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REVIEW

FDA-approved drugs that are spermatotoxic in animals and the utility of animal testing for human risk prediction

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Abstract
Purpose This study reviews FDA-approved drugs that negatively impact spermatozoa in animals, as well as how these findings reflect on observations in human male gametes.
Methods The FDA drug warning labels included in the DailyMed database and the peer-reviewed literature in the PubMed database were searched for information to identify single-ingredient, FDA-approved prescription drugs with spermatotoxic effects.
Results A total of 235 unique, single-ingredient, FDA-approved drugs reported to be spermatotoxic in animals were identified in the drug labels. Forty-nine of these had documented negative effects on humans in either the drug label or literature, while 31 had no effect or a positive impact on human sperm. For the other 155 drugs that were spermatotoxic in animals, no human data was available.
Conclusion The current animal models are not very effective for predicting human spermatotoxicity, and there is limited information available about the impact of many drugs on human spermatozoa. New approaches should be designed that more accurately reflect the findings in men, including more studies on human sperm in vitro and studies using other systems (ex vivo tissue culture, xenograft models, in silico studies, etc.). In addition, the present data is often incomplete or reported in a manner that prevents interpretation of their clinical relevance. Changes should be made to the requirements for pre-clinical testing, drug surveillance, and the warning labels of drugs to ensure that the potential risks to human fertility are clearly indicated.

Keywords Drug warning labels · Infertility · Reproductive toxicology · Spermatotoxicity

Introduction

It has been estimated that approximately 5–10% of men in developed countries are affected by infertility due to abnormalities in spermatozoa (number, morphology, motility, etc.) or semen (volume, composition, viscosity, etc.) [1]. There are numerous causes, including genetics, hormone imbalances, dietary insufficiencies, exposure to environmental or occupational toxicants, or the use/abuse of drugs (recreational, over-the-counter, or prescription). Given that approximately half of the US population has taken a prescription drug in the last month [2], prescription drugs may represent a common source of spermatotoxicity.

The present review focuses on the spermatotoxic effects (from the generation of spermatogonia to fertilization) of prescription drugs in various experimental animals. This review was prompted by a previous publication that examined the impact of FDA-approved drugs on human spermatogenesis [3]. In that study, frequent discrepancies were noted in the drug warning labels between the adverse effects of drugs on human and animal spermatogenesis, as well as some inconsistencies between the published peer-reviewed literature and the DailyMed database (a federal repository of drug warning

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labels). In addition to providing an overview of the spermatotoxicity of prescription drugs in animals, the review also provides a comparison to the reported human spermatotoxicity and addresses how the current data reflect the risk of these drugs to human sperm. This review also suggests ways to improve the current male reproductive toxicity testing and reporting of results.

Materials and methods

Database search and inclusion/exclusion criteria

The FDA indicates that any finding of toxicity should be reported on the drug labels in the "Warnings," "Adverse Reactions," and "Precautions" sections, as well as any other area where such a warning would be appropriate. The DailyMed database (http://dailymed.nlm.nih.gov/dailymed/index.cfm) is a federal database that contains approximately 85% of the US FDA-approved drug labels. This database represents the largest and most comprehensive database of the warning labels for FDA-approved drugs and is updated whenever a label changes.

Stemmed key words were used to search the full-text drug labels included in the DailyMed database (also available at: https://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm) as described in a previous study [4]. These stemmed keywords (deferen, epidid, interstitial, Leydig, semen, semin, Sertoli, sperm, and testi) covered numerous terms related to spermatogenesis, pathological changes of the male reproductive organs (such as testicular tumors, testitis, and epididymitis), and direct effects on the spermatozoa. To ensure that the effects were due to the specific drugs, drugs with indirect effects on sperm (i.e., drugs with teratogenic effects impacting the fertility of male offspring) were excluded. Only FDA-approved prescription drugs developed for administration to humans were examined. Over-the-counter (OTC) drugs were excluded because the information available on their labels was generally insufficient and most have not been subjected to rigorous reproductive toxicity testing. The drugs with multiple active ingredients were also excluded to reduce the complexity of the analysis. When there were redundant labels for drugs produced by different companies or drugs with more than one label that had been updated at different times, only the most recent label was analyzed. Other labels for drugs intended for veterinary use, medicinal foods, medical devices, dietary supplements, cosmetics, etc., were also excluded. When the final stemmed keyword search was performed on August 8, 2017, there were 95,873 labels included in the DailyMed database. After restricting the information to single-ingredient drugs as described above, a total of 251 unique prescription drug labels were identified that showed a negative impact on sperm, which were further narrowed down to 235 drugs because some of them were the same drug in different formulations that led to the same adverse effects (i.e., aripiprazole/aripiprazole lauroxil).

Data extraction and analysis

Two authors independently searched the DailyMed database and extracted relevant data. When there were differences in the descriptions extracted between these authors, they discussed the findings with additional authors, and the group's consensus regarding the findings was used for the analysis.

A PubMed search was also performed to determine whether animal or human toxicity had been reported for the 235 drugs identified to impact animal spermatogenesis based on the DailyMed labels. The PubMed database was searched using the terms ([generic drug name] AND sperm*, fertil*, semen, semin*, or testi*).

Results

The general findings of the database searches

A total of 235 FDA-approved drugs intended for human use and containing a single active ingredient were found to impact spermatogenesis in at least one type of animal. All of these drugs could result in a decrease in the sperm count/concentration or a decrease in sperm quality, viability, or fertilization capacity.

