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REVIEW ARTICLE

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The impact of drugs on male fertility: a review

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SUMMARY

Beside cytotoxic drugs, other drugs can impact men's fertility through various mechanisms. Via the modification of the hypothalamic–pituitary–gonadal axis hormones or by non-hormonal mechanisms, drugs may directly and indirectly induce sexual dysfunction and spermatogenesis impairment and alteration of epididymal maturation. This systematic literature review summarizes existing data about the negative impact and associations of pharmacological treatments on male fertility (excluding cytotoxic drugs), with a view to making these data more readily available for medical staff. In most cases, these effects on spermatogenesis/sperm maturation/sexual function are reversible after the discontinuation of the drug. When a reprotoxic treatment cannot be stopped and/or when the impact on semen parameters/sperm DNA is potentially irreversible (Sulfasalazine Azathioprine, Mycophenolate mofetil and Methotrexate), the cryopreservation of spermatozoa before treatment must be proposed. Deleterious impacts on fertility of drugs with very good or good level of evidence (Testosterone, Sulfasalazine, Anabolic steroids, Cyproterone acetate, Opioids, Tramadol, GhRH analogues and Sartan) are developed.

INTRODUCTION

Among the aetiological factors involved in male infertility, drug-related illnesses must be investigated (Jarow *et al.*, 2010). If a patient is taking a drug, the time when the treatment was started, its duration and the period during which it was taken (was it a critical period during testicular maturation?) and the dose are important factors to note (Jungwirth *et al.*, 2015). This information can be very useful in the event of an alteration of spermatogenesis or erectile or ejaculatory function.

However, up to now very little work has been performed to summarize the impact of drugs on male fertility with the exception of cancer treatments (Lee *et al.*, 2006; Lambertini *et al.*, 2016). It is important and demanded to establish levels of scientific proof for each molecule in question, to be able to determine the actual impact of the treatment among the other risk factors often associated in the same infertile patient.

This research aims to gather together the available data on the negative impact of pharmacological treatments on male fertility: the impacts on spermatogenesis and semen parameters, as well as impacts on sexual function are studied. This research also includes the recommendations for treating fertility and sexual function issues in men who take the various treatments studied. Medications with an effect on semen and/or sexual function proved with a good level of evidence are developed. The study does not involve the impacts of cytotoxic agents, that is, microtubule disrupting agents and DNA modifying agents, generally used for the treatment of cancer.

MATERIALS AND METHODS

This systematic literature review was performed by drawing on three biomedical literature and academic electronic databases: PubMed/MEDLINE, ScienceDirect and Google Scholar. This research collates data that is related to the effects of drug treatments (excluding cytotoxic molecules) on male fertility. These treatments were divided into subgroups depending on whether the incriminated molecule caused spermatogenesis/post-testicular maturation disorders (direct or indirect effect) or sexual function disorders. For each

subgroup the data search was performed using the following respective key words:

Impact of drugs on spermatogenesis and sperm parameters*: "Medical therapy, drugs… and… effects on spermatogenesis, toxicity on spermatogenesis, gonadal impact, sperm parameters, male infertility, fertility on men"* to begin with, then more specific terms were used after the initial data had been gathered: *"Immunosuppressive therapy dermatological medication, Sulphasalazine, opiates, antidepressants, antihypertensive drugs, Tamsulosine, antiepileptics, antiretrovirals therapy, antibiotics, Ketoconazole, anabolic steroids, testosterone, Finasteride, Colcicine, Cimetidine… and… effects on spermatogenesis, toxicity on spermatogenesis, gonadal impact, sperm parameters, male infertility, fertility on men"*.

Impact of drugs on sexual function: *"Medical therapy, drugs… and… erectile dysfunction/disorders, impotence, ejaculation disorders, retrograde ejaculation, anejaculation, sexual dysfunction, testosterone level, male infertility, fertility on men"* to begin with, then more specific terms were used after the initial data have been gathered: *"corticosteroid, antidepressants, antipsychotic drugs, benzodiazepines antihypertensive drugs, diuretics, alpha-blockers, Cyproterone acetate, Finasteride, antiepileptics, opiates, statins, fibrates … and… erectile dysfunction/disorders, impotence, ejaculation disorders, retrograde ejaculation, anejaculation, sexual dysfunction, testosterone level, male infertility, fertility on men"*.

Abstracts and citations identified via the three databases were reviewed and evaluated for relevance to the question. References cited in the reviewed articles were analysed for additional primary articles not identified in the first search. The search was limited to articles written in English language or in French language and published until May 01, 2016. The studies that were selected concerned men; studies on animal models were used in a handful of cases in which few studies on men were available.

We also drew on the recommendations of learned societies (American Society of Clinical Oncology, European Society of Human Reproduction and Embryology, American Society of Transplantation, European Society for Organ Transplantation, Society of Urology, Société Française d'Urologie, Society of Toxicology, European Federation of Endocrine Societies and International Society for Sexual Medicine), data from the Centre de Référence sur les Agents Tératogènes (CRAT) and the work of reference containing all the summaries of product characteristics of drugs used in France (VIDAL Hoptimal 2016).

Levels of scientific evidence were established for each drug from the type of studies available and the methodology that was used. To define these levels of evidence, we drew on data from Sackett and the Centre Cochrane Français (Sackett, 2000; Définir le meilleur type d'étude | Centre Cochrane Français 2016). Meta-analyses and randomized controlled trials with a high statistical power thus constituted a high level of scientific evidence. Randomized controlled trials with a low statistical power, prospective comparative studies and cohort studies provided a fairly good level of evidence. Case–control studies and retrospective studies constituted a low level of evidence. Lastly, case series and studies in animals constituted a very low level of evidence. Studies with a satisfactory level of evidence must also have had little bias, a high statistical power and a statistical analysis that was suited to the study objectives. In the case of literature reviews, we referred to the scientific papers that were selected in the review to obtain a level of evidence that would be as reliable as possible (Fig. 1).

RESULTS

A drug treatment can affect spermatogenesis by interfering with the exocrine function of the testes by altering the germ cells and/or the Sertoli cells. Sertoli cells play a support role in the survival and differentiation of germ cells. When a drug interferes with the endocrine function of the testes by altering Leydig cells or disrupts the hormone regulation system (at the level of the hypothalamic–pituitary axis), the resulting drop in testosterone can also impact spermatozoa production (Fig. 2). Lastly, any molecule that is likely to modify intratesticular vascularization or alter epididymal function can affect sperm parameters (Creasy, 2001) (Fig. 2).

The drug treatments that are responsible for spermatogenesis disorders or sperm parameter alterations, and the recommendations for treating infertile men, are given in Table 1.

The mechanisms of action (when they are described) through which a pharmaceutical molecule can affect sperm parameters are described in the sections below.

The effects of pharmaceutical molecules (excluding cytotoxic agents) on spermatogenesis and sperm parameters are generally reversible when the treatment is discontinued (provided that the medication is the sole causal factor). If it is impossible to stop a therapy, the use of antioxidant supplements is sometimes proposed.

Symptomatic treatment of sperm parameter alteration with antioxidants

Oxidative stress (resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant system activity) is thought to be involved in the pathophysiology of male infertility. It is responsible, among other things, for a loss of membrane and DNA integrity in the spermatozoa, thus altering their ability to fertilize the oocyte. A number of studies suggest that supplementation with oral antioxidants (vitamins C and E, zinc, selenium, folates, carnitine and carotenoids) could improve the sperm quality in infertile patients whose semen is found to contain excessive ROS (evidenced by reduced DNA fragmentation, increased sperm motility, etc.). However, the evidence that confirms a beneficial effect from these molecules is far from convincing, as other data do not indicate any improvement with this type of treatment (Ross *et al.*, 2010).

Studies that have evaluated a possible association between a drug treatment and elevated ROS in semen are almost non-existent. In animals, the administration of cytotoxic molecules (Cyclophosphamide) can reduce catalase (a component of the antioxidant enzyme system) activity in the testes, resulting in oxidative stress (Tremellen, 2008). Other drugs, such as Sulfasalazine, acetylsalicylic acid and antibiotics, could also stimulate ROS production (Narayana, 2008a; Tremellen, 2008; Alonso *et al.*, 2009).

Antioxidants are thought to be ineffective in men whose hypofertility is not caused by oxidative stress. Any alteration in the optimal balance between the concentration of antioxidant molecules and that of ROS could even prove to be harmful because the physiological production of ROS plays an important role in the spermatozoa capacitation and/or acrosome reaction process and in oocyte fertilization capability (Bolle *et al.*, 2002;

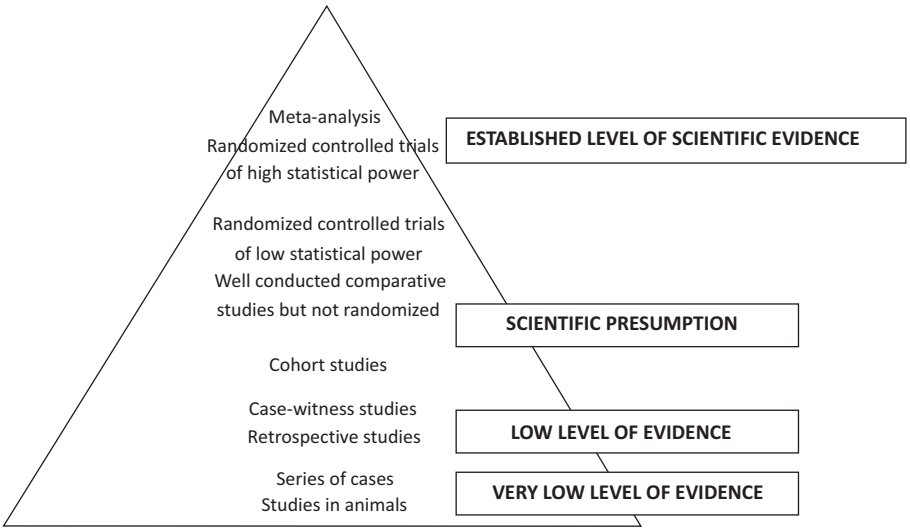

Figure 1 Scientific level of evidence given in the literature. Adapted from Sackett (2000) and the Centre Cochrane Français, (2016).

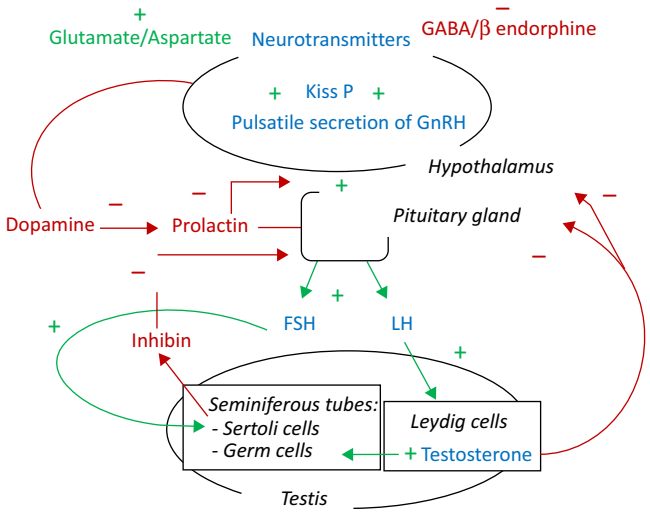

Figure 2 Endocrine regulation of the hypothalamic–pituitary–gonadal axis. Adapted from Dubest & Pugeat (2005) and Courtois & Bonierbale (2016).

Ménézo *et al.*, 2007; Desai *et al.*, 2009). Therefore, antioxidants should not be systematically prescribed in cases of sperm parameter alteration.

Mechanisms of drugs action on sexual functions and recommendations

An erection results from the swelling of the corpora cavernosa, which becomes engorged with blood after a series of neurological events and the activation of vascular mediators that are involved in the physiology of erectile function (Droupy, 2005; Gratzke *et al.*, 2010) (Fig. 4). When a bioactive molecule interferes with these mechanisms, erectile dysfunction can result. Nocturnal erections are androgen dependent (erections resulting from sexual stimulation are much less so). Therefore, an androgen deficiency can be a cause of erectile disorders (Courtois & Bonierbale, 2016).

Ejaculation occurs in response to a series of neuromuscular events that lead to the emission and then the expulsion of semen from the urethra. Any alteration in these events can modify ejaculatory function and can be a cause of ejaculatory disorders (total or partial retrograde ejaculation into the bladder, anejaculation, delayed ejaculation, etc.) (Rigot *et al.*, 2013).

Male sexual activity is dependent on the dopaminergic system and the sex hormones (androgens). Its cerebral control is subject to the inhibitory influence of the opioid system. A dopamine or androgen deficiency can thus cause a loss of sexual desire (Courtois & Bonierbale, 2016). Similarly, if a pharmaceutical substance affects the central nervous system, it can also have an adverse effect on male libido (Rigot *et al.*, 2013).

The drug treatments that are responsible for an alteration in sexual function are presented in Table 2.

The mechanisms of action (when they have been described) through which a pharmaceutical molecule can affect sexual function are described in the sections below.

The treatment of erectile and ejaculatory dysfunction is based initially on psychosexual therapy for the couple. When sexual disorders arise during drug treatments, the discontinuation of treatment with the incriminated molecule generally restores the reproductive function of men who wish to have children. When it is impossible to stop a therapy, symptomatic treatment of the disorders can be considered.

