Commentary: Risk/Benefit Ratio of Androgen Deprivation Treatment for Sex Offenders

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Androgen deprivation treatment (ADT) significantly lowers testosterone. That, in turn, can decrease sexual drive, facilitating better self-control and lower recidivism rates among sexually disordered offenders. Potential side effects can include: decreases in bone density; development of a metabolic syndrome involving weight gain, accompanied by changes in glucose and lipid metabolism; and rarely, depression. In the presence of a proper treatment protocol designed either to prevent or to minimize side effects, particularly the development of osteoporosis, the risks associated with ADT are generally within the same range as those associated with many other commonly prescribed psychotropic interventions.

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In their article, Giltay and Gooren[1] have importantly detailed the potential side effects of androgen deprivation treatment (ADT) for sex offenders. From a psychiatric perspective, ADT (a significant lowering of the level of circulating testosterone) can be most helpful for that subgroup of sex offenders who are considered to be sexually disordered—that is to have a paraphilia.[2] Its benefit is in diminishing the intensity of the eroticized urges that energize unacceptable paraphilic behaviors and it can, in turn, facilitate the resisting of those urges. ADT cannot effectively assist the antisocial nonparaphilic sex offender who lacks a sense of conscience and moral responsibility by somehow instilling appropriate values.

Giltay and Gooren make the essential point that prescribing psychiatrists and their patients should be fully informed of the possible side effects of ADT. At the same time, the information must be given in a fashion that puts any such side effects into proper context. Although providing full information regarding side effects of medications has always been necessary, it is especially important to do so in this instance, as many patients (and psychiatrists) may already be overly fearful because of the negative connotations associated with a form of treatment that has sometimes been labeled chemical castration.[3]

Historically, psychiatric patients in general have had to endure stigmatization. Although that situation has improved in recent years, at least with respect to certain mental disorders such as major depression, that has by no means been so with respect to the paraphilias. Beyond that, as just noted, the use of medication to suppress the intensity of sexual appetite has itself often been given a stigmatizing label. When one adds to that mix terms such as sex offender, along with the potential for the victimization of innocent others, maintaining a properly informed discussion about the paraphilias as legitimate psychiatric disorders and about their medical treatment, including the development of any untoward side effects, can be challenging at best.

For the reasons just noted, anyone reviewing the potential side effects of ADT, as done by Giltay and Gooren, must never consider those side effects in a vacuum. Instead, in each instance, full weight must be given to accessing properly the risk/benefit ratio of either prescribing or not prescribing such treatment. In some instances, any such risks may affect not only the patient, but others in the community as well. In conjunction with the provision of informed consent, the specific risks, or side effects, of failing to make ADT available must also be considered. In addition, patients need to know whether any proposed ADT

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medication will be prescribed on or off label.[4,5] Finally, special care must be given to the informed consent process when dealing with either legislatively mandated ADT (which can be imposed on sex offenders in several states), or when providing (or failing to provide) ADT to civilly committed sex offenders.[6–8]

When considering the possible side effects of ADT, one must be especially mindful of the potential to confuse or mislead inadvertently. For example, when discussing side effects, Giltay and Gooren often make use of the statistical concept of increased relative risk, suggesting, for instance, that ADT leads to a moderately increased risk of both fractures and diabetes mellitus (by 40%–50%). It is important that both patients and prescribing psychiatrists be able to put that assertion into a proper context.

To expand briefly, if among a group of men not receiving ADT, only 1 in 100 would ordinarily be expected to develop a specific side effect over a given period of time, then all else being equal, the risk of any given man within that group experiencing the side effect would be one percent (1/100). If the administration of an ADT medication to all of the men in that group were to then put one additional man at risk of developing that side effect, the increased relative risk attributable to that medication would be 100 percent. That is, the number of men at risk would double (i.e., increase by 100%) from one to two. Were a patient to be told that by taking the medication his relative risk of developing that side effect would be increased by 100 percent, he would most likely be much more alarmed than were he to be presented with the equally correct information that by taking the medication in question, his actual risk of developing that side effect would be increased from a baseline level of one to two percent. To put it yet another way, although the increased relative risk of developing that side effect would be 100 percent, the actual increased risk to the patient himself would be heightened from one to two percent.

Giltay and Gooren note that in a population-based cohort of elderly men with prostate cancer with a follow-up of up to 10 years, ADT reportedly increased the risk of development of diabetes mellitus by 44 percent. According to the American Diabetes Association, the current prevalence of diabetes mellitus in the United States is 7.8 percent.[9] All else being equal (which of course is not the case with respect to the development of diabetes), increasing that 7.8 percent risk by 44 percent would add an additional 3.4 percent risk ($7.8\% \times 44\% = 3.4\%$). Thus, theoretically, any given patient who does not receive ADT would be at a 7.8 percent risk of developing diabetes. A patient receiving ADT would be at an 11.2 percent risk ($7.8\% \pm 3.4\%$). Giltay and Gooren argue that ADT produces a moderately increased risk of developing diabetes mellitus. Although arguably that may be the case, informing any given patient that his risk of developing diabetes may increase from 7.8 percent without ADT to 11.2 percent should he elect to take it, may be more informative and potentially less misleading than referring to a relative increased risk of 44 percent. And that, of course, is without any potential prophylactic interventions.