Rats were the model most often reported to be affected by the drugs (specifically reported for 184 of the 235 drugs). This was expected, because rats are the most commonly used animal model for reproductive toxicity testing. Dogs are often used to confirm the findings in rats, and were thus also frequently reported to experience changes in spermatogenesis due to the exposure to prescription drugs. There were many instances where only rats were listed as having changes in spermatogenesis following drug exposure, either because there was no toxicity in other animals or because confirmation testing was not performed. Interestingly, in about half of the cases, spermatotoxicity was only reported for dogs. This suggests that dogs may be particularly sensitive to spermatotoxicants. Only 34 of the 235 drugs were reported to affect primate spermatogenesis. However, it is likely that many of the drugs were not tested in primates given the ethical concerns and high expenses associated with testing in primates. In addition, although spermatotoxicity was reported for 11 other drugs in DailyMed, the type of animal(s) affected was not specified in the drug label.

The FDA-approved drugs reported to adversely affect animal spermatogenesis

Unsurprisingly, antineoplastic agents were the category of drugs most often reported to have effects on animal spermatogenesis. Antineoplastic agents can cause temporary or permanent damage to the spermatozoa, germ cells, or support cells. Hormones and hormone antagonists were also expected to have adverse effects on spermatogenesis, so it is not surprising that they make up the other category of drugs most frequently noted to be spermatotoxic in this study. Both classes of drugs are well-recognized as having a potential negative impact on male fertility, and protocols are in place in most hospitals and clinics to counsel patients about these effects and the means to preserve spermatozoa for future use.

On the other hand, there were numerous other drugs with unexpected spermatotoxicity, where the intended target/mechanism of action is not generally considered to impact sperm. These drugs were from various classes, including adrenergic agents (icatibant, silodosin), analgesics (carbamazepine, morphine), antihypertensive agents (tamsulosin, reserpine), anti-infectious agents (metronidazole, miconazole), cardiovascular agents (bosentan, spironolactone), and immunosuppressants (sirolimus, azathioprine). Such agents are of greater concern because the adverse effects of these agents on fertility are not well-recognized and may not be addressed when the drugs are prescribed.

The types of spermatotoxic effects reported for animals

The most common adverse effect of the drugs was a reduced sperm count (due to reduced spermatogenesis or the death of developed and developing sperm), followed by reduced sperm motility, abnormal sperm morphology, testicular atrophy, and tumor formation (most frequently benign Leydig cell tumors in rodents). Similar observations of reduced sperm counts, reduced motility, and abnormal sperm morphology have been noted in humans for some of these drugs (see Table 1). In contrast to animal studies, where drug-related tumor formation was relatively common, drug-induced testicular tumors seem to be rare in humans. While some agents, such as anabolic steroids, are considered to cause testicular atrophy in men [44], the histological findings are generally not available, except for rare cases of injury or malignancy that require surgery. This makes it difficult to assess the full extent of the changes in humans.

Of note, most of the reports of adverse effects did not specify how many (what percentage) of the animals were affected. Therefore, it is unclear whether the observed adverse effect was common or relatively rare. The reporting was similarly vague for human effects, with many labels failing to indicate what percentage of the population was affected by the specific type of toxicity.

PubMed findings of human effects for these drugs

Only about 11% (26/235) of the drug warning labels that indicated that the agent had a negative impact on animal sperm (any aspect of spermatogenesis or toxicity to the sperm themselves) also had information in the drug label about a negative effect in humans. There were reports of adverse effects on human sperm for another 36 of these drugs in the PubMed database, although some of these publications were of in vitro studies, case studies, or studies of drug combinations that included the drug of interest (Table 1). Thus, between the drug labels in DailyMed and the reports included in PubMed, less than 30% of the drugs found to adversely affect animal sperm have been found to adversely affect human sperm.

For about half of the drugs that cited a negative impact on animal sperm, there were no data in DailyMed or PubMed about their impact on human sperm (Table 2). Eleven of the drugs without any publications in PubMed indicated that they had effects in humans in the DailyMed labels, although specific details were generally lacking regarding the number of patients affected. Interestingly, there were 33 drugs indicated to have negative effects in animals that were shown to have no effect or a positive impact on human sperm in the published literature (Table 3).

Discussion

The status of spermatotoxicity testing and relevance of the current testing

Testing for and reporting spermatotoxicity

The guidelines for industry issued by the FDA for new drug development stipulate that "…reproductive or developmental toxicity, whether in valid reproductive/developmental or other relevant nonclinical studies, should be evaluated to estimate the likelihood or other reproductive or developmental risk for humans". In addition, the "Females and Males of Reproductive Potential" section requires the inclusion of information when there are human and/or animal data suggesting drug-associated effects on fertility and/or preimplantation loss effects (§201.57(c)(9)(iii))" [102]. The FDA, as well as the US Environmental Protection Agency, Occupational Safety and Health Administration, and other national and international organizations, have made efforts to both streamline testing and make the testing as accurate as possible, specifically taking into consideration the route, dose, frequency, and duration of exposure, as well as species-associated differences. The guidelines also emphasize the need to understand the potential impact of drugs on fertility via both pre-clinical studies in animals and subsequent studies in patients, with an

Table 1 FDA-approved drugs with negative effects on sperm in both animals and humans