Symptomatic treatments for erectile disorders

Type 5 phosphodiesterase inhibitors (Sildenafil, Tadalafil and vardenafil) facilitate muscular relaxation in the corpus cavernosum that brings about an erection, the principal mediator of which is nitric oxide. These medications must be prescribed in strict accordance with their adverse effects and precautions for use (beware of nitro-derivatives, NO liberators, Ritonavir, alpha-blockers, cardiovascular conditions, etc.) (Cuzin *et al.*, 2011; VIDAL Hoptimal 2016). The efficacy of Yohimbine (an α2-adrenergic receptor antagonist) has not been demonstrated. The injection of PGE1 (Alprostadil) into the corpus cavernosum is a second-line treatment for erectile disorders. As the molecule passes into the semen, these treatments must not be used in men who wish to conceive. As a last resort, the use of a vacuum device (a mechanical system that brings about a passive erection) or penile implants may be proposed (Cuzin *et al.*, 2011).

Symptomatic treatments for ejaculatory disorders

The treatment of ejaculatory disorders that are induced by a pharmacological treatment becomes a complex matter when the discontinuation of the drug proves to be impossible. Before instigating this type of treatment in men of reproductive age, semen cryopreservation should be considered. In the case of retrograde ejaculation, the collection of alkalinized urine followed by a search for spermatozoa and cryopreservation can be proposed with a view towards the pursuit of assisted reproduction techniques. In the case of total anejaculation or if the quantity of spermatozoa that was collected in the urine is insufficient for freezing, spermatozoa (epididymal or testicular) can be retrieved surgically. The pharmacological treatments and penile vibratory stimulation techniques that are used to treat anejaculation in

Table 1 Impact of drugs on spermatogenesis and sperm parameters (Nudell *et al.*, 2002; Schlosser *et al.*, 2007; Brezina *et al.*, 2012)

Pharmacological class	Family and molecules (references)	Impact on spermatogenesis and sperm parameters	Guidelines
Immunosuppressive drugs	*mTOR inhibitors:* Sirolimus (Bererhi *et al.*, 2003; Huyghe *et al.*, 2007; Zuber *et al.*, 2008; Roa *et al.*, 2009; Rovira *et al.*, 2012; Chen *et al.*, 2013; He *et al.*, 2013; Leroy *et al.*, 2015; VIDAL Hoptimal 2016) *Calcineurin inhibitors*: Ciclosporine, Tacrolimus (Haberman *et al.*, 1991; Iwasaki *et al.*, 1995; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Chen *et al.*, 2013; He *et al.*, 2013; Millsop *et al.*, 2013; Palomba *et al.*, 2014; Grunewald & Jank, 2015; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016; VIDAL Hoptimal 2016) *Antimetabolites*: Mycophenolate mofetil, Azathioprine (Dejaco *et al.*, 2001; Østensen, 2004; Ligumsky *et al.*, 2005; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Hoeltzenbein *et al.*, 2012; Jones *et al.*, 2013; Millsop *et al.*, 2013; Palomba *et al.*, 2014; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016; VIDAL Hoptimal 2016) *Other*: Fingolimod (Karlsson *et al.*, 2014; Leroy *et al.*, 2015)	*Sirolimus:* Reversible alteration of sperm parameters; Decreased count, motility and morphology of spermatozoa Decreased testosterone level **Relatively Good Level of Evidence** *Ciclosporine:* Rat: Decreased count and motility of spermatozoa Inhibition of testosterone synthesis **Very Low Level of Evidence** Human being: Impact on spermatogenesis cannot be excluded A priori, no effect on male fertility (lack of data) **Low Level of Evidence** *Tacrolimus*: Rat: Decreased count ± motility of spermatozoa **Very Low Level of Evidence** *Azathioprine, Mycophenolate mofetil*: No known alteration of sperm parameters but mutagenic effect **Relatively Good Level of Evidence** *Fingolimod*: Rat: No effect on male fertility during pre-clinical safety studies **Very Low Level of Evidence**	*Sirolimus:* Cryopreservation Contraception is mandatory during treatment (teratogenic in animal and lack of data) *Ciclosporine*: Treatment discontinuation is not necessary in patients who want to conceive Cryopreservation is useless, sometimes proposed by precautionary measure *Tacrolimus*: Insufficient data to make recommendations *Azathioprine, Mycophénolate mofétil:* Cryopreservation or treatment discontinuation 3 months before the conception (mutagenic and teratogenic) Contraception is mandatory during treatment *Fingolimod*: Treatment discontinuation recommended (teratogenic in animal)
Corticosteroids	Prednisone, Prednisolone, Dexamethasone (MacAdams *et al.*, 1986; Fitzgerald *et al.*, 1997; Østensen, 2004; Mogilner *et al.*, 2006; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Whirledge & Cidlowski, 2010; Millsop *et al.*, 2013; Palomba *et al.*, 2014; Leroy *et al.*, 2015)	Rat: Inhibition of apoptosis in testicular germ cells **Very Low Level of Evidence** Human being: No known effect on spermatogenesis In theory, indirect action on spermatogenesis is possible by inhibiting the hypothalamic–pituitary–gonadal axis **Low Level of Evidence**	Insufficient data to make specific recommendations Steroids discontinuation is not necessary in patients who want to conceive
Non-steroidal Anti-inflammatory (NSAI) and Salicylates	*Non-steroidal Inflammatory (NSAI)* (Mendonça *et al.*, 2000; Martini *et al.*, 2003) *Salicylates:* Acetylsalicylic acid (Martini *et al.*, 2003) Sulfasalazine (Birnie *et al.*, 1981; Toovey *et al.*, 1981; O'Moráin *et al.*, 1984; Ragni *et al.*, 1984; Steeno, 1984; Kjaergaard *et al.*, 1989; Niederberger, 2002; Østensen, 2004; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Alonso *et al.*, 2009; Palomba *et al.*, 2014; Leroy *et al.*, 2015; VIDAL Hoptimal 2016) *Other salicylates*: Mesalazine (Chermesh & Eliakim, 2004; Palomba *et al.*, 2014; Leroy *et al.*, 2015)	*NSAI and Acetylsalicylic acid (+++)*: Chronic dose (>6 months): Reversible decrease in sperm parameters; Decreased count, motility, vitality and morphology of spermatozoa (dose-related effects) **Relatively Low Level of Evidence** In vitro: Decreased fertilizing ability of sperm **Very Low Level of Evidence** *Sulfasalazine* (*toxic metabolite: Sulphapyridine)*: Rat and human being (chronic dose > 2 months): Decrease in sperm parameters; Decreased count, motility and morphology of spermatozoa **Good Level of Evidence** Human being: Potential decrease in testosterone level (controversial) **Low Level of Evidence** Rat: May inhibit acrosomal reaction and reduce the fertilizing ability of spermatozoa **Very Low Level of Evidence** *Other salicylates:* Mesalazine: One individual case of reversible oligospermia **Very Low Level of Evidence**	Unnecessary cryopreservation *NSAI and Acetylsalicylic acid:* Treatment discontinuation is not necessary, especially when sperm parameters are normal *Sulfasalazine:* Reversible effect 2–3 months after treatment discontinuation If treatment discontinuation is not possible, cryopreservation is advised *Other salicylates*: Treatment discontinuation is not necessary Preferred alternative to sulfasalazine in patients who want to conceive
Immunomodulators	*Monoclonal antibodies*: Trastuzumab, Alemtuzumab, Rituximab, Cetuximab, Bevacizumab, Omalizumab, Anakinra (Grunewald & Jank, 2015; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte, 2016, VIDAL Hoptimal 2016) *TNFα inhibitors:* Infliximab, Adalimumab, Etanercept (Estrada *et al.*, 1997; Mahadevan *et al.*, 2005; Østensen *et al.*, 2006; Millsop *et al.*, 2013; Micu *et al.*, 2014; Palomba *et al.*, 2014; Ramonda *et al.*, 2014; Grunewald & Jank, 2015; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016; VIDAL Hoptimal 2016)	*Monoclonal antibodies*: Trastuzumab: No known effect in human No impact on male reproductive function in the Monkey Alemtuzumab: No known effect Rituximab: Limited data in human No impact on male reproductive organs in the Monkey Cetuximab: No known effect Bevacizumab: Potential toxicity on female reproductive organs in animals (and males?) Omalizumab : No known effect in human No impact on male reproductive organs in primates Anakinra : No known effect in human but limited data No impact on male reproductive organs in the Rabbit **Very Low Level of Evidence** **Little Data Available Monoclonal Antibodies on Male Fertility** *TNFα inhibitors:* unknown effect on spermatogenesis, but few studies are available In the case of Infliximab: Impairment of sperm quality (motility of spermatozoa) and increased volume of ejaculate However, no infertility described **Low Level of Evidence**	*Monoclonal antibodies*: Insufficient data to make recommendations *TNFα inhibitors:* Cryopreservation and treatment discontinuation are not necessary

(continued)

Table 1 (continued)

Pharmacological class	Family and molecules (references)	Impact on spermatogenesis and sperm parameters	Guidelines
Immunomodulators	*Targeted therapies:* Dabrafenib, Vismodegib, Ipilimumab (Dillard *et al.*, 2010; Grunewald & Jank, 2015; VIDAL Hoptimal 2016) Leflunomide (Østensen, 2004; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016) Thalidomide (Laffitte, 2006; Leroy *et al.*, 2015; VIDAL Hoptimal 2016) *Interferons α, β, γ* (Estrada *et al.*, 1997; Trotter & Zygmunt, 2001; Grunewald *et al.*, 2007; Leroy *et al.*, 2015; VIDAL Hoptimal 2016) *Immunoglobulins IV* (Østensen *et al.*, 2006)	*Dabrafenib*: Rat and Dog: Gonadal toxicity (low dose) with irreversible potential effect on spermatogenesis **Very Low Level of Evidence** *Vismodegib*: Animals: Potential irreversible gonadal toxicity with testicular germ cells damages and impaired motility of sperm **Very Low Level of Evidence** *Ipilimumab*: Animals: Decreased testicular volume Hypophysitis which can appear 6 months after initiation of treatment (decrease level of FSH and LH) **Very Low Level of Evidence** *Leflunomide*: Rat and rabbit (repeated doses): Toxicity on male reproductive organs during pre-clinical safety studies **Very Low Level of Evidence** Human being: No known effect In treated man, teratogenic effect not to be excluded *Thalidomide*: Rabbit: Testicular degeneration **Very Low Level of Evidence** Human being: Molecule found in seminal fluid In treated man, teratogenic effect not to be excluded *Interferons α, β* (usual doses): No known effect on spermatogenesis **Low Level of Evidence** *Interferon γ*: mouse (high doses): Reduction in the weight of the testes and epididymis Alteration of sperm parameters during pre-clinical safety studies (decreased sperm count) **Very Low Level of Evidence** **Not Relevant for Use in Man (Specified Dosage)** *Immunoglobulines IV*: No studies in animals No impact known on male fertility **Low Level of Evidence**	*Dabrafenib, Vismodegib:* Cryopreservation before treatment Treatment discontinuation before conception Safe sex when the female partner is pregnant (teratogenic in animals) *Ipilimumab*: Cryopreservation recommended (precautionary measure) *Leflunomide* : CRAT : Cryopreservation and treatment discontinuation are not necessary Manufacturer: Contraception recommended and treatment discontinuation in man who want to conceive (lack of data and teratogenic in animals) *Thalidomide*: Treatment discontinuation in man who want to conceive Safe sex when the female partner is pregnant (teratogenic in human being) *Interferons*: Cryopreservation and treatment discontinuation are not necessary *Immunoglobulines IV*: Insufficient data to make recommendations
Inhibitors of thyrosine Kinases	Sorafenib (Iyer *et al.*, 2010; Shetty & Bairy, 2015; VIDAL Hoptimal 2016)	Mouse: Alteration of sperm parameters; Decreased count and motility of spermatozoa Dog: Degeneration of seminiferous tubes **Very Low Level of Evidence** In vitro: Decreased sperm count **Very Low Level of Evidence**	Reversible effect 10 weeks after treatment discontinuation
Opiates	Morphine (Yilmaz *et al.*, 1999; Cicero *et al.*, 2002) Cocaine (Bracken *et al.*, 1990; George *et al.*, 1996) General reviews: (Pake *et al.*, 1994a; Daniell, 2002; Katz & Mazer, 2009)	*Opiates*: affect dopamine secretion (De Rosa *et al.*, 2003) Rat and human being: Potential reduction in testosterone level **Very Low Level of Evidence** *Morphine*: Rat (chronic dose): Fertility decline **Very Low Level of Evidence** *Cocaine:* Human being (chronic use): Alteration of sperm parameters; Decreased count, motility and typical morphology of spermatozoa **Relatively Good Level of Evidence** Rat: Germ cells apoptosis **Very Low Level of Evidence**	Treatment discontinuation before conception
Treatment of benign prostatic hyperplasia	*5-α-reductase inhibitors*: Finasteride, Dutasteride (Amory *et al.*, 2007; Millsop *et al.*, 2013; Samplaski *et al.*, 2013; VIDAL Hoptimal 2016) *Alpha-blockers*: Tamsulosin (Hellstrom & Sikka, 2009; Brezina *et al.*, 2012)	*Finasteride, Dutasteride*: Slight decrease in ejaculate volume Decreased count (± motility) of spermatozoa, but no effect on morphology **Relatively Good Level of Evidence** *Tamsulosin*: Reversible alteration of sperm parameters; Decreased count, motility and typical morphology of spermatozoa Decrease in ejaculate volume **Medium Level of Evidence**	*Finasteride*: Treatment discontinuation recommended before the conception Reversible effect in 3–4 months *Tamsulosine:* No specific recommendations
Hormonal treatments	Anabolic steroids (Torres-Calleja *et al.*, 2000; de Souza & Hallak, 2011; Nieschlag & Vorona, 2015) Testosterone, androgens, progestatifs, oestrogen, progestins, GnRH analogues (Rönnberg, 1980; Contraceptive Efficacy of Testosterone-Induced Azoospermia in Normal Men. World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990; Bebb *et al.*, 1996; Dohle *et al.*, 2003)	Chronique posology: Inhibition of spermatogenesis (± complete) from oligospermia to azoospermia, depending on the type of molecule *Testosterone*: Azoospermia appearing on average 4 months after treatment initiation **Very Good Level of Evidence** *Anabolic steroids*: Cryptozoospermia or azoospermia with testicular atrophy (Testosterone-like effect, DHT-like effect, Nandrolone-like effect) **Good Level of Evidence**	*Testosterone*: Recovery of initial sperm parameters in 3–7 months after treatment discontinuation *Anabolic steroids*: Effects generally reversible in 4–12 months after treatment discontinuation *Addition of HCG or antiE2*: Possible stability of spermatogenesis, but persistent alteration of sperm quality **Low Level of Evidence**
Antiandrogenic drugs	Cyproterone acetate (Meriggiola *et al.*, 1997; VIDAL Hoptimal 2016) Flutamide (Viguier-Martinez *et al.*, 1983)	*Cyproterone acetate*: decrease in sperm parameters; Oligospermia and sometimes azoospermia **Good Level of Evidence** *Flutamide*: Monkey/Rat: Reduction in testicular volume and decrease in spermatogenesis (spermatocytes and spermatids) Decreased intratesticular testosterone level **Very Low Level of Evidence**	*Cyproterone acetate*: Reversible effect in 6–22 weeks after treatment discontinuation If treatment discontinuation is not possible, cryopreservation can be proposed
Diuretics	*Potassium-sparing diuretics*: Spironolactone (Caminos-Torres *et al.*, 1977; Wong & Lee, 1982; Millsop *et al.*, 2013)	*Spironolactone*: Possible impairment of sperm motility **Low Level of Evidence**	Reversible effect after treatment discontinuation