Giltay and Gooren point out that there can be three major categories of potential risk when prescribing ADT: a decrease in bone mineral density, accompanied by an increased risk of fracture; development of a metabolic syndrome, manifested by changes in glucose and lipid metabolism, as well as weight gain[10,11]; and the possibility of depression. Over the past decade, psychiatrists who prescribe ADT have generally been aware of the importance of monitoring for changes in bone density while providing such care. That has been so since 1998, when Rösler and Witztum[12] published an important article in the *New England Journal of Medicine* about their work in Israel involving the use of a long-acting analogue of gonadotropin-releasing hormone to treat pedophilia. In that article, they documented the importance of monitoring for changes in bone density over time when ADT is prescribed. As noted by Giltay and Gooren, appropriate treatment should be initiated immediately, should signs of osteopenia be detected.[13]

Potential risks associated with the development of a metabolic syndrome have, perhaps in some instances, not previously been adequately addressed when prescribing ADT—a situation that is probably also true with respect to the use of psychotropic medications in general.[10] That said, psychiatrists prescribing ADT certainly should keep track of any changes in the patient's weight (and blood pressure) on at least a monthly basis, which is the frequency at which most ADT medications are ordinarily injected. Appropriate laboratory testing relevant to the possible development of a metabolic syndrome should be done at baseline before ADT is initiated,

and again, at minimum, on a yearly basis, in association with the patient's annual comprehensive physical examination and assessment. Should a patient begin to gain significant weight or show other signs or symptoms of a metabolic syndrome, appropriate treatment should be prescribed.

The extent to which ADT is associated with the development of depression when treating patients for a paraphilic disorder is unclear. Giltay and Gooren conclude that there is a small increased risk of depression associated with ADT—a conclusion based, at least in part, on studies of elderly patients undergoing treatment for advanced prostate cancer. The degree to which such data can be extrapolated to generally younger and healthier patients afflicted with a paraphilic disorder is debatable. Be that as it may, treating psychiatrists should always be sensitive to the development of any comorbid conditions, whether iatrogenically caused or not. Psychiatrists cannot always accurately predict which patient may be at risk of developing a comorbid disorder such as depression, but generally it can be managed via appropriate treatment when present.

Giltay and Gooren have correctly noted that there can be a transient increase in the level of circulating testosterone following the initial injection of an antiandrogen such as leuprolide; but the testosterone level will then decline dramatically, remaining significantly lowered with repeated injections. To protect patients from experiencing an increased sexual drive during the transient elevation of testosterone that follows the initial injection of an ADT medication, the clinician should prescribe a testosterone-receptor blocker, such as flutamide (250 mg orally three times daily, for 14 days) following that initial injection only.

Currently, in the United States, all of the medications that are used to deplete androgen levels are prescribed under FDA guidelines regarding the use of an approved drug for a nonlabeled indication.[5] There is absolutely no doubt that such medications, when prescribed in adequate dosages, will significantly reduce testosterone; a fact that can be corroborated by a simple blood test. Beyond that, there is a large body of scientific data documenting the relationship between significantly lowered levels of testosterone and lowered sexual drive.[14] Prescribing a medication off label for such a purpose is not considered to be experimental,[15] and there is good evidence that sexual recidivism rates can be lowered via ADT.[16]

Let us return, then, to the risk/benefit ratio. ADT, by lowering testosterone, has shown itself to be an effective means of enhancing self-control in paraphilic patients and of significantly decreasing sex offender recidivism rates.[8] That can clearly be viewed as a benefit not only to the patient himself, but in many instances to the larger community as well. As with any psychotropic medication, as has been documented by Giltay and Gooren, ADT can also be associated with potentially significant side effects. Clozaril, an effective treatment for schizophrenia, can cause agranulocytosis. Selective serotonin reuptake inhibitors (SSRIs) now contain a black-box warning about the risk of suicide. Some antidepressants can cause cardiac arrhythmias, and many psychotropics can produce irreversible tardive dyskinesia. The point here is not to minimize the potential risks of ADT, but rather to insist that they be viewed within the larger context of other generally prescribed psychiatric medications. Arguably, when properly administered, with an appropriate protocol in place to detect and treat side effects should they develop, ADT, in general, constitutes no more or less of a risk than most other forms of frequently prescribed psychopharmacological agents.

The decision about prescribing or not prescribing ADT should, as in any other case, also include a consideration of the availability, or lack thereof, of comparably effective treatment options. Once again, decisions about prescribing ADT should not be influenced by connotations of a term such as chemical castration, and the potential side effects of ADT, which should of course be taken quite seriously, should never be considered out of context. Arguably, given the serious nature of many of the paraphilic disorders, along with the obvious benefits of successful treatment, despite the possibility of significant though generally manageable side effects, ADT may be underprescribed, rather than overprescribed.

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