Main category	Drug name (generic)	Effect(s) in animals	Type of animal(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Support in PubMed	Reported effect(s)
5-Alpha-reductase inhibitor	Dutasteride	Leydig cell adenomas, reduced cauda epididymal sperm counts, reduced weights of the epididymis, prostate, and seminal vesicles	Rats	Yes	Decreased sperm count, motility, and semen volume	[5]	Reversible decrease in the number and motility of sperm
Adrenergic agent	Silodosin	Decreased sperm viability and counts, changes in the testes and epididymides	Rats	No		[6]	Prevents sperm emission, but no direct effects on spermatozoa
Alpha-blocker	Tamsulosin hydrochloride	Changes in semen content	Rats	No		[7]	Decreased sperm count
Analgesic	Acetaminophen	Increased abnormal sperm, reduced spermatogenesis	Mice	No		[8]	Reduced motility, DNA fragmentation
	Buprenorphine	Leydig cell tumors	Rats	No		[9]	Leads to anejaculation
	Carbamazepine	Benign interstitial cell adenomas in the testes, testicular atrophy, aspermatogenesis	Rats	No		[10]	Decreased sperm motility and vitality
	Morphine sulfate	Changes in hormone levels (incl. testosterone and luteinizing hormone)	Rats	No		[11]	Decreased sperm motility
Anticonvulsant	Divalproex sodium	Reduced spermatogenesis, testicular atrophy	Rats and dogs	No		[12]	Decreased counts and motility, increased abnormal morphology, decreased testicular volume
	Oxcarbazepine	Benign testicular interstitial cell tumors	Rats	No		[13]	Increased abnormal morphology, decreased testicular volume
	Valproate sodium/ valproic acid	Reduced spermatogenesis and testicular atrophy	Rats and dogs	No		[12]	See divalproex above
Antidepressant	Clomipramine hydrochloride	Phospholipidosis and testicular changes	Not specified	Yes	Testicular tumors	[14]	Reduced motility and abnormal morphology
	Paroxetine	Spermatogenic arrest, atrophic changes in the seminiferous tubules	Rats	Yes	Decreased sperm quality, epididymitis	[15]	Increases DNA fragmentation
	Vasopressin[b]	Decrease in the function and fertilizing ability of spermatozoa	Mice	No		[16]	Decreased sperm count and motility
Antifungal	Ketoconazole	Increased abnormal sperm, decreased sperm mobility	Rats	No		[17]	Oligospermia, azoopermia
Antihyperlipidemic agent	Rosuvastatin calcium[b]	Spermatidic giant cells	Dogs and monkeys	No		[18]	Reversible azoospermia
Anti-infective agent	Miconazole	Chromosomal aberrations in spermatocytes, morphological abnormalities in sperm	Mice	No		[19]	Reduced vitality
	Lindane	Reduced spermatids	Rats	No		[20, 21]	Decreased quality, AR
	Quinine sulfate	Atrophy or degeneration of the seminiferous tubules, decreased sperm count and motility	Mice	No		[22]	Decreased motility, altered semen volume
Antineoplastic agent	Busulfan[c]	Decreased spermatogenesis	Rats	Yes	Damaged sperm and testicular tissue, testicular atrophy, azoospermia	[23]	Decreased spermatogenesis
	Carmustine[c]	Testicular degeneration	Rats	No		[24]	Germ/Leydig cell failure
	Cyclophosphamide	Decreased weights, atrophy, changes in spermatogenesis	Mice and rats	Yes	Interference with spermatogenesis, testicular atrophy,	[25]	Azoospermia/oligospermia, decreased motility, abnormal morphology

Table 1 (continued)

Main category	Drug name (generic)	Effect(s) in animals	Type of animal(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Support in PubMed	Reported effect(s)
					azoospermia, oligospermia		
	Daunorubicin hydrochloride[c]	Testicular atrophy, aplasia of spermatocytes, complete aspermatogenesis	Dogs	No		[26]	Decreased sperm count, motility and vitality
	Doxorubicin hydrochloride[a, c]	Decreased testicular weights and hypospermia, diffuse degeneration of the seminiferous tubules, decreased spermatogenesis	Mice	No		[26, 27]	Damages DNA, decreased sperm count, motility and vitality
	Etoposide[c]	Testicular atrophy	Rats	No		[28]	Decrease in sperm count (possibly reversible)
	Fludarabine phosphate[b]	Decreased testicular weights, degeneration and necrosis of spermatogenic epithelium of the testes	Mice, rats and dogs	Yes	Damaged sperm and testicular tissue	[29]	DNA damage
	Hydroxyurea	Testicular atrophy, decreased spermatogenesis	Rats	No		[30]	Adverse effects on sperm production
	Ifosfamide (alphabetize)	Testicular atrophy with degeneration of the seminiferous tubular epithelium, decreased spermatogenesis	Dogs, rats	No		[31]	Sub-fertility, increased FSH and decreased inhibin-B
	Imatinib mesylate[b]	Decreased testicular and epididymal weights and percent motile sperm	Rats	No		[32]	Oligozoospermia
	Leuprolide acetate	Testicular interstitial cell adenomas	Rats	Yes	Suppressed testicular steroidogenesis, testicular atrophy	[33]	Decreased sperm count
	Temozolomide[b]	Testicular atrophy, syncytial cells/immature sperm formation	Rats and dogs	No		[34]	Decreased motiity, abnormal morphology
	Vincristine sulfate[c]	Testicular degeneration and atrophy, epididymal aspermia	Rats	No		[35]	Increased infertility
Antipsychotic	Risperidone[b]	Decreased sperm motility and concentration	Beagle dogs	No		[36]	Retrograde ejaculation
Antiulcer agent	Cimetidine	Benign Leydig cell tumors	Rats	No		[37]	Reduced sperm count, increased FSH and prolactin
Antiviral agent	Ribavirin	Abnormalities in sperm	Mice	No		[38]	Decreased density, motility and abnormal morphology
Cardiovascular agent	Nitroglycerin	Testicular tumors, increased interstitial cell tissue and aspermatogenesis	Rats	No		[39]	Reversible decrease in motility
Hormones, hormone substitutes, and hormone antagonists	Finasteride	Testicular Leydig cell adenomas, decreased weights of seminal vesicles and prostate	Mice, rabbits	Yes	Reversible decrease in ejaculate volume and sperm per ejaculation	[5]	Reversible decrease in number and motility
	Oxandrolone[b, c]	Reduction of spermatogenesis and decreased weights of the testes, prostate, and seminal vesicles	Rats	Yes	Suppressed spermatogenesis, testicular atrophy, epididymitis, oligozoospermia	[40]	Reversible azoospermia
	Testosterone	Suppressed spermatogenesis	Rats	Yes	Suppressed spermatogenesis, oligozoospermia	[41]	Decreased concentration
Hypoglycemic agent	Atorvastatin calcium		Rats	No		[42]	