(continued)

Table 1 (continued)

Pharmacological class	Family and molecules (references)	Impact on spermatogenesis and sperm parameters	Guidelines
Antibiotics	*Nitrofurantoin* (Nelson & Bunge, 1957; Yunda & Kushniruk, 1974; Schlegel *et al.*, 1991 VIDAL Hoptimal 2016) *Macrolides*: Erythromycine (Schlegel *et al.*, 1991; Hargreaves *et al.*, 1998; Millsop *et al.*, 2013)	*Nitrofurantoin*: Human being: Decreased count and motility of spermatozoa High dose: Potential blockage of spermatogenesis **Relatively Low Level of Evidence** *Erythromycine*: In vitro/Animals: Decreased motility and survival of spermatozoa (high dose) **Very Low Level of Evidence**	Reversible effect after discontinuation Antibiotic therapy recommended for testicular infections and epididymis (Haidl *et al.*, 2008; Yániz *et al.*, 2010; Hamada *et al.*, 2011; Boitrelle *et al.*, 2012)
Antibiotics	*Cotrimoxazole* (Sulfamethoxazole/Trimethoprime) (Murdia *et al.*, 1978; Schlegel *et al.*, 1991) *Tetracyclines* (Schlegel *et al.*, 1991; Hargreaves *et al.*, 1998) *Aminosides:* Gentamicine, Neomycine, Streptomycine (Schlegel *et al.*, 1991; Narayana, 2008b; Khaki, 2008) *Penicillines* (Schlegel *et al.*, 1991; Hargreaves *et al.*, 1998) *Quinolones:* Ofloxacine (Khaki, 2008)	*Cotrimoxazole*: In vitro: Decreased sperm motility **Very Low Level of Evidence** Human being: Decreased count, motility and morphology of spermatozoa **Low Level of Evidence** *Tetracyclines*: In vitro: Decreased motility and fertilizing ability of sperm (weak acrosome reaction) **Very Low Level of Evidence** *Aminosides*: Rat**:** decrease in sperm parameters Less effect with Streptomycine **Very Low Level of Evidence** Human being: Decreased count and motility of spermatozoa described for Neomycine **Low Level of Evidence** *Penicillines, Quinolones*: Animals: moderate decrease in sperm parameters **Very Low Level of Evidence** Human being: No reported effect **However**: Positive impact of antibiotic therapy on sperm quality in a context of testicular infections and epididymitis (Haidl *et al.*, 2008; Yániz *et al.*, 2010; Hamada *et al.*, 2011; Boitrelle *et al.*, 2012)	Reversible effect after discontinuation Antibiotic therapy recommended for testicular infections and epididymitis (Haidl *et al.*, 2008; Yániz *et al.*, 2010; Hamada *et al.*, 2011; Boitrelle *et al.*, 2012)
Antimalarials	Chloroquine (Okanlawon *et al.*, 1993; Adeeko & Dada, 1994; Hargreaves *et al.*, 1998; Østensen, 2004; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Millsop *et al.*, 2013; Leroy *et al.*, 2015)	Rat/In vitro: Decreased sperm motility **Very Low Level of Evidence** Theoretical decrease in fertilizing ability of spermatozoa **No Evidence**	Insufficient data to make recommendations
Antifungals drugs	*Azole antifungals*: Ketoconazole, Fluconazole (Pont *et al.*, 1982; Joshi *et al.*, 1994; el-Medany & Hagar, 2002; Millsop *et al.*, 2013; VIDAL Hoptimal 2016)	*Ketoconazole*: Mouse: Decrease in sperm parameters; Decreased count and motility of spermatozoa **Very Low Level of Evidence** Chronic use: Decreased serum testosterone **Low Level of Evidence**	*Kétoconazole*: Treatment discontinuation before the conception Reversible effect after discontinuation
Antifungals drugs	*Azole antifungals*: Ketoconazole, Fluconazole (Pont *et al.*, 1982; Joshi *et al.*, 1994; el-Medany & Hagar, 2002; Millsop *et al.*, 2013; VIDAL Hoptimal 2016) Amphotericine B (Swierstra *et al.*, 1964)	*Fluconazole*: Rabbit: Decreased sperm motility (unless ketoconazole) and ejaculate volume Decreased serum testosterone **Very Low Level of Evidence** *Amphotericine B*: Rabbit: Potential impact during spermiation **Very Low Level of Evidence**	*Fluconazole*: Reversible effect in 2 months after treatment discontinuation *Amphotericine B*: Insufficient data to make recommendations
Antiparasite drugs	Metronidazole (McClain *et al.*, 1989)	Rat (chronic dose > 1 month): Reduction in the weight of the testes and epididymis Decrease in spermatogenesis and sperm parameters **Very Low Level of Evidence**	Reversible effect in 4 months after treatment discontinuation
Antiviral drugs	*Ribavirine* (Narayana *et al.*, 2002; Durazzo *et al.*, 2006; Pecou *et al.*, 2009; Hofer *et al.*, 2010; VIDAL Hoptimal 2016) *Acyclovir* (Kapranos *et al.*, 2003; Douglas *et al.*, 1988; Narayana, 2008b)	*Ribavirine*: Rat: Decreased sperm production **Very Low Level of Evidence** Human being: Reversible decrease in sperm parameters; Decreased motility and morphology of spermatozoa Increase in sperm DNA fragmentation index up to 8 months after drug discontinuation **Low Level of Evidence** **Confounding Factors Related to Infection of Hepatitis C** *Chronic hepatitis C:* Decreased motility and morphology of spermatozoa Decreased testosterone level *Acyclovir*: Mouse: Cytotoxic effect on germ cells with decrease in sperm parameters; Decreased count, motility and morphology of spermatozoa **Very Low Level of Evidence** **Controversy Results With Confounding Factors Related To Infection of Virus** Human being: One study without significant difference on sperm parameters **Low Level of Evidence**	*Ribavirine*: Recover of initial sperm parameters in 4 months after treatment discontinuation Contraception mandatory during antiviral therapy Cryopreservation or treatment discontinuation 7 months before the conception (mutagenic effect) *Acyclovir*: Reversible effect in 70 days after treatment discontinuation *Antiretroviral therapy*: Negative effects on sperm parameters balanced by the medical benefits of the multitherapy Discontinuation of antiretroviral therapy NOT recommended

(continued)

Table 1 (continued)

Pharmacological class	Family and molecules (references)	Impact on spermatogenesis and sperm parameters	Guidelines
Antiviral drugs	*Antiretroviral therapy (ARVs)* (Nicopoullos *et al.*, 2004; Sergerie *et al.*, 2004; Bujan *et al.*, 2007; van Leeuwen *et al.*, 2008; Kehl *et al.*, 2011; Brezina *et al.*, 2012; Frapsauce *et al.*, 2015)	*Antiretroviral therapy:* Potential decrease in sperm parameters; Decreased volume, count, motility (progressive motility+++) and morphology of sperm One study: No effect on sperm parameters (patients infected with HIV, treated or not) **Low Level of Evidence** **Controversy Results With Confounding Factors Related to HIV Infection** Saquinavir: In vitro, could negatively impact the acrosome reaction of spermatozoa **Very Low Level of Evidence** *Although some studies suggest an adverse effect of ARVs on sperm parameters, no conclusion is retained on the gametic impact of these drugs*	*Antiretroviral therapy*: Negative effects on sperm parameters balanced by the medical benefits of the multitherapy Discontinuation of antiretroviral therapy NOT recommended
Retinoic agents	Isotretinoin, Retinoic acid, Acitretine (Parsch *et al.*, 1990; Geiger & Walker, 2002; Comitato *et al.*, 2006; Sengör *et al.*, 2006; Grunewald *et al.*, 2007; Millsop *et al.*, 2013; Çinar *et al.*, 2015; Grunewald & Jank, 2015; VIDAL Hoptimal 2016)	*Isotretinoin*: Animals: Increased apoptosis of germ cells **Very Low Level of Evidence** Human being (usual doses in dermatology): no reported effect on sperm parameters **Relatively Low Level of Evidence** *Acitretine:* Lizard: Alteration of seminiferous epithelium **Very Low Level of Evidence** Human being: No impact reported	Unnecessary cryopreservation Treatment discontinuation in patients who want to conceive Safe sex when the female partner is pregnant (severely teratogenic) [However, no teratogenic effect reported in this context]
Antigastro-oesophageal reflux	*Antihistamines:* Cimetidine (Van Thiel *et al.*, 1979; Winters *et al.*, 1979; Wang *et al.*, 1982; França *et al.*, 2000; Millsop *et al.*, 2013) *Proton pump inhibitors:* Lansoprazole (Coulson *et al.*, 2003; Meikle *et al.*, 2012)	*Cimetidine*: Rat: Direct toxicity on seminiferous tubes Indirect toxicity by competition with testosterone receptors **Very Low Level of Evidence** Human being: Decreased sperm count **Low Level of Evidence** *Lansoprazole:* Rat: Inhibition of testosterone synthesis Increase LH level is involved in the induction of Leydig cell tumours **Very Low Level of Evidence** Human being: No impact reported	Cimetidine: Reversible effect in 3 months after treatment discontinuation
Antidepressant therapy	*Tricyclic antidepressants*: Imipramine (Tanrikut & Schlegel, 2007) *Selective Serotonin Reuptake Inhibitors (SRI):* Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Venlafaxine (Safarinejad, 2008; Tanrikut *et al.*, 2010; Brezina *et al.*, 2012; Erdemir *et al.*, 2014)) *Monoamines Oxidases Inhibitors (MOAI):* Moclobemide (Tanrikut & Schlegel, 2007), Buspirone (Tanrikut & Schlegel, 2007) and Lithium salts (Toghyani *et al.*, 2013)	*Tricyclic antidepressants, selective Serotonin Reuptake Inhibitors ± Monoamines Oxidases Inhibitors:* Potential indirect effect on spermatogenesis (hyperprolactinemia) (De Rosa *et al.*, 2003) *Imipramine*: In vitro: Decreased sperm motility **Very Low Level of Evidence** **SSRI**: Decrease in sperm parameters; Decreased count, motility and morphology of spermatozoa (controversial) **Low Level of Evidence** Increased sperm DNA fragmentation (Paroxetine +++) **Medium Level of Evidence** Buspirone: Potential impact on sperm quality **Low Level of Evidence** Lithium Salts: Rat: Impact on sperm parameters and impairment of sperm quality **Very Low Level of Evidence**	*Tricyclic antidepressants and SSRI:* discontinuation or change in class is preferred in patients who want to conceive *Serotonin Reuptake Inhibitors*: Reversible effect in 1–2 months after treatment discontinuation
Antipsychotic therapy	*Classical neuroleptics:* Phenothiazines: Chlorpromazine Butyrophenones: Haloperidol *« Hidden neuroleptics »:* Metoclopramide (antiemetic) (Panidis *et al.*, 1997)	Hyperpolactinemia with theoretical impact on spermatogenesis and sperm quality (De Rosa *et al.*, 2003) **Very Low Level of Evidence**	Insufficient data to make recommendations
Antiepileptic treatment	Valproate (Chen *et al.*, 1992; Rättyä *et al.*, 2001; Isojärvi *et al.*, 2004; Røste *et al.*, 2005; Lossius *et al.*, 2007; Brezina *et al.*, 2012) Phenytoin (Chen *et al.*, 1992; Brezina *et al.*, 2012) Carbamazepine (Chen *et al.*, 1992; Rättyä *et al.*, 2001; Isojärvi *et al.*, 2004; Røste *et al.*, 2005; Lossius *et al.*, 2007; Brezina *et al.*, 2012) Oxcarbazepine (Chen *et al.*, 1992; Rättyä *et al.*, 2001; Isojärvi *et al.*, 2004) General reviews: (Webber *et al.*, 1986; Herzog, 2008)	*Valproate*: Rat: Decreased testicular volume **Very Low Level of Evidence** Human being: Decrease in sperm parameters; Decreased count, motility (++) and morphology of spermatozoa Increased androgens level (androstenedione) **Low Level of Evidence** *Phenytoin*: Decreased sperm count and motility (++) **Low Level of Evidence** *Carbamazepine*: Decrease in sperm parameters; Decreased count, motility and morphology of spermatozoa **Low Level of Evidence** *Oxcarbazepine*: Decreased morphology of spermatozoa **Low Level of Evidence** **Controversial Results** **Confounding Factors Related To Epileptic Disease Difficult To Study Patients Without Epileptic Treatment For Ethical Considerations**	Reversible effect after treatment discontinuation during pre-clinical safety studies But most of the time, drug discontinuation is impossible No specific recommendation for the use of antiepileptic drugs in infertile man Reversible effect after treatment discontinuation during pre-clinical safety studies But most of the time, drug discontinuation is impossible No specific recommendation for the use of antiepileptic drugs in infertile man
Goutte medicine	Colchicine (Haimov-Kochman & Ben-Chetrit, 1998; Mijatovic *et al.*, 2003; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016; VIDAL Hoptimal 2016)	Some cases reported with decrease in sperm parameters In vitro: Decreased sperm count **Very Low Level of Evidence (Case Series)** **Alteration Depends Rather On Associated Factors (Disease = Familial Méditerranéan Fever)**	CRAT: Drug can be continued in patients who want to conceive

