more important for sexual arousal in heterosexual men [7].

The basis for the present study was the observation that different anti-androgen treatment methods produce different sexual side effects. Thus, bicalutamide, which blocks the androgenic receptors and increases the plasmatic level of oestradiol (gynecomastia being a common side effect of drug) [16] has fewer sexual side effects than cyproterone acetate, which blocks the androgenic receptors and decreases the plasmatic level of oestradiol (gynecomastia being quite rare for this drug) [17]. Such observations imply that oestrogens could be responsible for maintaining sexual function in some patients treated with bicalutamide or that, androgens and oestrogens having antagonistic effects [18], in some men androgens modulate sexual function while in others oestrogens play the more critical role.

The results of several studies are relevant to the implied involvement of oestrogens in male sexuality. Male rodents with a deficiency of oestrogens exhibit impaired sexual behaviour and fertility [19]. In almost 30% of men undergoing treatment, the administration of Tamoxifen (an oestrogenic antagonist) for male breast cancer leads to a significantly decreased libido [20,21]. Consistent with this idea, the administration of oestradiol in men with a congenital lack of oestrogens may restore libido and frequency of intercourse [22,23]. In contrast, in some men with low androgen levels erectile function is preserved [24]. Furthermore, hypogonadal men with impaired sexual function show a greater response to testosterone than to dihydrotestosterone with regard to libido, erectile capacity and psychological well being [25]. The difference between the effectiveness of these androgens may result from the fact that testosterone can generate oestrogens (through aromatization), whereas dihydrotestosterone not only cannot be metabolized into oestrogens, but can also act as an oestrogenic blocker [26].

The results of the present study suggest that sexual orientation may be one factor relevant to possible differentiated roles for androgens and oestrogens in men's sexuality. In homosexual men, androgen blockade with bicalutamide significantly decreased sexual function, although it did not eliminate it completely (libido may be under pheromonal control and sexual arousal and libido can perhaps induce each other), whereas in heterosexual men bicalutamide seems not to affect sexual function. When sexual orientation is not parsed out (that is, heterosexual and homosexual groups are not studied separately), the sexual side effects of bicalutamide would be less pronounced (taking into account the fact that the unaffected heterosexual men could be more numerous than homosexual men in the general population), as suggested by the current literature [27].

The conclusions drawn from this study need qualification for several methodological reasons. First, we used dichotomous categories for sexual orientation rather than a Kinsey-type scaling and in doing so we missed an opportunity to study men who may have been bisexual (a factor that might help explain the anomalous findings in four heterosexual men who showed a response pattern more typical of homosexual men). Second, data collected on pre-treatment sexual function were retrospective and therefore may have been influenced by the disease and diagnosis. Although we were unable to assess sexual function prospectively before beginning the treatment with bicalutamide (because this would mean a substantial delay to treatment), we believe our methodology minimized

possible bias that might have resulted from retrospective assessment. Furthermore, heterosexual and homosexual men did not differ in their retrospective assessment of their pre-treatment sexual function. Third, although bicalutamide is known to block androgen action at the dose levels we administered, we have no direct biological assay to determine the degree to which it was blocked in our patients, or whether the blockade might have differentially affected the groups. Finally, the study was carried out in a patient population undergoing treatment for a life-threatening disease. Although this situation provided a non-invasive platform for implementing this study, it does raise questions regarding the generalizability of our results to non-patient populations.

In conclusion, the results of this study suggest that the basis for sexual libido, arousal and response may be different in heterosexual and homosexual men. Indeed, this study is one of the few that has systematically attempted to understand basic sexual response mechanisms within the framework of sexual orientation, as well as drug effects that might differentially impact men having different sexual orientations. As such, these results reiterate the importance of resisting general models that purport to explain sexual response without regard to important variables such as gender, gender identity and sexual orientation, as well as the importance of developing models that include the possible contribution of such variables.

Oestrogen therapies present numerous side effects, the most important being represented perhaps by male and female breast cancer. However, it would be interesting to determine if an oestrogenic approach (perfectible and not necessarily as monotherapy) could have substantial benefits in heterosexual patients with prostate cancer, taking into account the antiandrogenic action of oestrogens on the prostate cells and also the possible oestrogenic modulation of the cerebral sexual events.

Finally, although the present results imply a role for androgen in cerebral sexual processes such as libido, sexual arousal, and even possibly orgasm of homosexual men, this should not assume that androgens are unimportant for heterosexual men; androgens have multiple peripheral effects on erectile function, intervening in the activity of nitric oxide, phosphodiesterases, and the maintaining of penile tissues and erectile nerves [28], and they are also necessary for numerous central actions, perhaps most importantly the genesis of oestrogens through aromatization of testosterone.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **IIEF**, International Index of Erectile Function; **PET**, positron emission tomography.