Table 1 (continued)

Main category	Drug name (generic)	Effect(s) in animals	Type of animal(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Support in PubMed	Reported effect(s)
		Aplasia and aspermia in the epididymis, decreased sperm motility and concentration, and increased abnormal sperm					At least one abnormal parameter in 35% of men (number, viability, motility, morphology, etc.)
Immunosuppressive agent	Sirolimus	Atrophy of the testes, epididymides, prostate, and seminiferous tubules and/or reduction in sperm counts	Rats	Yes	Reversible azoospermia	[43]	Decreased concentration and motility

[a] PubMed data based on in vitro studies

[b] PubMed data based on small studies involving 10 or fewer patients, including case reports

[c] PubMed data based on studies of combination therapy, no data exist for the agent administered alone in humans

understanding that there are some inherent disadvantages associated with testing in animals [103].

Despite the various considerations made to improve the testing process and provide the best predictions of toxicity, there have been numerous studies that reported a lack of efficacy for toxicity testing, including reproductive toxicity testing [104–107]. In a previous study, a total of 65 labels for single-ingredient FDA-approved drugs were found in DailyMed that indicated that the drugs had a negative impact on human spermatogenesis [3]. In agreement with our present findings suggesting that animal studies have limited predictive power for human spermatotoxicity, fewer than half of the drug labels (26 of 65) indicated that they had effects on animal spermatogenesis. There was support in the literature for an additional six drugs affecting animal spermatogenesis, but this means that approximately half of the prescription drugs that negatively affect human spermatogenesis did not have an animal correlate reported in either the drug label or the peer-reviewed literature. This may reflect the inadequacy of the animal model(s) tested, insufficient testing, and/or ineffective reporting of the findings of animal studies.

The relationship between the reported effects in animals and the effects in humans

In the present study, approximately 17% of the single-ingredient, FDA-approved, clinically prescribed drugs included in the DailyMed database (235/1318) had an adverse effect on spermatogenesis in at least one animal. Less than 30% of these drugs have been reported to adversely affect human sperm (in either the drug warning label or the published literature included in PubMed). However, this finding does not indicate that the "false positive" rate of animal toxicity testing is > 70%, because there were no data in either database about the impact of more than half of the drugs on human sperm (see Table 2). Therefore, the "false positive" rate for animal testing of the drugs with reported findings was about 35% (33/93).

Interestingly, of the 33 drugs indicated to have negative effects in animals that were shown to have no effect or a positive impact on human sperm in the literature (Table 3), four had data in their FDA labels (included in the DailyMed database) indicating that they had a negative impact on human sperm. Since the DailyMed database is supposed to contain up-to-date information, it is possible that new data had been generated since the PubMed studies were published demonstrating the negative effect reported in the label.

It is also possible that there were differences in the experimental conditions (different ages of subjects, subjects of different ethnicities, subjects with different background diseases or stages of disease, or different timing of sample collection after administration, etc.), and these could have led to the different results. Because details were not present in the FDA labels included in the DailyMed database, it is unknown

