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Flutamide-induced hepatotoxicity: ethical and scientific issues

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Abstract. – OBJECTIVE: Flutamide (FLU) is a non-steroidal antiandrogen drug approved for the treatment of advanced prostate cancer. While this indication limits the use to male patients, FLU is widely prescribed to women, off-label, for the treatment of polycystic ovary syndrome (POCS) related hirsutism and acne. According to the literature, its assumption is associated with a higher incidence of adverse events in women than in male patients.

MATERIALS AND METHODS: A literature search was conducted in main databases targeting unwilling FLU effects in hepatic and reproductive function. References in the selected paper were also considered as an additional source of data. Human- and animal-based studies were separately considered.

RESULTS: Twenty-three human-based studies were evaluated: ten were case reports, six were retrospective studies, four were prospective, two were surveillance studies, while the last was an observational study. Nine animal-based studies were also evaluated.

CONCLUSIONS: Scientific contributions highlight that FLU is responsible for specific hepatotoxic profiles in the female gender. From the ethical point of view, off-label prescribing of FLU in women is not only substantially unlawful, but also, without major safeguards being granted, a potential source of liability for prescribers.

Key Words
Flutamide, Hepatotoxicity, Off-label, Gender medicine.

Introduction

Flutamide (FLU), 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide, is a non-steroidal antiandrogen drug with a nitroaromatic chemical structure.

Notwithstanding its non-steroidal structure, FLU acts as a competitor for testosterone and dihydrotestosterone receptors, having a role in the treatment of hormone-sensitive tumours as the prostatic one, usually in combination with luteinizing hormone-releasing hormone agonists (LHRH)[1]. This association appears to be the only FDA-approved application of the drug for stages B2-D2 of male prostate cancer.

Nevertheless, FLU is also used in a broad range of clinical settings, including male exhibitionism[2] and paraphilia[3]. The drug has not yet been approved for pediatric and geriatric patients since specific safety data lacks for these special populations.

Polycystic ovary syndrome (POCS) affects 5-10% of women of reproductive age[4]. It is associated with infertility problems, uterine bleeding, as well as aesthetic problems like hirsutism and acne, which are mainly connected to the hyperandrogenic state of PCOS. Therefore, the aim of POCS-related hirsutism and acne therapies is to suppress androgens production, thus reducing the hormonal free fraction and the effect on target organs. Hyperandrogenism-related clinical manifestations in PCOS may be counteracted by many therapeutic options, with oral contraceptives (OCPs) playing a major role[5].

On the one hand, the estrogenic component allows the suppression of luteinizing hormone (LH) secretion reducing androgen production by ovaries. On the other, it increases the production of sex hormone-binding globulin (SHBG), then reducing circulating free testosterone[5].

An additional therapeutic option for PCOS is represented by antiandrogens, the most used of which are cyproterone acetate and spironolactone[5]. These compounds block androgen receptors and inhibit 5α-reductase, which converts testosterone to the more powerful 5α-dehydrotestosterone. The androgen receptor blocker FLU and the 5α-reductase inhibitor finasteride are also applied for this purpose. Specifically, in the case of FLU, this is an off-label use of the drug itself.

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Although randomized trials, comparing the effectiveness of oral contraceptives and antiandrogens in PCOS treatment, have failed to highlight significant differences[6], due to its efficacy to treat hirsutism, a psychosocial distress in a consistent part of the feminine word, particularly among teenagers, an extensive use of FLU has been recorded within this population.

Nevertheless, FLU consumption has been associated with severe detrimental side effects, thus raising some ethical-deontological issues related to its pharmaco-toxicological characteristics, especially in its off-label use in female hirsutism.

The present review was undertaken to evaluate the toxicity of FLU and its active metabolite hydroxyflutamide, in animal and human models.

Materials and Methods

A literature search was conducted in main databases (e.g. Pubmed, Biosis and Google Scholar) targeting side FLU effects in hepatic and reproductive function.

Searched keywords included "flutamide" and "flutamide treatment", "women", "hepatotoxicity", "reproduction", "teratogenesis", "side effect". Studies reported within the references in the publications selected for the review were also considered as an additional source of data.

Hepatotoxicity of flutamide

Twenty-three human-based studies and full articles were evaluated (Table I). Nine animal-base studies were also considered for pathogenetic mechanisms (Table II).