(continued)

Table 1 (continued)

Pharmacological class	Family and molecules (references)	Impact on spermatogenesis and sperm parameters	Guidelines
Antihypertensive drugs	*Beta-blockers*: Propranolol: non-cardioselective β-Blockers Carvedilol: non-cardioselective β-Blockers and action on α-adrenergic receptors Metoprolol: cardioselective β-Blockers Atenolol: cardioselective β-Blockers Acebutolol: cardioselective β-Blockers Nebivolol: cardioselective β-Blockers and NO• liberator (el-Sayed *et al.*, 1998) *Calcium channel blockers*: Nifedipine, Amlodipine, Verapamil and Diltiazem (Kanwar *et al.*, 1993; Benoff *et al.*, 1994; Brezina *et al.*, 2012) *Angiotensin-Converting Enzyme (ACE):* Captopril, Enalapril (Yao and Liu 2006; Foresta *et al.*, 1991) *Antihypertensive drugs with central action:* Methyl-dopa (Dunnick *et al.*, 1986; Hua-Xiong & Liu, 2006)	*Beta-blockers*: In vitro: Decreased sperm motility Animals: Decreased testosterone level Histological deterioration of testicular tissue **Very Low Level of Evidence** *Calcium channel blockers:* In vitro: Decreased viability and motility of sperm Reduced fertilizing ability of spermatozoa (not in vivo) Rat: Amlodipine decreases sperm density and number of mature spermatids and Sertoli cells **Very Low Level of Evidence** *ACE:* In vitro/Animals: Decreased sperm motility May be potentially harmful for capacitation or acrosome reaction of spermatozoa (controversial) **Very Low Level of Evidence** **No Reliable Data in Human Being** *Methyl-dopa*: Rat: Indirect impact on spermatogenesis by inhibiting the hypothalamic–pituitary–gonadal axis (hyperprolactinemia) (De Rosa *et al.*, 2003) **Very Low Level of Evidence**	No available recommendations Limited prescription of antihypertensive drugs in young patients in the reproductive age
Anticholesterol	*Statins*: Pravastatin, Simvastatin, Atorvastatin (Bernini *et al.*, 1998; Dobs *et al.*, 2000) *Fibrates*: Gemfibrozil (VIDAL Hoptimal 2016)	*Statins*: Pravastatin, Simvastatin, Atorvastatin Human being (usual doses): No effect on sperm parameters Rat (High dose): Decrease in sperm parameters during pre-clinical safety studies for Pravastatin **Very Low Level of Evidence** *Gemfibrozil*: Rat (high dose): Reduced fertility during pre-clinical safety studies **Very Low Level of Evidence**	Insufficient data to make recommendations
Inhibitors of 5-phosphodiesterase	Sildenafil (Glenn *et al.*, 2007)	In vitro*:* Increased sperm motility Premature acrosome reaction **Very Low Level of Evidence**	

patients with spinal cord injuries do not appear to be indicated in this context (Colpi *et al.*, 2004).

Immunosuppressants

Sirolimus, which is used to prevent organ transplant rejection, causes seminiferous tubule dystrophy with a reversible alteration of the sperm parameters characterized by decreased count, motility and morphology of spermatozoa (Bererhi *et al.*, 2003; Huyghe *et al.*, 2007; Zuber *et al.*, 2008; Chen *et al.*, 2013; He *et al.*, 2013; Leroy *et al.*, 2015; VIDAL Hoptimal 2016). Indeed, Sirolimus blocks spermatogenesis at the level of the spermatogonia, gradually lowering the number of spermatocytes, spermatids and spermatozoa (Rovira *et al.*, 2012). Sirolimus also reduces StAR protein expression, which plays a role in the transport of cholesterol, a precursor for testosterone synthesis in the Leydig cells. This lowers the level of intratesticular testosterone, on which spermatogenesis depends to function correctly. Sirolimus may also inhibit the kiss system (and hence pulsatile GnRH secretion) at the hypothalamic level (Roa *et al.*, 2009).

Anti-inflammatories and salicylates

Sulfasalazine at chronic dose causes a reversible alteration of sperm parameters. Indeed, a chronic dose taken for more than 2 months results in a decreased sperm count, motility and morphology (Toovey *et al.*, 1981; O'Moráin *et al.*, 1984; Leroy *et al.*, 2015). In the study of O'Moráin *et al.*, Sulfasalazine was associated with oligoasthenospermia in over 60% of treated men with inflammatory bowel disease. However, sperm counts in patients receiving discontinued Sulfasalazine treatment for more than 3 months were not significantly different than in patients without treatment (O'Moráin *et al.*, 1984).

The precise alteration mechanism remains unexplained. The mechanism may consist of a direct toxic effect of the molecule on immature spermatozoa. The active metabolite of Sulfasalazine, Sulphapyridine, may cause oxidative stress, with a knock-on effect on sperm quality (Alonso *et al.*, 2009). Sulfasalazine may also affect the serum testosterone level as a result of an inhibitory effect at the level of the hypothalamic–pituitary–gonadal axis, although this theory is controversial. The harm to sperm parameters can be reversed 2–3 months after stopping the treatment (Birnie *et al.*, 1981; Toovey *et al.*, 1981; O'Moráin *et al.*, 1984; Ragni *et al.*, 1984; Steeno, 1984; Kjaergaard *et al.*, 1989; Niederberger, 2002; Nudell *et al.*, 2002; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Schlosser *et al.*, 2007; Palomba *et al.*, 2014; VIDAL Hoptimal 2016).

Acetylsalicylic acid and, more rarely, non-steroidal anti-inflammatories (administered chronically) can affect sperm quality by decreasing sperm count, motility, vitality and morphology. The effects are reversible and dose related (Mendonça *et al.*, 2000; Martini *et al.*, 2003). They reversibly or irreversibly inhibit the cyclo-oxygenase enzymes that are responsible for prostaglandin synthesis. However, prostaglandins may be involved in the control of spermatogenesis and testicular steroidogenesis and in the acrosome reaction of spermatozoa (Joyce *et al.*, 1987).

Opiates

Opiates stimulate prolactin secretion by inhibiting the tuberoinfundibular dopaminergic activity of hypothalamus (Fig. 3); it inhibits the hypothalamic–pituitary axis and causes hypogonadotropic hypogonadism. This may lower the intratesticular testosterone level, however, the gametic effects remain difficult to evaluate (Bracken *et al.*, 1990; Pake *et al.*, 1994a;

George *et al.*, 1996; Yilmaz *et al.*, 1999; Freeman *et al.*, 2000; Cicero *et al.*, 2002; Daniell, 2002; Schlosser *et al.*, 2007; Katz & Mazer, 2009). Chronic use of cocaine affects sperm quality by decreasing sperm count, motility, vitality and morphology (Bracken *et al.*, 1990). According to the literature review of Katz & Mazer (2009), long-term opioid therapy induces hypogonadism owing to central suppression of hypothalamic secretion of gonadotropin-releasing hormone (Fig. 2). As a matter of facts, opioids cause infertility, loss of libido and impotence in men (Pake *et al.*, 1994a; Yilmaz *et al.*, 1999; Daniell, 2002; Schlosser *et al.*, 2007; Katz & Mazer, 2009; Gratzke *et al.*, 2010).

Antiandrogens

Finasteride, which is used to treat benign prostatic hyperplasia, is a specific inhibitor of 5α-reductase. This intracellular enzyme converts testosterone into dihydrotestosterone, which has a stronger affinity than testosterone for the androgen receptors in the target cells. A drop in dihydrotestosterone expression can have adverse effects on sperm parameters and male reproductive function. Amory *et al.* conducted a randomized, double-blinded, placebo-controlled trial in 99 healthy men randomly assigned to receive dutasteride, finasteride or placebo once daily for 1 year. They concluded that 5 alpha-reductase inhibitors significantly decrease sperm count and mobility (but not morphology) with reversible effects 3–4 months after stopping the treatment (Amory *et al.*, 2007). Men are advised to stop taking Finasteride before conceiving (Millsop *et al.*, 2013; Samplaski *et al.*, 2013; VIDAL Hoptimal 2016).

Erectile and, more rarely, ejaculatory disorders can also arise during treatment. The precise mechanism of the sexual dysfunction has not been clearly established (Carbone & Hodges, 2003; Wessells *et al.*, 2003; Giuliano, 2006; Mondaini *et al.*, 2007; Hellstrom *et al.*, 2009; Giuliano & Droupy, 2013; VIDAL Hoptimal 2016).

Cyproterone acetate is a palliative treatment for prostate cancer. This powerful antiandrogen competitively inhibits the binding of 5-α-dihydrotestosterone to its cystolic receptor in the target cells. At a central level, cyproterone acetate has an antigonadotropic effect, which reduces testosterone synthesis by the testes (Meriggiola *et al.*, 1997; Schlosser *et al.*, 2007; VIDAL Hoptimal 2016). A prospective study of 25 volunteer men treated or not with cyproterone acetate during 16 weeks showed a decrease in sperm concentration, motility and morphology. For one patient, azoospermia was described (Wang & Yeung, 1980). The molecule's effect on sperm parameters is reversible within 6–22 weeks of stopping the treatment (Meriggiola *et al.*, 1997; Schlosser *et al.*, 2007; VIDAL Hoptimal 2016).

Cyproterone acetate and non-steroidal antiandrogens are used in the treatment of prostate cancer. By preventing androgens from acting on their targets, these medications also cause a loss of erectile function and libido. In a prospective study of 310 patients with metastatic prostate cancer, the sexual function was evaluated before and after the introduction of antiandrogens treatments. Under cyproterone acetate treatment, spontaneous erections and sexual activity has declined but the loss was slow. However, the initial rate of sexual dysfunction was probably higher than in the age-matched general population (Schröder *et al.*, 2000). Non-steroidal antiandrogens do not have any antigonadotropic effects, indeed these medications are targeted to the prostate. Consequently, their sexual tolerance profile appears to be better than the other antiandrogens, particularly Bicalutamide (Schröder *et al.*, 2000; Iversen *et al.*, 2001; Droupy, 2005; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; Giuliano & Droupy, 2013; VIDAL Hoptimal 2016).

Alpha-blockers

Alpha-blockers are antagonists of the α_1-adrenergic receptors of smooth muscle cells, including those of the urinary tract. They are used to treat high blood pressure and benign prostatic hyperplasia. Some alpha-blockers, such as Tamsulosin, also have an affinity for dopamine and serotonin receptors at the central level. The interaction between Tamsulosin and certain central neurotransmitters could contribute to the observed effects on sperm parameters but the mechanism of the alteration remains unknown (Hellstrom & Sikka, 2009; Brezina *et al.*, 2012). Use of Tamsulosin results in reversible semen alteration characterized by decreased ejaculate volume, sperm count, motility and morphology (Hellstrom *et al.*, 2009). The chemical structure of Afluzosin, a quinazoline derivative, is very different from that of Tamsulosin, which is a sulphonamide derivative. These structural differences could explain why the harmful effects of Tamsulosin on sperm parameters do not occur with Afluzosin use (Hellstrom & Sikka, 2009).