Table 2 Drugs without clear information about the impact on men

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
Analgesic	Capsaicin	Reduction in the number and percent of motile sperm, reduced sperm counts	Rats	No		May affect motility by binding RPV1, but currently unproven	[45]
Anesthetic	Lidocaine hydrochloride monohydrate[a]	Decreased homogenization-resistant sperm head count, daily sperm production, and spermatogenic efficiency	Rats	No		Increases the spermicidal effects of other compounds	[46]
Antibacterial agent	Dapsone	Reduced sperm motility	Rats	Yes	Orchitis, infertility	No studies identified	
	Moxifloxacin/moxifloxacin hydrochloride	Adverse effects on sperm morphology (head-tail separation)	Rats	No		No studies identified	
	Telavancin hydrochloride	Altered sperm parameters	Rats	No		No studies identified	
	Cefotetan disodium	Reduced testicular weight and seminiferous tubule degeneration	Rats	No		No studies identified	
	Trovafloxacin mesylate	Testicular degeneration	Rats and dogs	No		No studies identified	
Anticholinergic agent	Glycopyrrolate	Diminished seminal secretions	Dogs	No		No studies identified	
Anticonvulsant	Clobazam	Increased abnormal sperm	Rats	No		No studies identified	
Antidepressant	Fluoxetine[a]	Testicular and epididymal microscopic lesions and decreased sperm concentrations	Rats	No		In vitro spermicidal effects	[47]
	Fluvoxamine maleate[a]	Decreased sperm count, decreased epididymal weight	Rats	Yes	Hematospermia	In vitro spermicidal effects	[47]
	Goserelin acetate	Atrophic histological changes in the testes, epididymis, seminal vesicles and prostate gland, suppressed spermatogenesis	Rats	No		No studies identified	
	Imipramine pamoate[a]	Atrophy of the seminiferous tubules, spermatogenic arrest	Dogs	No		Decreased viability and motility	[48]
	Methyldopa/methyldopate hydrochloride	Decreased sperm count, sperm motility, number of late spermatids	Rats	No		No studies identified	
	Nimodipine[a]	Leydig cell adenomas	Rats	No		Blocks the AR	[49]
	Selegiline	Epididymal and testicular hypoplasia, decreased sperm count and concentration	Dogs, rats	No		No studies identified	
	Trimipramine maleate	Degeneration of seminiferous tubules	Not specified	No		No studies identified	
	Nebivolol hydrochloride	Testicular Leydig cell hyperplasia and adenomas, effects on spermatogenesis	Mice and rats	No		No studies identified	
Antidote for ethylene glycol	Fomepizole	Decreased testicular mass	Rats	No		No studies identified	
Antiemetic	Dronabinol[a]	Decreases in spermatogenesis, number of developing germ cells, and number of Leydig cells	Rats	No		Decreased motility and AR	[50]
Antiepileptic	Felbamate	Benign interstitial cell tumors of the testes	Rats	No		A case report suggested that it was safe	[51]
	Rufinamide	Decreased sperm count and motility	Rats	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
Antihypertensive agent	Hydralazine hydrochloride	Benign interstitial cell tumors	Rats	No		No studies identified	
	Isradipine	Benign Leydig cell tumors and testicular hyperplasia	Rats	No		No studies identified	
	Eplerenone	Decreased weights of seminal vesicles and epididymides	Rats	No		No studies identified	
	Reserpine[a]	Malignant tumors of the seminal vesicles	Mice	No		Reduced motility and fertilization capacity	[52]
Anti-infective agent	Metronidazole[a]	Effects on testes and sperm production	Rats	No		Spermicidal	[53]
	Trimetrexate glucuronate	Degeneration of the testes and spermatocytes, spermatogenic arrest	Mice and rats	No		No studies identified	
	Linezolid	Reversible reductions in sperm motility and altered sperm morphology, epithelial cell hypertrophy in epididymis	Rats, dogs	No		No studies identified	
	Mefloquine hydrochloride	Histopathological lesions in the epididymides	Rats	No		No studies identified	
	Micafungin sodium	Vacuolation of epididymal ductal epithelial cells and reduced sperm count, seminiferous tubular atrophy and decreased epididymal sperm	Rats, dogs	No		No studies identified	
	Luliconazole	Decreased sperm counts	Rats	No		No studies identified	
	Miltefosine	Testicular Leydig cell adenoma, testicular atrophy, reduced numbers of viable sperm	Rats	No		No studies identified	
Anti-inflammatory agent	Suprofen	Testicular atrophy/hypoplasia	Rats	No		No studies identified	
	Celecoxib	Epididymal hypospermia, slight dilation of the seminiferous tubules	Juvenile rats	No		No studies identified	
	Zileuton	Benign Leydig cell tumors	Rats	No		No studies identified	
Antimigraine agents	Eletriptan hydrobromide	Testicular interstitial cell adenomas	Rats	No		No studies identified	
Antineoplastic agent	Abiraterone acetate	Testicular atrophy, aspermia/hypospermia, reduced sperm counts and motility, altered morphology	Rats and monkeys	No		Decreased testosterone and decreased weights of androgen-responsive organs in a xenograft fetal testis model	[54]
	Ado-trastuzumab emtansine	Degeneration of seminiferous tubules with hemorrhage in the testes, decreased weights of the epididymides, prostate, and seminal vesicles	Rats, monkeys	No		No studies identified	
	Afatinib	Oligo- or azoospermia, increased apoptosis in the testes and atrophy in the seminal vesicles and prostate	Rats	No		No studies identified	
	Alemtuzumab	Adverse effects on sperm parameters, decreased sperm count and motility	Transgenic mice	No		The target of the antibody (CD52) may have homology with gp20 on the sperm membrane, but the clinical impact is unknown	[55]