FLU is mainly metabolized into 2-hydroxyflutamide (OH-FLU) by CYP1A2[7]. This metabolite has been known to be dangerous showing an additive toxic effect with FLU[7]. Nevertheless, OH-FLU toxicity has not been confirmed *in vitro* by cultured rat hepatocytes. Another metabolite, 5-amino-2-nitrobenzotrifluoride (FLU-1) is obtained from FLU hydrolyzation. FLU-1 is then oxidized to metabolites that may have an additional, or even a prominent role in FLU hepatic toxicity[8,9]

Studies on animal models showed that FLU-related hepatotoxicity mainly depends on hydrolysis operated by an arylacetamide deacetylase[10] on the compound, similarly to what happens to phenacetin[11]. Not surprisingly, FLU and acetaminophen (paracetamol), whose prodrug is phenacetin, seem to have an additive-synergic effect in cultured human hepatocytes[12].

Bile canalicular network alteration was proposed as a process involved in Drug-Induced Liver Injury (DILI) and Flutamide Induced Liver Injury (FILI)[13], confirming the evidence of reduced taurocholate efflux in human hepatocytes[12].

It has been suggested that both immunological[14,15] or idiosyncratic[16,17] mechanisms may have a role in FLU induced hepatotoxicity in both mice and human models. Enzyme-linked immunosorbent assay (ELISA) tests in humans failed to reveal the presence of antibodies against FLU metabolites[14], whereas it has been cleared that FLU alters Th2-cells immunological factors in mice models[15] and polymorphonuclear leukocytes (PMN) *in vitro*[18].

In vitro[19] and *in vivo* studies also support the hypothesis of FILI as the consequence of the production of pro-oxidant radicals and other reactive oxygen species (ROS). The effects appear clearly dose-related *in vitro*[20]. This is confirmed by the detrimental effect of glutathione (GSH) deficiency in cytochrome P450 1A2 (CYP1A2) knockout rats treated with FLU[8] or by GSH depletion following drug administration[9,21].

FLU appears to be so effective in determining hepatotoxicity, via an oxidative stress, that it has used as a model compound in experimental designs[22,23].

FILI is generally monitored and revealed by elevation of aspartate and alanine aminotransferases concentration in plasma. Lipid peroxidation products have been proposed as markers for early detection of FILI[22], while the Multidrug And Toxin Extrusion protein 1 (MATE1) mRNA level may have a role as innovative predictive biomarkers of FILI[24].

The FLU-related injury is highly variable, being acute and cholestatic hepatitis the most common and early described manifestations of hepatotoxicity[25-,30], as demonstrated for other antiandrogens[28,29]. However, FLU emerges as more closely associated with hepatic detrimental effect than its newer structural analogs bicalutamide or cyproterone (CPA)[28,29]. FLU cross-reactivity with CPA has been also suspected[31,32]. This is an additional matter of concern since newer OCPs contain CPA.

Harm to hepatic tissue ranges from fully developed and severe manifestations (e.g. ascites, hypoalbuminemia, hyperammonemic encephalopathy, lethargy, and confusion, bleeding and clotting disorders[33,34]), to isolated biochemical alterations[35,36]. Transaminases elevation could represent a challenge for clinical detection and, therefore, may be more rarely spontaneously reported, widening the spectrum of unreported side effects of FLU[29].

Table I. Hepatotoxicity of Flutamide.