Tamsulosin and Silodosin frequently cause ejaculatory disorders, such as retrograde ejaculation or anejaculation. Retrograde ejaculation can occur as a result of reduced smooth muscle tone at the neck of the bladder. Anejaculation is thought to be caused by the defective emission or the defective contraction of the bulbospongiosus muscles; indeed, the thoracic and lumbar adrenergic sympathetic nervous system is responsible for the contraction of the smooth muscle fibres of the seminal tract and the bladder neck. Most of the time, orgasms are maintained. If ejaculatory disorders arise, the use of a different alpha-blocker may be recommended (Hendry, 1998; Nudell *et al.*, 2002; Carbone & Hodges, 2003; Giuliano, 2006; Hellstrom & Sikka, 2006; Hellstrom *et al.*, 2009; Shimizu *et al.*, 2010; Roehrborn *et al.*, 2011; Brezina *et al.*, 2012; Giuliano & Droupy, 2013; VIDAL Hoptimal 2016). Alpha-blockers do not cause erectile dysfunction (Droupy, 2005; Giuliano, 2006).

Anabolic steroids and testosterone

Hormone-based treatments and testosterone inhibit the hypothalamic–pituitary–gonadal axis and lead to hypogonadotropic hypogonadism (Fig. 2). This results in the partial or complete inhibition of spermatogenesis, leading to oligospermia, cryptozoospermia or even azoospermia. (Rönnberg, 1980; Contraceptive Efficacy of Testosterone-Induced Azoospermia in Normal Men. World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990; Bebb *et al.*, 1996; Torres-Calleja *et al.*, 2000; Nudell *et al.*, 2002; Dohle *et al.*, 2003; Schlosser *et al.*, 2007; de Souza & Hallak, 2011; Nieschlag & Vorona, 2015). A multicenter study (10 centres) has evaluated the contraceptive efficiency of hormonally induced azoospermia in 271 healthy fertile men. Sixty-five per cent of these men became azoospermic 6 months after one intramuscular injection of testosterone per week. The average duration to become azoospermic was 120 days. The effects on sperm parameters are generally reversible within 3–12 months of stopping treatment with the incriminated molecule (Contraceptive Efficacy of Testosterone-Induced Azoospermia in Normal Men. World

Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990).

Diuretics

Spironolactone has a peripheral antiandrogen effect by inhibiting the adrenal and testicular cytochromes P450 that are involved in testosterone biosynthesis. In addition, it is thought to prevent androgens from binding to the target cells through a competition phenomenon at the receptor level (Caminos-Torres *et al.*, 1977; Wong & Lee, 1982; Millsop *et al.*, 2013). These antiandrogen properties can cause erectile dysfunction and decreased desire (Clark, 1965; Caminos-Torres *et al.*, 1977; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; VIDAL Hoptimal 2016). Moreover, impairment of sperm motility can be observed (Caminos-Torres *et al.*, 1977; Millsop *et al.*, 2013).

The effect of thiazide diuretics on sexual function is more controversial as a result of the presence of confounding factors: reduced vascular resistance, volume depletion and electrolytic changes. Erectile dysfunction appears relatively soon after the initiation of treatment but remains tolerable most of the time. In hypertensive subjects, the discontinuation of treatment is not recommended. However, in young men, it is preferable to use a different class of antihypertensives such as sartans, in order to limit the occurrence of these disorders (Grimm *et al.*, 1997; Hendry, 1998; Ferrario & Levy, 2002; Nudell *et al.*, 2002; Giuliano *et al.*, 2004; Boydak *et al.*, 2005; Droupy, 2005; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; Karavitakis *et al.*, 2011; Manolis & Doumas, 2012; VIDAL Hoptimal 2016; VIDAL Hoptimal 2016).

Anti-infective agents

Most antibiotics alter sperm motility in vitro, but in vivo data are almost non-existent.

Nitrofurantoin is described as being potentially harmful for spermatogenesis through a direct gonadotoxic effect at the level of primary spermatocytes and spermatids (a lower nucleic acid level in the affected germ cells) (Nelson & Bunge, 1957; Yunda & Kushniruk, 1974; VIDAL Hoptimal 2016). At high dose, nitrofurantoin may stop germ cell maturation by preventing the uptake of the carbohydrates and oxygen that are required for the correct function of cells involved in spermatogenesis. The effects on sperm parameters, characterized by decreased sperm count and motility, are reversible after stopping the antibiotic treatment. However, in the context of testicular infections and epididymitis, antibiotic treatment is recommended as a result of its favourable impact on sperm quality (Schlegel *et al.*, 1991; Hargreaves *et al.*, 1998; Kilarkaje Narayana, 2008a; Khaki, 2008; Murdia *et al.*, 1978; Nudell *et al.*, 2002; Millsop *et al.*, 2013; Schlosser *et al.*, 2007; Haidl *et al.*, 2008; Yániz *et al.*, 2010; Boitrelle *et al.*, 2012; Hamada *et al.*, 2011; VIDAL Hoptimal 2016).

Ketoconazole is an antifungal drug that inhibits the action of the cytochromes P450 enzymes, involved in steroidogenesis. The blockade of the enzyme complexes 17α Hydroxylase and 17-20 Desmolase therefore results in the reduced synthesis of androgens and intratesticular testosterone. A reversible alteration in sperm parameters is possible. Men are advised to stop taking Ketoconazole before conceiving (Pont *et al.*, 1982; Joshi *et al.*, 1994; Millsop *et al.*, 2013; VIDAL Hoptimal 2016).

Chloroquine is an antimalarial drug, a lysosome stabilizer that acts as a protease inhibitor. It can theoretically inhibit the acrosome reaction of spermatozoa and reduce their fertilization capacity. However, the data in the literature that describe the impact of Chloroquine on male fertility are still insufficient (Okanlawon *et al.*, 1993; Adeeko & Dada, 1994; Hargreaves *et al.*, 1998; Østensen *et al.*, 2006; Grunewald *et al.*, 2007; Millsop *et al.*, 2013).

Ribavirin, which is used to treat chronic hepatitis C, reversibly alters germ cells. Sperm motility and morphology are reversibly altered and recover 4 months after stopping the drug (Pecou *et al.*, 2009). This nucleoside synthesis analogue inhibits inosine monophosphate dehydrogenase, an enzyme that is involved in the biosynthesis of guanosine triphosphate in DNA and RNA, thus preventing cell growth. This results in increased apoptosis, defective multiplication and cellular differentiation in the germ cells of the seminal epithelium (Narayana *et al.*, 2002; Durazzo *et al.*, 2006; Pecou *et al.*, 2009; Hofer *et al.*, 2010; VIDAL Hoptimal 2016).

Some studies suggest that antiretroviral drugs have a negative effect on sperm parameters, especially motility. To date, no final conclusion has been reached as to the actual gametic effects of these treatments because of the presence of confounding factors may be related to the HIV infection. Moreover, the possible toxicity of antiretroviral treatments for sperm parameters must be qualified as it is greatly outweighed by the medical benefits of the combined therapy. Nucleoside reverse transcriptase inhibitors (Zidovudine, Stavudine) could inhibit mitochondrial DNA replication (polymerase γ) in the spermatozoa, whereas properly functioning mitochondria are vital to the energy supply that is required for their motility. Protease inhibitors are thought to prevent apoptosis that cause an alteration in sperm quality (Nicopoullos *et al.*, 2004; Sergerie *et al.*, 2004; Bujan *et al.*, 2007; van Leeuwen *et al.*, 2008; Kehl *et al.*, 2011; Brezina *et al.*, 2012; Frapsauce *et al.*, 2015).

Cimetidine

Cimetidine is an antihistamine that is used in the symptomatic treatment of gastro-oesophageal reflux disease. It has antiandrogen properties that result from a competition phenomenon at the level of the dihydrotestosterone receptors in the target cells; nevertheless, hyperprolactinemia is theoretically also possible (Fig. 3). In animals, this molecule could also damage the peritubular myoid cells of the testis, leading to abnormal spermatogenesis. In men, the drop in spermatozoa production causing decreased sperm count is reversible 3 months after stopping the treatment (Van Thiel *et al.*, 1979; Winters *et al.*, 1979; Wang *et al.*, 1982; França *et al.*, 2000; Nudell *et al.*, 2002; Schlosser *et al.*, 2007; Millsop *et al.*, 2013).

Antidepressants

Serotonin reuptake inhibitors (SRIs) are the standard treatment for depression. Tricyclic antidepressants act by inhibiting catecholamine recapture at a central level. Tricyclic antidepressants and serotonin reuptake inhibitors (SRIs) are responsible for hyperprolactinemia, which inhibits the hypothalamic–pituitary axis (Fig. 3). In the case of hypogonadism, there may be adverse effects on sperm parameters (Nudell *et al.*, 2002; De Rosa *et al.*, 2003; Schlosser *et al.*, 2007; Tanrikut & Schlegel, 2007). SRIs could alter sperm count and motility. Adverse effects on sperm morphology are controversial. SRIs could also alter sperm quality via a mechanism that affects sperm transport. In particular, they increase DNA fragmentation in the spermatozoa,

especially Paroxetine (Tanrikut & Schlegel, 2007; Safarinejad, 2008; Tanrikut *et al.*, 2010; Brezina *et al.*, 2012; Erdemir *et al.*, 2014).

The pharmacological substances that affect the central nervous system are also likely to modify erectile or ejaculatory functions. Antidepressants are often described as being responsible for sexual disorders, but in practice it is difficult to make a distinction between the effect of the drug treatment and the condition itself. Indeed, uncertainty arises regarding the central neuropharmacology of erectile function and the complex nature of the mode of action of antidepressants and psychiatric conditions (Baldwin & Mayers, 2003; Giuliano & Droupy, 2013).

Serotonin reuptake inhibitors (SRIs) boost the neurotransmission of serotonin, a substance that inhibits male sexual behaviour. A loss of desire and anorgasmia are frequently reported during SRI treatment. Delayed ejaculation, or even anejaculation, also begins to occur a few weeks after the initiation of treatment. Paroxetine and Venlafaxine could also cause erectile dysfunction, by inhibiting NO production and increasing norepinephrine levels, respectively (Fig. 4) (Hendry, 1998; Montejo *et al.*, 2001; Nudell *et al.*, 2002; Baldwin & Mayers, 2003; Rosen & Marin, 2003; Droupy, 2005; Schlosser *et al.*, 2007; Dording *et al.*, 2008; Althof *et al.*, 2010; Gratzke *et al.*, 2010; Giuliano & Droupy, 2013; Taylor *et al.*, 2013; Clayton *et al.*, 2014; VIDAL Hoptimal 2016).

During treatment by tricyclic antidepressants, anorgasmia, loss of desire, delayed ejaculation/anejaculation and erectile disorders are possible.

Monoamine oxidase inhibitors (MAOIs), which are less frequently prescribed, rarely cause erectile disorders because they are less associated with hyperprolactinemia (De Rosa *et al.*, 2003) (Fig. 3).

Bupropion, Mirtazapine and Buspirone do not cause sexual disorders (Hendry, 1998; Montejo *et al.*, 2001; Nudell *et al.*, 2002; Baldwin & Mayers, 2003; Rosen & Marin, 2003; Schlosser *et al.*, 2007; Althof *et al.*, 2010; Gratzke *et al.*, 2010; Giuliano & Droupy, 2013; Taylor *et al.*, 2013; Clayton *et al.*, 2014; VIDAL Hoptimal 2016).

Depression is a chronic condition, and in most cases the discontinuation of antidepressant treatment is not an option. In the event that sexual disorders arise during treatment with SRIs or tricyclic antidepressants, treatment with Bupropion, Mirtazapine, Buspirone or Moclobemide could be considered. However, it is always difficult to change the treatment of a depressive illness. There is insufficient data regarding the benefits of "treatment breaks" or a reduced dosage in terms of improving sexual function in depressive subjects (Droupy, 2005; Taylor *et al.*, 2013; Clayton *et al.*, 2014).

Antipsychotics

Like tricyclic antidepressants and SRIs, "typical" neuroleptics are responsible for hyperprolactinemia by blocking central dopamine secretion, and indirectly cause hypogonadism (Fig. 3). Adverse effects on spermatogenesis and sperm quality are theoretically possible by this pathway (Panidis *et al.*, 1997; De Rosa *et al.*, 2003; Schlosser *et al.*, 2007); "typical" neuroleptics also affect the sexuality of patients who are receiving these treatments by inducing anorgasmia, decreased libido, ejaculation and erection disorders (Fig. 3). In contrast, the "atypical" neuroleptics barely raise prolactin levels, if at all (De Rosa *et al.*, 2003; Howes *et al.*, 2007; Gratzke *et al.*, 2010; Giuliano & Droupy, 2013). The dysfunctions that are observed during treatment also result from an antipsychotic-induced anticholinergic effect and the blockage of β-adrenergic transmission (Fig. 4).

It is extremely difficult to distinguish between sexual disorders that can be attributed to a psychotic illness, and those that can be attributed to the use of a medication. Moreover, the information that has been gathered comes from psychiatric patients and is often difficult to interpret. As psychoses are chronic conditions, stopping the neuroleptic treatment is impossible in most cases. If sexual dysfunction arises while taking Haloperidol or Amisulpride (phenothiazines: "typical" neuroleptics), it may be possible to switch to a medication in a different therapeutic class, such as Quetiapine, Aripiprazole, Olanzapine or Clozapine ("atypical" neuroleptics). However, most of the time it is difficult to modify antipsychotic treatment (Hendry, 1998; Baldwin & Mayers, 2003; Howes *et al.*, 2007; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; Serretti & Chiesa, 2011; Giuliano & Droupy, 2013).