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
	Altretamine	Testicular atrophy, decreased spermatogenesis, atrophy of testes, seminal vesicles and ventral prostate	Rats	No		No studies identified	
	Asparaginase	Decreased sperm count and motility	Rats	No		No studies identified	
	Axitinib	Testicular atrophy, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, reduced sperm density and count	Rats	No		No studies identified	
	Belinostat	Reduced organ weights of the testes/epididymides, delay in testicular maturation	Dogs	No		No studies identified	
	Bexarotene	Testicular degeneration	Dogs	No		No studies identified	
	Bortezomib	Degenerative changes in the testes	Rats	No		No studies identified	
	Brentuximab vedotin	Seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis or aspermia	Rats	No		No studies identified	
	Cabazitaxel	Degeneration of seminal vesicles and seminiferous tubule atrophy, minimal epithelial single cell necrosis in epididymis	Rats, dogs	No		No studies identified	
	Cabozantinib	Decreased sperm counts and reproductive organ weights, testicular degeneration and decreased spermatocytes and spermatids	Rats, mice	No		No studies identified	
	Chlorpromazine[a]	Chromosomal aberrations in spermatocytes and abnormal sperm	Rodents	No		Decreased motility	[56]
	Cladribine	Testicular degeneration	Monkeys	No		No studies identified	
	Clofarabine	Seminiferous tubule and testicular degeneration, atrophy of interstitial cells	Mice, rats and dogs	No		No studies identified	
	Cobimetinib	Testicular degeneration	Dogs	No		No studies identified	
	Crizotinib	Testicular pachytene spermatocyte degeneration	Rats	No		No studies identified	
	Dabrafenib	Testicular degeneration/depletion	Rats and dogs	Yes	Impaired spermatogenesis, decreased sperm count	No studies identified	
	Decitabine	Abnormal histology, decreased sperm number	Mice	No		No studies identified	
	Docetaxel	Testicular atrophy or degeneration	Dogs	No		No studies identified	
	Enzalutamide	Atrophy of the prostate and seminal vesicles	Rats	No		No studies identified	
	Eribulin mesylate	Testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia)	Rats and dogs	No		No studies identified	
	Everolimus		Rats	Yes			[57]