Study	Type	Patient# (gender)	Median age (range)	Treatment (dose)	Hepatotoxicity (patient % and #)	Outcome
Gomez et al (1992)[35]	Obs	1091 (M)	66 years (35-97)	FLU (250 mg tid) + LHRH (500 mg/day for 1 month then 250 mg for 8 months)	0.36% (4/1091) mild 0.18% (2/1091) moderate	100% Heal
Wallace et al (1993)[44]	CR	1 (F)	20 years	FLU (250 mg tid	Moderate-severe	Heal
Dourakis et al (1994)[51]	CR	2 (M)	70 years; 84 years	FLU (750 mg/day)	Moderate-severe	50% (1/2) Heal; 50% (1/2) Dea
Wysowski et al (1996)[52]	Ret	46 (45 M/1 F)	70 years (47-85)	FLU (750 mg/day) for 3 months	Severe	57% (26/46) Heal; 43% (20/46) Dea
Pontiroli et al (1998)[14]	CR	1 (M)	69 years	FLU (250 mg tid) + LHRH (3.75 mg/month) for 5 months	Severe	Heal
Andrade et al (1999)[47]	CR	1 (F)	14 years	FLU (250 mg/day)	Severe	Tr
Pu et al (1999)[37]	Ret	56 (M)	74 years	FLU (500-1000 mg/day)	23% (13/56) mild-moderate	100% Heal
Cetin et al (1999)38	Pro	22 (M)	66 years (47-79)	FLU 750 mg/day + LHRH or orchiectomy	9% (2/22)	4.5% Heal; 4.5% Dea
Garcia Cortés et al (2001)[16]	Ret	185 (M/F)	75 years (M); 14 years (F)	FLU (250-750 mg/day)	4.9% (9/185): 86% (7/9) moderate; 22% (2/9) severe	69% (6/9) Heal; 22% (2/9) Dea; 11% (1/9) Tr
Lin et al (2003)[39]	Ret	124 (M)	47-89 years	FLU (750 mg/day)	15.3% (19/124) Moderate-severe	100% (19/19) Heal
Famularo et al (2003)[50]	CR	1 (M)	74 years	FLU (250thrice/day) + LHRH (3.6 mg/28 days)	Moderate	Heal
Lubbert et al (2004)[53]	CR	2 (M)	77 years; 66 years	FLU (250 mg/day)	Moderate-severe	50% (1/2) Heal; 50% (1/2) Dea
Ibáñez et al (2005)[32]	Pro	190 (F)	13-16 years	FLU (62.5-125 mg/day)	None	Heal
De Amorim et al (2005)[36]	CR	1 (F)	21 years	FLU 250 mg/day)	Mild	Heal
Osculati et al (2006)[54]	CR	1 (F)	18 years	FLU (250-375 mg/day) for 3 months	Severe	Tr; Dea
Miquel et al (2007)31	CR	1 (M)	78 years	FLU (750 mg/day + LHRH (22.5 mg/3 months); CPA (150 mg/day) + LHRH (22.5 mg/3 months)	Moderate Moderate	Moderate
Dikensoy et al (2009)[76]	Pro	214 (F)	20.3 years (18-34)	FLU (125-250 mg, with/without OC)	None	Heal
Castelo-Branco et al (2009)[41]	CR	1 (F)	26 years	FLU (250 mg/day)	Severe	Heal
Castelo-branco et al (2009)[42]	Pro	83 (F)	26 years	FLU (250 mg/day) (27/83); FLU (250 mg/day) + OC (0.02 mg + 0.15 mg) (56/83)	40.96% mild-moderate	Heal
Paradisi et al (2010)[45]	Ret	414 (F)	24 years	FLU (250, 125 and 62.5 mg/day) ± OC fro 3-8 years	Mild-moderate	Heal
Brahm et al (2011)48	Ret	10 (3 M/7 F)	75 years (M), 29 years (F)	FLU (750 mg/day, M; 125-250 mg/day, F)	50% mild-moderate 50% severe	50% (F 5/7) Tr; 90% Heal; 10% (F 1/7) Dea
Bruni et al (2012)[43]	Sur	203 (F)	20.9 years	FLU (62.5-125 mg/day) with/without OC	9.4% mild-moderate	100% Heal
Castelo-Branco et al (2016)[46]	Sur	120 (F)	28.6 years	FLU (125-250 mg/day) with/without OC	10% mild-moderate	100% Heal

Type of study: Case Report (CR); Observational study (Obs); Prospective (Pro); Retrospective study (Ret); Surveillance study (Sur). ***Treatment:*** Cyproterone (CPA); Flutamide (FLU); Luteinizing hormone-releasing hormone (LHRH); Oral contraceptive (OC). ***Hepatotoxicity:*** Mild (transaminase increase, prolonged prothrombin time); Moderate (asthenia, anorexia, weight loss, nausea, vomiting, jaundice); Severe (fulminant hepatitis, encephalopathy, fulminant hepatic failure). ***Outcome:*** Healing (Heal); Liver transplantation (Tr); Death (Dea).

Table II. Effects of Flutamide on animal reproduction.