Antiepileptics

There are several hypotheses as to the possible impact of antiepileptics on the sperm parameters. Valproate, Carbamazepine and Phenytoin could reduce sperm motility by interfering with sperm membrane function, indeed Valproate reduces the L-carnitine/T-carnitine ratio. Similarly, Carbamazepine is thought to interact directly with germ cells, inducing a greater number of necrotic germ cells in the lumen of the seminiferous tubules. Valproate is responsible for reduced testicular weight in animals, which would indicate that the molecule has a harmful effect on spermatogenesis (Chen *et al.*, 1992; Isojärvi *et al.*, 2004; Isojärvi *et al.*, 2005; de Oliva & Miraglia, 2009; Brezina *et al.*, 2012). Some anticonvulsants (Carbamazepine, Phenytoin and Phenobarbital) are hepatic enzyme inducers. They increase the synthesis of the SHBG protein, which is involved in testosterone transport, and they raise the total testosterone level. However, a lower level of bioactive serum androgens (testosterone) is sometimes observed when these molecules are used; bioavailable testosterone should always be measured in the framework of an antiepileptic treatment. Valproate does not increase SHBG, but it does raise the level of GABA in the central nervous system, thus modifying GnRH pulsatility. Valproate may also be responsible for increased serum androgen levels, and a possible reduction in LH owing to feedback. The impact of the new antiepileptics (Felbamate, Levetiracetam, Tiagabine, Topiramate, Vigabatrin, etc.) on hormone function has not been studied (Webber *et al.*, 1986; Rättyä *et al.*, 2001; Isojärvi *et al.*, 2004, 2005; Røste *et al.*, 2005; Lossius *et al.*, 2007; Herzog, 2008).

Sexual dysfunction in epileptic patients has multifactorial causes. It results from the pathophysiology of the epileptic illness and the associated anticonvulsant treatments. It is generally impossible to distinguish between the sexual disorders that can be attributed to the epilepsy and those that can be attributed to the use of medication. Indeed, for ethical reasons, epileptic men are rarely antiepileptic treatment naïve. During seizures, the epileptiform (temporolimbic) discharges disrupt neuroendocrine functions and modify hypothalamic and pituitary hormone release (resulting in elevated prolactin and fluctuating LH levels). Some antiepileptics may contribute to neuroendocrine disorders that could alter male reproductive functions (the

Table 2 Impact of drugs on sexual function (Gratzke *et al.*, 2010; Giuliano & Droupy, 2013; Droupy, 2005; Hendry, 1998; Colpi *et al.*, 2004; Schlosser *et al.*, 2007; Nudell *et al.*, 2002)

Pharmacological class	Family and molecules (references)	Effects on sexual function	Guidelines
Corticosteroids	Prednisone, Prednisolone, Dexamethasone (Fitzgerald *et al.*, 1997; MacAdams *et al.*, 1986; Whirledge & Cidlowski, 2010)	Chronic use, high dose: Potential inhibition of the hypothalamic–pituitary–gonadal axis (low testosterone levels) Erectile dysfunction and decreased libido not excluded **Low Level of Evidence**	No specific recommendations
Immunomodulators	Ipilimumab (Dillard *et al.*, 2010; Grunewald & Jank, 2015; VIDAL Hoptimal 2016)	Animals: Hypophysitis which can appear 6 months after initiation of treatment (decrease level of FSH and LH) Potential erectile dysfunction and decreased libido **Very Low Level of Evidence**	Cryopreservation recommended (precautionary measure)
Inhibitors of Protein kinases	Sorafenib (Iyer *et al.*, 2010; VIDAL Hoptimal 2016)	Erectile dysfunction cases described **Low Level of Evidence**	Absence of specific recommendations
Opioids	Morphine, Cocaïne (Pake *et al.*, 1994a; Yilmaz *et al.*, 1999; Daniell, 2002; Katz & Mazer, 2009; VIDAL Hoptimal 2016)	Chronic use: Erectile dysfunction and decreased libido **Good Level of Evidence**	Discontinuation before conception
Analgesics	Tramadol (Bar-Or *et al.*, 2012; VIDAL Hoptimal 2016)	Delayed ejaculation Sedation and decreased desire (action on opioid receptors in the central nervous system) **Good Level of Evidence**	Used (off-label) for the treatment of premature ejaculations (Althof *et al.*, 2010)
Treatment of benign prostatic hyperplasia	*Alpha-blockers*: Tamsulosin, Doxazosin, Silodosin, Alfuzosin and Terazosin (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Carbone & Hodges, 2003; Giuliano, 2006; Hellstrom & Sikka, 2006; Hellstrom *et al.*, 2009; Roehrborn *et al.*, 2011; Shimizu *et al.*, 2010; VIDAL Hoptimal 2016)	*Alpha-blockers*: No impairment of erectile function Ejaculation disorders (anejaculation/retrograde ejaculation) especially for Tamsulosin and Silodosin Orgasmic maintained **Relatively Good Level of Evidence despite the Presence of Confounding Factors (Disease)**	*Tamsulosin*: Ejaculation disorders: prefer another alpha-blocker (e.g. Alfuzosin/Terazosin)
Treatment of benign prostatic hyperplasia	Finasteride (Carbone & Hodges, 2003; Wessells *et al.*, 2003; Mondaini *et al.*, 2007; Hellstrom *et al.*, 2009; VIDAL Hoptimal 2016)	*Finasteride*: Erectile dysfunction and decreased libido Ejaculatory dysfunction (more rarely) **Relatively Good Level of Evidence despite the Presence of Confounding Factors (Disease)**	*Finasteride*: Absence of specific recommendations
Antiandrogenic drugs	Cyproterone acetate (Schröder *et al.*, 2000; Basaria *et al.*, 2002; VIDAL Hoptimal 2016) *Non-steroidal antiandrogens*: Bicalutamide, Flutamide, Nilutamide (Schröder *et al.*, 2000; Iversen *et al.*, 2001; Basaria *et al.*, 2002; VIDAL Hoptimal 2016)	*Cyproterone acetate*: Erectile dysfunction (gynaecomastia associated) Decreased libido **Good Level of Evidence** *Non-steroidal antiandrogens*: Erectile dysfunction and decreased libido **Relatively Good Level of Evidence**	Better safety profile for Click here to enter text.Non-steroidal Anti-inflammatory androgens (Bicalutamide +++)
Hormonal treatments	*GnRH analogues*: Triptorelin, Leuprorelin, Goserelin, Buserelin (Basaria *et al.*, 2002; VIDAL Hoptimal 2016)	Erectile dysfunction and decreased libido (gynaecomastia) **Good Level of Evidence**	*GnRH analogues*: Prostate cancer: Intermittent androgen blockage to limit side effects on sexual function
Diuretics	*Potassium-sparing diuretics*: Spironolactone, Eplerenone (Clark, 1965; Caminos-Torres *et al.*, 1977; Ferrario & Levy, 2002; VIDAL Hoptimal 2016) *Thiazide diuretics:* Hydrochlorothiazide, Chlorthalidone (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Boydak *et al.*, 2005; Manolis & Doumas, 2012; VIDAL Hoptimal 2016) General reviews: (Giuliano *et al.*, 2004; Karavitakis *et al.*, 2011)	*Spironolactone*: Erectile dysfunction (gynaecomastia) Anti-androgenic effect **Relatively Good Level of Evidence** *Eplerenone:* Small impact *Thiazide diuretics*: Erectile dysfunction Ejaculation disorders (delayed ejaculation/retrograde ejaculation) and decreased libido **Medium Level of Evidence** **Controversial Studies with Presence of Confounding Factors (Hypertensive Disease)** **Often Used in Combination**	*Spironolactone*: Absence of specific recommendations *Thiazide diuretics:* Treatment of hypertension: Treatment discontinuation is not recommended (benefit of antihypertensive drugs on the occurrence of cardiovascular events) In young patients, prefer (if possible) another antihypertensive therapy (Sartans)
Antifungals drugs	Ketoconazole (Pont *et al.*, 1982)	High dose, chronic use: In theory, potential erectile dysfunction by decline in testosterone level **No Level of Evidence**	No specific recommendations

(continued)

Table 2 (continued)

Pharmacological class	Family and molecules (references)	Effects on sexual function	Guidelines
Antiretroviral therapy	*Protease inhibitors*: Ritonavir, Saquinavir (Schrooten *et al.*, 2001; Colson *et al.*, 2002; Lallemand *et al.*, 2002)	Erectile dysfunction and decreased libido **Low Level of Evidence** **Confounding Factors**	Discontinuation NOT recommended (benefit of antiretroviral therapy +++)
Antihistamines	Cimetidine (Van Thiel *et al.*, 1979; Winters *et al.*, 1979; Wang *et al.*, 1982; Louis *et al.*, 2004)	High dose: Potential erectile dysfunction and decreased libido (antiandrogenic effect) **Low Level of Evidence**	No specific recommendations
Antidepressant therapy	*Tricyclic antidepressants*: Imipramine, Clomipramine, Amitryptine (Montejo *et al.*, 2001; Baldwin & Mayers, 2003) *Serotonin Reuptake inhibitors*: Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Venlafaxine (Montejo *et al.*, 2001; Baldwin & Mayers, 2003; Rosen & Marin, 2003; Dording *et al.*, 2008; Clayton *et al.*, 2014) *Monoamine Oxidase Inhibitors (MOAI)*: Moclobemide, Doxepine (Montejo *et al.*, 2001; Baldwin & Mayers, 2003) *Catecholamines Reuptake inhibitors (norepinephrine, dopamine)*: Bupropion (Montejo *et al.*, 2001; Baldwin & Mayers, 2003; Clayton *et al.*, 2014) *Other antidepressants:* Mirtazapine, Buspirone (Montejo *et al.*, 2001; Baldwin & Mayers, 2003; Clayton *et al.*, 2014) Lithium salts (Ghadirian *et al.*, 1992)	*Tricyclic antidepressants and Serotonin Reuptake inhibitors*: Erectile dysfunction, ejaculation disorders (anejaculation/ delayed ejaculation/retrograde ejaculation) and decreased libido Anorgasmia *Moclobemide*: less common erectile dysfunction *Bupropion, Mirtazapine, Buspirone*: Reduced erectile dysfunction *Lithium salts*: Potential erectile dysfunction and decreased libido (search for an underlying hypothyroidism) **Confounding Factors** **Difficulty of Separating Effect of Drugs and Effect of Disease** **But Relatively Good Level of Evidence on Global Impact of Antidepressants on Sexual Dysfunction**	Most of the time, discontinuation of drug is impossible (depression = chronic condition) *Serotonin Reuptake Inhibitors and tricyclic antidepressants*: Used for the treatment of premature ejaculation (Althof *et al.*, 2010) *Moclobemide, Bupropion, Mirtazapine:* To prefer in case of sexual dysfunction Occurrence of sexual dysfunction: Change drug class if possible Interest of drug holidays ? Dosage adjustment?! **Caution**! *Changing antidepressant therapy is delicate* (Clayton *et al.*, 2014; Taylor *et al.*, 2013) *Nb: No proven efficacyon sexual function of adding Amantadine or Granisetron*
Antipsychotic therapy	*Classical neuroleptics*: Phenothiazines: Chlorpromazine Butyrophenones: Haloperidol Benzamides: Amisulpride, Sulpiride (Serretti & Chiesa, 2011; Baldwin & Mayers, 2003; Howes *et al.*, 2007; VIDAL Hoptimal) *Atypical neuroleptics*: Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole (Serretti & Chiesa, 2011; Baldwin & Mayers, 2003; Howes *et al.*, 2007; VIDAL Hoptimal)	*Classical neuroleptics*: Erectile dysfunction and decreased libido (Phenothiazines ++) Ejaculation disorders (delayed ejaculation, anejaculation, retrograde ejaculation) Anorgasmia **Relatively Low Level of Evidence** **Impact on Sexual Function Difficult to Determine owing to the Association of Psychiatric Disease** *Atypical neuroleptics*: Sexual dysfunction less frequent compared to typical neuroleptics Risperidone: Atypical antipsychotic that causes most of erectile dysfunction Olanzapine, Clozapine: Potential erectile dysfunction Clozapine, Risperidone, Olanzapine: Retrograde ejaculation cases reported Quetiapine, Aripiprazole: Lower incidence of sexual dysfunction **Relatively Low Level of Evidence** **Impact on Sexual Function Difficult to Determine owing to the Association of Psychiatric Disease**	Most of the time, drug discontinuation is impossible (psychiatric disease = chronic condition) Occurrence of sexual dysfunction: Change drug class if possible ! **Caution** ! *Changing antispychotic therapy is delicate* *Aripiprazole, Quetiapine, Clozapine, Olanzapine*: to prefer in case of sexual dysfunction
Antiemeticdrugs	Metoclopramide («Hidden neuroleptic») (Panidis *et al.*, 1997)	Erectile dysfunction and decreased libido (hyperprolactinemia) (De Rosa *et al.*, 2003) **Low Level of Evidence**	No specific recommendations
Antiepileptic treatment	*Inducting agents*: Phenobarbital, Phenytoin, Carbamazepine (Isojärvi *et al.*, 1995; Isojärvi *et al.*, 2005; Røste *et al.*, 2005; Lossius *et al.*, 2007; Calabrò *et al.*, 2011) Valproate (Isojärvi *et al.*, 2005; Røste *et al.*, 2005; Lossius *et al.*, 2007; Calabrò *et al.*, 2011) Lamotrigine (Calabrò *et al.*, 2011) Gabapentine (Kaufman & Struck, 2011) General review: (Herzog, 2008)	*Valproate, Lamotrigine*: No or reduced effect on erectile function *Phenobarbital, Carbamazepine, Phenytoin*: Erectile dysfunction and decreased libido *Gabapentine*: 1 case of sexual dysfunction is described (anorgasmia, erectile/ ejaculatory disorders) **Low Level of Evidence** **Confounding Factors Related to Epileptic Disease Difficult to Study Patients Without Epileptic Treatment for Ethical Considerations** *Epilepsic disease*: Causes sexual dysfunctions	Antiepileptic drugs must not be discontinued *Valproate, «new antiepileptic drugs»:* to prefer in case of erectile dysfunction? ! **Caution** ! *Changing antiepileptic therapy is delicate*