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
		Decreased sperm motility, sperm count, and plasma testosterone levels			Azoospermia or oligozoospermia (< 1% of patients)	Increases testosterone, but clinical impact unclear	
	Fulvestrant	Testicular Leydig cell tumors, loss of spermatozoa from seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides	Rats	No		No studies identified	
	Gemcitabine hydrochloride	Hypospermatogenesis	Mice	No		No studies identified	
	Idarubicin	Testicular atrophy, inhibition of spermatogenesis and sperm maturation with few or no mature sperm	Dogs	No		No studies identified	
	Idelalisib	Decreased epididymidal and testicular weights, reduced sperm concentration	Rats	No		No studies identified	
	Irinotecan hydrochloride	Atrophy of male reproductive organs	Rodents	No		No studies identified	
	Ixabepilone	Testicular atrophy or degeneration	Dogs	No		No studies identified	
	Lenvatinib	Testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides	Dogs	No		No studies identified	
	Nilutamide	Benign Leydig cell tumors	Rats	Yes	Testicular atrophy	No studies identified	
	Omacetaxine mepesuccinate	Degeneration of the seminiferous tubular epithelium, hypospermia/aspermia in the epididymides	Mice	No		No studies identified	
	Oxaliplatin	Testicular degeneration, hypoplasia, and atrophy	Dogs	No		Reduced inhibin-B (predictive of poor spermatogenesis and infertility)	[58]
	Palbociclib	Decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density	Rats and dogs	No		No studies identified	
	Panobinostat	Prostate atrophy accompanied by reduced secretory granules, testicular degeneration, oligospermia, and increased epididymal debris	Dogs	No		No studies identified	
	Pazopanib hydrochloride	Reduced sperm production and testicular sperm concentrations, epididymal sperm concentrations and sperm motility, atrophy and degeneration of the testes, aspermia, hypospermia, and cribiform changes in the epididymis	Rats	No		No studies identified	
	Pemetrexed disodium	Reduced fertility, hypospermia, and testicular atrophy	Mice	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
	Pentostatin	Seminiferous tubular degeneration	Dogs	No		No studies identified	
	Ponatinib	Degeneration of the epithelium of the testes	Rats and monkeys	No		No studies identified	
	Porfimer sodium	Discoloration and hypertrophy of the testes	Rats	No		No studies identified	
	Regorafenib	Tubular atrophy and degeneration in the testes, atrophy in the seminal vesicle, and cellular debris and oligospermia in the epididymides	Rats	No		No studies identified	
	Romidepsin	Testicular degeneration	Rats	No		No studies identified	
	Sorafenib	Testicular atrophy or degeneration; degeneration of the epididymis, prostate, and seminal vesicles; oligospermia	Rats, dogs	No		No studies identified	
	Topotecan	Multinucleated spermatogonial giant cells	Dogs	No		No studies identified	
	Trabectedin	Histopathological signs of hemorrhage and degeneration in the testes	Rats	No		No studies identified	
	Trifluoperazine[a]	Chromosomal aberrations in spermatocytes and abnormal sperm	Rodents	No		Decreased motility	[49]
	Valrubicin	Testicular degeneration, germ cell depletion, spermatid giant cells and karyomegaly	Dogs	No		No studies identified	
	Venetoclax	Testicular toxicity (germ cell loss)	Dogs	No		No studies identified	
	Vinorelbine	Decreased spermatogenesis and prostate/seminal vesicle secretions	Rats	Yes	Damage to spermatozoa	No studies identified	
	Vismodegib	Decreased % motile sperm, hypospermia, germ cell degeneration	Rats, dogs	No		Present in semen, but impact unclear	[59]
	Ziv-aflibercept	Decreased sperm motility, alterations in sperm morphology	Monkeys	No		No studies identified	
Anti-osteoporosis agents	Risedronate sodium	Testicular and epididymal atrophy	Rats	No		No studies identified	
Anti-Parkinson agent	Apomorphine hydrochloride	Leydig cell tumors	Rats	No		No studies identified	
	Ropinirole hydrochloride	Testicular Leydig cell adenomas	Rats	No		No studies identified	
	Rotigotine	Leydig cell tumors, decreased epididymal sperm motility	Rats	No		No studies identified	
	Pimavanserin tartrate	Decreased density and motility of sperm, cytoplasmic vacuolation in the epididymis	Rats	No		No studies identified	
Antipsychotic agent	Aripiprazole/aripiprazole lauroxil	Disturbances in spermatogenesis	Rats	No		No studies identified	
	Paliperidone/paliperidone palmitate	Decreased sperm motility and concentration	Beagle dogs	No		No studies identified	
	Prochlorperazine edisylate/-prochlorperazine maleate	Chromosomal aberrations in spermatocytes and abnormal sperm	Rodents	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
Antituberculosis agent/anti--infectious	Rifabutin	Testicular atrophy	Baboons and rats	No		No studies identified	
Antiulcer	Dexlansoprazole	Testicular interstitial cell adenomas	Rats	No		No studies identified	
	Lansoprazole	Testicular interstitial cell adenomas, proliferative changes in the Leydig cells, including benign neoplasia	Rats	No		No studies identified	
Antiviral agent	Boceprevir	Testicular degeneration	Rats	No		No studies identified	
	Cidofovir	Inhibition of spermatogenesis	Rats and monkeys	No		No studies identified	
	Daclatasvir	Reduced prostate/seminal vesicle weights, minimally increased dysmorphic sperm	Rats	No		No studies identified	
	Entecavir	Seminiferous tubular degeneration	Rodents and dogs	No		No studies identified	
	Famciclovir	Atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility	Rats, mice and dogs	No		No studies identified	
	Ganciclovir	Hypospermatogenesis	Mice, dogs	Yes	Testicular hypotrophy, aspermatogen-esis (dose--dependent)	No studies identified	
	Penciclovir	Atrophy of the seminiferous tubules, increased sperm with abnormal morphology, reduced motility	Rats and dogs	No		No studies identified	
	Trifluridine	Testicular atrophy	Mice	No		No studies identified	
	Valganciclovir	Hypospermatogenesis	Mice, rats and dogs	Yes	Inhibited spermatogene-sis	No studies identified	
Attention deficient disorder agent	Atomoxetine hydrochloride	Decreased epididymal weight and sperm number	Rats	No		No studies identified	
Bone density conservation agent	Ibandronate sodium	Decreased sperm production and altered sperm morphology	Rats	No		No studies identified	
Cardiovascular agent	Dexrazoxane	Testicular atrophy	Rats	No		No studies identified	
	Naratriptan hydrochloride	Testicular/epididymal atrophy accompanied by spermatozoa depletion	Rats	No		No studies identified	
	Propafenone hydrochloride	Decreased spermatogenesis	Rabbits, dogs, and monkeys	No		No studies identified	
	Ambrisentan	Testicular tubular degeneration, effects on the sperm count and morphology	Rats and mice	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
	Bosentan	Testicular tubular atrophy	Rodents	Yes	Decreased sperm count	No studies identified	
	Dofetilide	Testicular atrophy and epididymal oligospermia	Rats, mice and dogs	No		No studies identified	
	Spironolactone	Testicular interstitial cell tumors	Rats	No		2/9 men showed decreased sperm density, but overall, no significant difference	[60]
	Macitentan	Testicular tubular atrophy	Rats	No		No studies identified	
Central nervous system agent	Carisoprodol	Reduced testes weight and sperm motility	Mice	No		No studies identified	
	Eszopiclone	Decreased sperm number and motility, increase in morphologically abnormal sperm (mid and high doses)	Rats	No		No studies identified	
	Fentanyl citrate[a]	Decreased percent mobile sperm, sperm concentrations, increased abnormal sperm	Rats	No		Modest inhibition of motility (based on a CASA)	[61]
	Oxazepam	Testicular interstitial cell adenomas	Rats	No			
	Caffeine citrate	Spermatogenic cell degeneration	Rats	No		Different studies have shown conflicting (potentially dose-related) effects	[62, 63]
Contrast medium	Gadobenate dimeglumine	Abnormal spermatogenic cells	Rats	No		No studies identified	
	Gadopentetate dimeglumine	Decreased testes and epididymis weights	Rats	No		No studies identified	
	Gadoversetamide	Reduction and degeneration of spermatocytes, degeneration of the germinal epithelium of the testes, presence of germ cells in the epididymides, reduced sperm count	Rats	No		No studies identified	
Dermatological agent	Dimethyl fumarate	Leydig cell adenomas, increased nonmotile sperm, testicular atrophy, hypospermia, testicular hyperplasia	Mice, rats, and dogs	No		No studies identified	
	Tretinoin	Decreased sperm count and motility	Rats	No		Other retinoids had no effect on sperm	[64]
Dispersing agent	Hyaluronidase, ovine	Testicular degeneration	Not specified	No		The hyaluronidase level is associated with the fertilization rate, but the clinical impact of systemic or nonreproductive treatment is unclear	[65]
Enzyme inhibitor	Eliglustat	Adverse effects on sperm morphology, testes (germ cell necrosis), and sloughed cells in the epididymis	Rats	No		No studies identified	
	Tofacitinib	Benign Leydig cell tumors	Rats	No		No studies identified	
Epithelial growth factor	Palifermin	Decreased epididymal sperm counts	Rats	No		No studies identified	
	Desloratadine	Decreased sperm numbers and motility	Rats	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
Histamine antagonist							
Hormones, hormone substitutes, and hormone antagonists	Conjugated estrogens, estradiol, estradiol acetate, estradiol cypionate	Increased frequency of carcinomas of testis	Not specified	No		Estrogen decreases the acrosome reaction in vitro, but is required for normal sperm production. Therefore, effects are likely concentration-dependent	[66, 67]
	Estropipate	Increased frequency of carcinomas of testis	Not specified	No		No studies identified	
	Flutamide	Testicular interstitial cell adenomas of the testes	Rats	Yes	Interference with testosterone, decreased sperm count	Unclear, suggested to have minimal transient effects on sperm	[68]
	Ospemifene	Atrophy of the prostate and seminal vesicles	Rats	No		No studies identified	
	Histrelin acetate	Testicular Leydig cell tumors	Rats	Yes	Testicular atrophy	No studies identified	
Hypnotic agent	Doxepin hydrochloride	Increased percentages of abnormal sperm and decreased sperm motility	Rats	No		No studies identified	
	Ramelteon	Benign Leydig cell tumors	Rats	No		No studies identified	
	Rozerem	Leydig cell tumors	Rats	No		No studies identified	
Hypoglycemic agent	Acarbose	Benign Leydig cell tumors	Rats	No		No studies identified	
	Canagliflozin	Testicular Leydig cell tumors, decreased sperm velocity, increased number of abnormal sperm	Rats	No		No studies identified	
	Chlorpropamide	Suppression of spermatogenesis	Rats	No		No studies identified	
	Fenofibrate/fenofibric acid	Benign testicular interstitial cell tumors	Rats	No		No studies identified	
	Fluvastatin sodium	Tubular degeneration and aspermatogenesis in testes, vesiculitis of seminal vesicles	Hamsters, rats	No		No studies identified	
	Mifepristone[a]	Reduced testicular size	Rats	No		Decreased AR	[69]
Immunosuppressive agent	Azathioprine sodium	Reduced spermatogenesis, sperm viability and sperm count	Mice	No		Conflicting findings, may be age-dependent or related to the disease status	[70, 71]
Immunological factor	Interferon gamma-1b	Decreased spermatogenesis and sperm counts, increased abnormal sperm (very high doses)	Mice and monkeys	No		Effect of local or systemic treatment unclear, but no effect on sperm treated in vitro	[72]
	Pimecrolimus	Decreased testicular and epididymal weights, testicular sperm counts, motile sperm	Rats	No		Other mTOR inhibitors had adverse effects	[43]
	Teriflunomide	Reduced epididymal sperm count	Rats	No			
	Thalidomide	Testicular pathological and histopathological effects	Rabbits	Yes	Orchitis	Present in semen, but impact unclear	[73]
Muscle relaxant agent	Dantrolene sodium	Testicular tumors	Rats	No		No studies identified	