Study	Test subject	Administered dose	Effects
Luthy et al (1987)[61]	Female rat	5 mg bid/day	Minor endocrine effects
Goto et al (2004)[62]	Pregnant rat	3-10-30 mg/kg/day	Effects on fetuses: cryptorchidism, testicular hypoplasia, absence of prostate gland and seminal vesicles Abnormal sexual behavior
Jensen et al (2004)[67]	Minnow	50-500 µg/l for 21 days	Reduction of fertility, reduced embryo hatching, sexual gland degeneration
Yamasaki et al (2005)[68]	Pregnant rat	0.4-2-10 mg/kg/day	Abortion, changes in sexual organs
Foster et al (2005)[63]	Pregnant rat	50 mg/kg single shots in GD 16, 17, 18, 19	Permanent nipples, epi-hypospadias, missing epididymal components, vaginal pouch, cleft prepuce, missing prostate lobes, abnormal seminal vesicles
Nagaosa et al (2007)[69]	Mouse	20 µl	Impaired spermatogenesis
Anway et al (2008)[70]	Gestating rat	5 and 20 mg/kg/day	F1 generation: increased spermatogenic cell apoptosis and decreased epididymal sperm numbers. F2, F3: /
Anhara et al (2008)[71]	Newborn and adult mice	0.012 mg/kg/day for 5 days	Abnormal spermatids
Inakawa et al (2009)[72]	Gestating rat	10 mg/kg/day	No spermatogenesis and fertility effect

While most of the cases show a reversible alteration after drug withdrawal[29,30,33-46], fulminant or prolonged and progressive anatomical-functional deteriorations, from cirrhosis[29,34,44,47,48-50] until death[37,50-54]. have been also described. Manifestations occurred 1 to 10 months[29,30,39] (3 on average[29,43]) following the beginning of FLU intake, being the latency widely shorter than what observed for CPA[28,39].

Pathological findings correspond to an extensive liver necrosis[35,44,50] mixed with cholestatic signs[35,44] both in male and female patients, according to aforementioned supposed mechanisms of injury.

Focusing on off-label therapies, a higher rate of complications was reported, exceeding 40%, in female patients.[40,56]. Therefore, it is not surprising that a conspicuous number of women in treatment with FLU stopped the drug intake, both because of intolerance, side effects or required discontinuation [42, 45].

It was stated that clinical symptoms do not correlate with female patient age[28]. However, this aspect was not analyzed in female-only patients so that this evidence could be due to the low number of female toxicity cases evaluated. Even though male patients are older and multidrug-taker[28,29], female patients seem to have a lower rate of recovery and a need for transplantation occurred more frequently[47,48]. Therefore, if an age-related effect could be considered, it may consist in a tendency toward hypersensitivity for young people. Likewise, it is still not clear if a dose-related effect exists. Adverse events incidence appeared much lower with low and ultra-low doses (62.5 – 125 mg/day)[40,45,57,58], as sometime used in combination therapies[59]. According to some studies, a correspondence between injury and dose can hardly be identified[28], while an epi-analysis questioned the possibility of an idiosyncratic effect[60].

Patients with viral hepatitis, as well as those suffering an inflammatory disease of different origin[19,61] were at greater risk of liver toxicity[37].

According to some investigators, the incidence of FLU-related fatal adverse events is underreported and consequently underestimated[16]. This evidence has led the FDA to request a black box warning on the drug label to highlight the drug side effects, particularly those on liver.

Although androgen levels are low in the first stages of gonadal development, testis seem to express androgen receptors. There are no reports of FLU-related teratogenesis in humans. Conversely, animal studies have found effects on primary and accessory reproduction organs, leading to reduction or absence of prostate gland[62,63,64], seminal glands alterations[63,64], and testicular hypoplasia[63]. Single-shot administration of FLU also determined hypo-epispadias and feminization marks[64]. Both cryptorchidism and ectopic testis were discovered, allowing to demonstrate a FLU effect on testicular descent[63,64,65]. It is also notable that some rat models of cryptorchidism are based upon flutamide injections to pregnant rat[66,67].

Reduction of conception rate[68], fertility[69], and impaired spermatogenesis[70,71] were also discovered being responsible for reproductive function deterioration. Histological alterations in spermatids were also found[72]. This spermatogenesis alteration was not confirmed in other studies, as happened for others anti-androgen drugs[73].

Reprotox[74] summarizes the results of animal studies as follows: "*Administration during pregnancy results in adverse effects on male genital development in experimental animals. Flutamide is not indicated for use in* women". FDA classified FLU as a pregnancy risk category D drug: "*There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*"[75].

Profiles of FLU-associated hepatotoxicity, from a molecular to subcellular level, until clinical manifestations, which may be particularly severe, has sufficiently been clarified by the revision of the scientific literature.

For a long time after its introduction in 1989, FLU has been looked at as a safe drug[40] and unwilling events thought to be rare, reversible and only high doses and male employment restricted.