(continued)

Table 2 (continued)

Pharmacological class	Family and molecules (references)	Effects on sexual function	Guidelines
Tranquilizer	*Benzodiazepines* (Ghadirian *et al.*, 1992; VIDAL Hoptimal 2016)	Potential erectile dysfunction **Low Level of Evidence** **Confounding Factors Related to the Disease**	No specific recommendations
Antihypertensive drugs	*Beta-blockers*: Propranolol: non-cardioselective β-Blockers Carvedilol: non-cardioselective β-Blockers and action on α-adrenergic receptors Metoprolol: cardioselective β-Blockers Atenolol: cardioselective β-Blockers Acebutolol: cardioselective β-Blockers Nebivolol: cardioselective β-Blockers and $NO^{\bullet}$ liberator (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Manolis & Doumas, 2012; Boydak *et al.*, 2005) *Antihypertensive vasodilators*: Urapidil, Minoxidil (Ferrario & Levy, 2002) *Calcium channel blockers*: Nifedipine, Amlodipine, Verapamil, Diltiazem (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Manolis & Doumas, 2012) *Alpha-blockers*: Prazosine (Ferrario & Levy, 2002) *Angiotensin-Converting Enzyme (ACE)*: Captopril, Enalapril (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Manolis & Doumas, 2012) *Sartans*: Losartan, Valsartan (Becker *et al.*, 2001; Ferrario & Levy, 2002; Shindel *et al.*, 2008; Manolis & Doumas, 2012) *Antihypertensive drugs with central action:* Methyl-dopa, Clonidine (Ferrario & Levy, 2002) *Other*: Reserpin (Ferrario & Levy, 2002) General reviews: (Giuliano *et al.*, 2004; Karavitakis *et al.*, 2011)	*Beta-blockers*: Relatively uncommon erectile dysfunction (controversial) and decreased libido Propranolol, Carvedilol (non-selective): Erectile dysfunction more frequently compared with other beta-blockers Metoprolol, Atenolol (selective): Uncommon erectile dysfunction Acebutolol (major selectivity): Uncommon erectile dysfunction Nebivolol ($NO^{\bullet}$ liberator): Reduced erectile dysfunction **Medium Level of Evidence** **Confounding Factors Related To hypertensive Disease** **Antihypertensive vasodilatators**: Potential erectile dysfunction **Low Level of Evidence** **Calcium channel-blockers**: very few erectile dysfunction reported; impotence described with Verapamil (hyperprolactinemia?) **Low Level of Evidence** **Alpha-blockers:** No impairment of erectile function **Relatively Good Level of Evidence** **ACE:** Erectile dysfunction reduced in comparison with other antihypertensive drugs **Relatively Good Level of Evidence** **Sartans**: Erectile function preserved **Good Level of Evidence** **Antihypertensive drugs with central action**: Erectile dysfunction, ejaculation disorders (anejaculation/retrograde ejaculation) and decreased libido Methyl-dopa: Hyperprolactinemia **Medium Level of Evidence (Controversial Studies)** **Confounding Factors Related to Hypertensive Disease** *Reserpin*: Erectile dysfunction and ejaculation disorders (hyperprolactinemia) **Medium Level of Evidence** **Confounding Factors Related to Hypertensive Disease**	Discontinuation of antihypertensive therapy is NOT recommended (benefit of antihypertensive drugs on the occurrence of cardiovascular events) *Beta-blockers*: Prefer cardioselective β-Blockers (Nebivolol++) in case of erectile dysfunction *Sartans, ACE, Calcium channel blockers*: To prefer in sexually active young patients *Antihypertensive drugs with central action and Reserpin*: Use in second line Change drug class or adjust posology if possible in case of sexual dysfunction
Anticholesterol	*Statins*: Pravastatin, Simvastatin, Atorvastatin (Bruckert *et al.*, 1996; Rizvi *et al.*, 2002; Saltzman *et al.*, 2004; Solomon *et al.*, 2006; Do *et al.*, 2009; VIDAL Hoptimal 2016) *Fibrates*: Fenofibrate, Gemfibrozil, Clofibrate (Bain *et al.*, 1990; Bruckert *et al.*, 1996; Rizvi *et al.*, 2002; VIDAL Hoptimal 2016)	*Statins*: Simvastatin, Pravastatin: Erectile dysfunction reported Atorvastatin: No erectile dysfunction (not appears to be a class effect of Statins) **Low Level of Evidence** Pravastatin: Potential confounding factor for evaluation of testosterone levels **Very Low Level of Evidence** *Fibrates*: erectile dysfunction **Relatively Low Level of Evidence** **Confounding Factors Related to the Disease**	Anticholesterol treatment: Prefer Atorvastatin in case of erectile dysfunction
Digitalis drugs	Digoxin (Neri *et al.*, 1987; Gupta *et al.*, 1998)	Erectile dysfunction and decreased libido **Low Level of Evidence (Confounding Factors)**	No specific recommendations

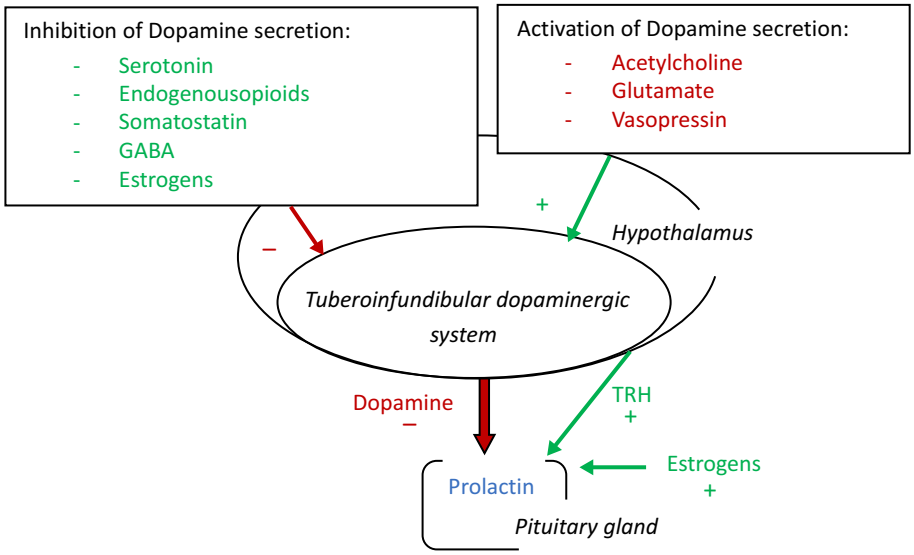

Figure 3 Neuroendocrine regulation of prolactin. Adapted from Freeman *et al.* (2000).

effects of Felbamate, Levetiracetam, Topiramate, Tiagabine and Vigabatrin on the neuroendocrine system remain unknown) (Isojärvi *et al.*, 1995; Isojärvi *et al.*, 2005; Røste *et al.*, 2005; Lossius *et al.*, 2007; Herzog, 2008; Calabrò *et al.*, 2011; Kaufman & Struck, 2011).

Antihypertensives

Calcium channel blockers are thought to reduce the fertilization capacity of the sperm by decreasing sperm viability and motility and also by preventing spermatozoa–oocyte interaction as a result of the modified transmembrane movement of calcium, which has been described in vitro (Kanwar *et al.*, 1993; Benoff *et al.*, 1994; Schlosser *et al.*, 2007; Brezina *et al.*, 2012).

Numerous data suggest that antihypertensives have a harmful effect on erectile function. However, it is difficult to determine the actual impact of these treatments as a result of the adverse effects of hypertension on erectile function, related to endothelial dysfunction (Giuliano *et al.*, 2004). There is still a great deal of controversy that surrounds the most commonly prescribed antihypertensives. The mechanisms through which these treatments affect sexual function are still largely unknown and may include a drop in blood pressure associated with a specific class effect (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Manolis & Doumas, 2012).

Beta-blockers are thought to prevent corpora cavernosa vasodilatation by blocking the smooth muscle relaxation that is induced by the stimulation of β2 adrenergic receptors. Moreover, some of these molecules could reduce testosterone secretion as a result of an action at the central nervous system level. So-called "cardioselective" beta-blockers of the β1 adrenergic receptors have little (if any) effect on erectile function (Fig. 4) (Grimm *et al.*, 1997; Ferrario & Levy, 2002; Nudell *et al.*, 2002; Boydak *et al.*, 2005; Droupy, 2005; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; VIDAL Hoptimal 2016).

Centrally acting antihypertensives stimulate pre-synaptic α2-adrenergic receptors, thus reducing central sympathetic tone with possible repercussions for ejaculatory function (delayed reflex contractions of the bulbospongiosus muscles). Erectile dysfunction can also arise through the stimulation of the peripheral α-adrenergic receptors (Fig. 4). Methyldopa is also responsible for hyperprolactinemia, which can inhibit the hypothalamic–pituitary–gonadal axis (Fig. 2) (Hendry, 1998; Ferrario & Levy, 2002; De Rosa *et al.*, 2003; Droupy, 2005; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; VIDAL Hoptimal 2016).

Alpha-blockers and calcium channel blockers do not cause erectile dysfunction, but ejaculatory disorders resulting from the use of these medications have been described, owing to the inhibition of bulbospongiosus muscle contractions.

Angiotensin-converting enzyme inhibitors and sartans do not alter erectile function. Indeed, angiotensin II is an important penile detumescence mediator. The literature review of Shindel *et al.* described the effects of drugs which improve endothelial function on the penile erection: Angiotensin II antagonists appeared to hold great promise in this regard (Shindel *et al.*, 2008). Moreover, Beker *et al.* showed that angiotensine II plasma levels are generally high in patients with an organogenic aetiology of erectile dysfunction; as a consequence, angiotensin inhibitors could be used in the treatment of vasculogenic erectile dysfunction (Becker *et al.*, 2001). Lastly, a recent literature review on implication of antihypertensive drugs on erectile dysfunction suggests that sartans are not associated with development of sexual dysfunction and that they may offer a therapeutic option to prevent or correct erectile dysfunction in patients with hypertension (Grimm *et al.*, 1997; Becker *et al.*, 2001; Ferrario & Levy, 2002; Nudell *et al.*, 2002; Droupy, 2005; Schlosser *et al.*, 2007; Gratzke *et al.*, 2010; VIDAL Hoptimal 2016).

In hypertensive subjects, the discontinuation of treatment is not recommended owing to the significant beneficial effect of antihypertensives in preventing cardiovascular events. However, it is important for practitioners to select the treatment carefully to limit the occurrence of sexual disorders. Angiotensin II antagonists thus appear to be the treatment of choice for sexually active men who are newly diagnosed with hypertension. When it is not possible to modify an antihypertensive treatment, an adjustment of the dose may be beneficial (Ferrario & Levy, 2002; Droupy, 2005; Karavitakis *et al.*, 2011; Giuliano & Droupy, 2013).

Hormonal treatments

GnRH analogues used in the treatment of prostate cancer temporarily raise gonadotrophin levels ("flare-up" effect). When

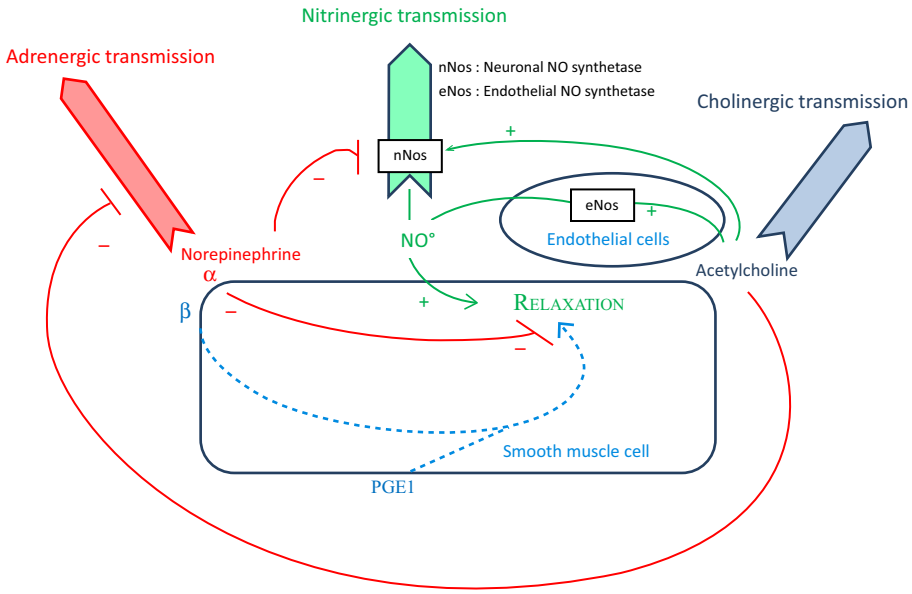

Figure 4 Peripheral mechanism of erection. Adapted from Droupy (2005).

administered daily, they subsequently inhibit gonadotrophin secretion via the desensitization of the pituitary receptors. The observed androgen blockage results in genuine chemical castration, which causes erectile dysfunction and a loss of libido (Basaria *et al.*, 2002; Droupy, 2005; Giuliano & Droupy, 2013; VIDAL Hoptimal 2016). A cross-sectional study of 58 men suggested that sexual dysfunction is noted in patients receiving androgen deprivation therapy for at least 12 months (Basaria *et al.*, 2002).

More recently, a prospective study from 2008 to 2010 including 39 patients treated by androgen deprivation therapy showed that the administration of luteinizing hormone-releasing agonists induced significant decrease in penis length (Park *et al.*, 2011).

Intermittent androgen deprivation, when this is possible, reduces sexual function disorders and improves quality of life for men who suffer from prostate cancer (Iversen *et al.*, 2001; Basaria *et al.*, 2002).

Tranquilizers

Benzodiazepines could induce erectile disorders via the inhibition of the proerectile central dopaminergic pathway (Ghadirian *et al.*, 1992; Droupy, 2005; VIDAL Hoptimal 2016).

A randomized double-blind, placebo-controlled multicenter study, including 604 patients, has shown that tramadol extended ejaculation latency time. This drug could become an effective treatment for premature ejaculation (use off-label) (Bar-Or *et al.*, 2012).

Anticholesterolemics

By activating PPARα, fibrates induce testosterone esterification, which results in erectile disorders.

Statins inhibit HMG-CoA reductase, an enzyme that is involved in cholesterol biosynthesis. As cholesterol is a precursor for steroid hormone synthesis, these molecules can theoretically affect erectile function in men who are being treated with medications that reduce androgen synthesis. However, only Simvastatin and Pravastatin are described as being potentially harmful; no disorders have been reported with Atorvastatin use. This is therefore not a class effect of statins (Bruckert *et al.*, 1996; Rizvi *et al.*, 2002; Saltzman *et al.*, 2004; Solomon *et al.*, 2006; Do *et al.*, 2009; Gratzke *et al.*, 2010).

Digoxin

Digoxin could alter erectile function via the reduction in serum testosterone levels. It also has anticholinergic properties that prevent smooth muscle relaxation, an essential factor in the swelling of the corpora cavernosa (Neri *et al.*, 1987; Gupta *et al.*, 1998).

DISCUSSION

In the framework of a male infertility workup, a history of drug treatments (present and past) taken by the patient must be obtained.

This systematic literature review has collated data related to all of the drugs with potential impacts on sperm parameters and/or sexual function.

Some pharmaceutical treatments are described in the literature as being potentially harmful for male fertility, and yet it is not always easy for practitioners to access the available data. Furthermore, an evaluation of the actual gametic effects of these treatments remains to be performed.

Drug treatments and risks of infertility (excluding cytotoxic agents)

The (sometimes irreversible) gonadal damage caused by anticancer agents is now better understood and well documented Trottmann *et al.*, 2007. Conversely, data on the impact of drug treatments (excluding cytotoxic molecules) on male fertility are scarcer and sometimes controversial. Most of these data are nevertheless reassuring, with effects on spermatogenesis being reversible when described (Table 1). A notable exception is the use of certain targeted therapies (Dabrafenib and Vismodegib) that are used to treat metastatic melanoma or basal-cell carcinoma. These medications exhibited a potentially irreversible impact on spermatogenesis in animals as a result of testicular degeneration,

which was noted during pre-clinical safety studies. Given the potential risk of sterility in men, cryopreservation is indispensable prior to treatment. These molecules are teratogenic (but not mutagenic in vitro or in vivo in animals). The use of contraception during treatment is necessary with the cessation of drug in men who want to conceive (Grunewald & Jank, 2015; VIDAL Hoptimal 2016).

Although some molecules have reversible effect on sperm parameters, the cryopreservation can be proposed. This is the case, for Sulfasalazine, used for Crohn disease or ulcerative colitis (VIDAL Hoptimal 2016). It has been observed that spermatogenesis generally recovers approximately 2–5 months after stopping Sulfasalazine therapy (O'Moráin *et al.*, 1984; Østensen *et al.*, 2006; Silva Clovis *et al.*, 2010). In patients with ulcerative colitis, the therapy with enteric-coated mezalasine (5-aminosalicylic acid preparation) allows the recovery of sperm alterations induced by Sulfasalazine (Kjaergaard *et al.*, 1989; Silva Clovis *et al.*, 2010). Contraception and sperm banking are not necessary in patients treated with Sulfasalazine (Østensen *et al.*, 2006), but family planning must be discussed with all patients who need a treatment causing transient infertility (Silva Clovis *et al.*, 2010). Sperm banking can be proposed in men with a long-term treatment.

This is also the case with Cyproterone acetate used for palliative treatment of prostate cancer (VIDAL Hoptimal 2016). As the average age at the time of diagnosis is 66 years, sperm banking is generally not proposed before treatment. Nevertheless, in younger patients and/or in patients with a parental project, sperm banking should be discussed, especially as this treatment may also induce loss of erectile function and libido.

Finally, these therapy are often long-term treatment and stopping drug (or establish "drug holiday") is not often recommended.

Another important point is the frequency of bodybuilders taking testosterone supplementation therapy/anabolic steroids, being unaware of its negative impact on fertility, and presenting with azoospermia/severe oligozoospermia in infertility clinics (Wenker *et al.*, 2015). After withdrawal of exogenous testosterone, spermatogenesis is spontaneously reversible in an average of 3.2 months (Ly *et al.*, 2005) and testicular sperm extraction should not be proposed.

Special case of mutagenic and/or teratogenic therapies

Even though they do not alter spermatogenesis, some immunosuppressants are likely to harm male fertility as a result of their mutagenic and teratogenic effects. This is the case with Azathioprine and Mycophenolate mofetil, for which cryopreservation must be proposed prior to the initiation of treatment, especially when subsequently stopping treatment cannot be envisaged (Dejaco *et al.*, 2001; Ligumsky *et al.*, 2005; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016). However, several recent studies have suggested no significant increase in the number of congenital anomalies in children born of fathers who were treated with Azathioprine or Mycophenolate mofetil (Hoeltzenbein *et al.*, 2012; Jones *et al.*, 2013). In men who want to conceive, the discontinuation of treatment for a minimum of 3 months before conception is essential.

Sirolimus does not appear to definitively harm male fertility. This molecule is not mutagenic (in vitro or in vivo), but has been demonstrated to be embryotoxic and foetotoxic in animals. Owing to a potential clinical risk for descendants, conception while taking Sirolimus is not recommended (Leroy *et al.*, 2015; VIDAL Hoptimal 2016).

Methotrexate, a cytotoxic agent that is also indicated for numerous autoimmune conditions, is gonadotoxic, mutagenic and probably teratogenic, but its effects are reversed after the discontinuation of treatment. It is, therefore, important to reassure patients with regards to their future fertility. However, cryopreservation must be considered prior to the initiation of treatment if it cannot subsequently be stopped (Weber-Schoendorfer *et al.*, 2014; Leroy *et al.*, 2015; CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016; VIDAL Hoptimal 2016).

Treatment with a mutagenic drug must be discontinued for a minimum of 3 months before conception. (CRAT – Centre de référence sur les agents tératogènes chez la femme enceinte 2016). For only teratogenic molecules, studies recommend the discontinuation of treatment before the conception and the practice of safe sex when the partner is pregnant. In fact, the drug can be found in the seminal fluid and can possibly cross female mucus membranes (Millsop *et al.*, 2013; Grunewald & Jank, 2015; Leroy *et al.*, 2015).

Variability in levels of evidence

Part of this summary work consisted of an examination of the level of evidence of the available studies and reviews, the results of which vary and depend on the molecules that are involved and their impact on male fertility.

Drugs and the impact on sperm parameters

For most of the drugs that are likely to affect spermatogenesis and/or sperm parameters, the levels of scientific evidence are still insufficient (with the exception of Sirolimus, Sulfasalazine, exogenous testosterone, Finasteride and Cyproterone acetate, for which the levels of evidence are higher) (Table 1). In some cases, data in men do not even exist, and the toxicity of a drug for the male reproductive organs is determined solely on the basis of animal models (rodents +++). When a pharmaceutical substance is developed with a view to obtain marketing authorization, pre-clinical safety studies that are performed in animals (rodents + other mammal species) are a means of predicting potential adverse effects on human fertility. The performance of future clinical trials (in men) therefore depends directly on the results of the data obtained in animals. However, care must be taken when extrapolating data from animals to humans. Indeed, the predictive power of pre-clinical animal toxicity studies for human reproductive functions, particularly male fertility (best evaluation of teratogenicity), is by no means infallible in terms of assessing the reprotoxicity of a pharmaceutical substance (Guittin *et al.*, 1998).

In humans, most studies are performed on small samples or even on case series (Tanrikut & Schlegel, 2007; Pecou *et al.*, 2009) and do not always include a placebo group or a control group (Hofer *et al.*, 2010). Nor do a certain number of studies take into account the relationship between the dose of a drug and its impact, the effects of the residual illness on male fertility (impact of the illness itself) (Isojärvi *et al.*, 2004; Bujan *et al.*, 2007) or the presence of other confounding factors that could be associated with the treatment (Schill *et al.*, 2008). Moreover, inter-/

intraindividual fluctuations in sperm parameters (caused by environmental factors, periods of abstinence, stress, smoking, etc.) and delayed repercussions of drug exposure on spermatogenesis (the complete spermatogenesis process takes 74 days) make it more difficult to analyse the results (studies with high statistical powers minimize this problem) (Levitas *et al.*, 2005; Aitken, 2006). Furthermore, in many cases the sole criterion that is considered in the evaluation of male fertility is the quality of the semen analysis. However, an alteration in sperm parameters does not always reflect the ability of the spermatozoa to fertilize the oocyte, or the likelihood of a pregnancy or a subsequent live birth.

Drugs and impact on sexual function

The impact of drug treatments on sexual function is most accurately assessed with higher levels of scientific evidence, as is the case with opiates, GnRH analogues, antiandrogens and alpha-blockers (Table 2). The mechanisms of action through which GnRH analogues and antiandrogens are likely to cause erectile dysfunction are better defined and are closely related to the physiology of the erection. The blockage or reduction in androgens as a result of the administration of these treatments is thought to be the cause of the decreased peripheral expression of neuronal nitric oxide synthase, an enzyme that is involved in the synthesis of NO, which plays a vital role in the relaxation of the smooth muscle cells of the corpora cavernosa during tumescence (Schirar *et al.*, 1997; Droupy, 2005; Courtois & Bonierbale, 2016). As for alpha-blockers, these interfere with the physiological processes of ejaculation. Their sympatholytic effects result in defective seminal tract contraction and bladder neck closure, two mechanisms that depend on thoracic and lumbar sympathetic afference (Courtois & Bonierbale, 2016).

For a certain number of pharmaceutical molecules that are likely to affect the sexual function of men being treated, the actual imputability of the drug is often difficult to pinpoint owing to the effect of the illness itself on sexuality (cardiovascular disease and erectile dysfunction; depressive illness and loss of desire, etc.) (Ferrario & Levy, 2002; Baldwin & Mayers, 2003). When an erectile and/or ejaculatory disorder arises during treatment, it is important to retrace the patient's precise sexual history to establish any connection between the time when the treatment was started and the disorder first arose. If normal sexual function returns after the patient stops taking the drug, this would appear to indicate that the therapy was the true causal factor of the sexual dysfunction.

The low levels of evidence that were found are owing to the methodological difficulties inherent in the performance of reprotoxicity studies. Randomized controlled trials are scarce and require a sound methodological strategy at the outset. The meticulous monitoring of the selected patients along with high-quality data collection throughout the study are vital. It is not easy to set up a placebo/control group, especially as the impact of the illness is a causal factor that is difficult to eliminate in practice (there are few treatment-naïve patients, for ethical reasons). It is difficult to perform meta-analyses owing to the insufficient quantity of data available and the difficulties of harmonizing the studies that are selected for the population being studied (as a result of numerous associated confounding factors), the illness and the associated type of treatment (doses, duration of treatment, drug combinations, etc.).

CONCLUSION AND PERSPECTIVES

Medications are a frequent exogenous factor found in systematic evaluation of infertile men, but drugs' effects on the reproductive function (spermatogenesis, sperm parameters and sexual function) are often unclear, apart from few well-known reprotoxic pharmacological classes. Although the data should be updated regularly, this systematic review could be helpfully used in the framework of treating male infertility: it gives reproductive clinicians and biologists rapid access to pertinent information on a drug they suspect of being incriminated, and to clinical recommendations for patient fertility and sexual management.

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