However, at present, a non-negligible number of patients declared to have experienced unwilling effects. This appears to happen, even in very low dosages cases, weeks to months after the onset or the withdrawal from FLU therapy. Liver failure progresses in an undoubtedly significant quantity of cases too, requiring a transplant or leading to death[47].

Because of the limited knowledge of the previously exposed effect, only few generic suggestions have until now reported, e.g. hepatic functionality monitoring for some months and early treatment suspension in case of transaminases elevation[16,28,30,38,41,76]. Others propose systematic biochemical and clinical controls and promptly discontinuation of therapy if only severe manifestations occur[16,34,41].

At the present time, those recommendations do not seem to be risk-based and relevant. This is a matter of concern especially in women, for whom specific features should also be considered:

- patients are often young, the majority being teenagers, while FLU therapy commonly target just male population;
- unwilling effects appear with higher frequency in spite of lower doses;
- the most serious cases are concentrated in this population;
- teratogenic effects are non-negligible;
- only postmarketing surveillance strategy has been conducted; therefore, security data have not been obtained from experimental studies on women. Indeed, as the only approved use is prostate cancer, no phase II trial was performed on female patients.

Then, it must be stressed that the risk/benefit ratio for the treatment of hirsutism and acne is actually different from the one stated for metastatic prostate cancer, for which the drug is indicated[77].

The intake of FLU out of the indication of prostate cancer therapy cannot be simply considered as not recommended: the off-label use of a drug should only be possible when both its efficacy and safety of the treatment have been documented and established.

This is not the case of FLU, for which there is a clear demonstration of the contrary.

We should also consider that for the treatment of hirsutism in premenopausal women, the use of oral contraceptives as monotherapy is recommended[78].

FLU is contraindicated as a first-line treatment[79]. Nevertheless, if a therapeutic alternative cannot be found, it should be given with clear and solid precautions:

- after the collection of a valid, specific, detailed, documented and subscribed informed consent;
- the minimum effective dose should be used;
- carefully and strictly monitoring of the liver function during the whole period of therapy and for some months afterwards;
- carefully monitoring of the onset of symptoms such as asthenia, fatigue, jaundice, nausea, vomiting;
- immediate discontinuation of therapy at clinical or chemical signs of liver injury presentation.

The FDA has no policy restricting the use of medications employed in un-authorized treatments[80]. This aims to avoid the limitation of physician judgment. However, the physician is required to record any off-label drug use and any side effects. The EU has not specifically regulated the matter, and a similar situation exists in Japan, Canada, and Australia. According to some authoritative Australian scientists[81], off-label use is legitimate if it is supported by high-quality evidence, by data obtained in clinical trials and exceptional cases. Outside these conditions, off-label prescribing is unlawful[82].

Conclusions

The present review reported several studies documenting a high incidence of hepatic side effects of FLU, especially in women using the drug off-label. Effects on reproductive function have been also reported in an animal model. Thus, evidence-based assessments advise to not prescribe antiandrogens, including FLU, to treat hirsutism and acne, given that other safer and likewise effective drugs are available.

The requirements governing off-label FLU prescription for hyperandrogenic symptoms in Western countries are rarely met: this is due to both its well-documented risk profile and to the availability of safer medications with documented efficacy. FLU is also significantly more expensive compared with other effective medications[83].

Since FLU is exclusively indicated to treat advanced prostate cancer, data on secondary effects affecting female patients have not been collected in the pre-marketing phase. This deficiency has been overcome by off-label FLU administration to treat hirsutism and acne in women, subjecting them to experimentation without any of the safeguards granted by formal clinical trials (study approval by an ethics committee; insurance coverage; monitoring during drug administration and follow-up; compliance with the ethical principles of international declarations). These evidences demonstrate the urgent need for addressing gender medicine also in relation to off-label prescribing, given its wide-ranging scientific and ethical implications. Off-label FLU prescription to female patients, particularly adolescents, raises serious ethical problems[84].

Treatment of hirsutism and acne with FLU in women is not appropriate, as demonstrated by others in the literature[85], nor does it meet the fundamental ethical principle "*beneficence non-maleficence*", since the risk/benefit ratio is strongly tilted toward the risk.

Although current legislation substantially authorizes off-label prescribing of FLU, the authors believe that given the drug unfavorable risk profile, there is neither scientific nor ethical basis warranting the use of FLU to treat an aesthetic problem. This is even more crucial when a drug that is not completely safe is used to manage a non-rare disease for which other effective therapeutic options are available.

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Conflicts of interest

The Authors declare that they have no conflict of interests.

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