Table 2 (continued)

Drug category	Generic name	Effect(s) on animal spermatogenesis	Animal type(s) affected	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Notes based on the PubMed search	PubMed reference(s)
Ophthalmic drug	Aflibercept	Changes in sperm morphology and motility	Monkeys	No		No studies identified	
PDE5 inhibitor	Avanafil	Reduced sperm motility, increased percentage of abnormal sperm (broken sperm with detached heads)	Rats	No		No studies identified	
PDE4 inhibitor	Roflumilast	Tubular atrophy, degeneration in the testes and spermiogenic granuloma in the epididymides	Rats	No		No studies identified	
Purgative agent	Lubiprostone	Interstitial cell adenoma of the testes	Rats	No		No studies identified	
	Naloxegol oxalate	Leydig cell adenomas	Rats	No		No studies identified	

[a] PubMed data based on in vitro studies

why there were conflicting data. These findings illustrate the difficulties associated with reproductive toxicity testing. Moreover, they demonstrate the need for better record-keeping and transparency in terms of the data generated, because it is very difficult to interpret the findings in the drug labels based on the data available.

Difficulties associated with animal testing for spermatotoxicity

The current reproductive toxicity testing should be able to provide useful results for clinical extrapolation. However, as noted above, our current study and previous studies about spermatotoxicity [3, 105, 106] have shown that studies in animals have relatively low predictive value for human toxicity. In some cases, the lack of useful findings is due to the high doses of the compounds used in the toxicity studies. Nevertheless, even if the dose is proper in terms of the allometric scaling for animals based on body surface area (~ 12× the human dose (mg/kg b.w.) for a mouse, ~ 2× for a dog, etc. [108]), the plethora of differences between humans and animals reduces the utility of the findings. For example, the pharmacokinetics and pharmacodynamics of drugs may not be similar between the animal model and humans, there may be organ/tissue-related differences that make it impossible to adequately predict or extrapolate the effects, and there may be other fundamental differences between species that abrogate the utility of testing [106]. This is particularly relevant for spermatotoxicity studies, where there are many important differences between rodents and humans, including the time required for spermatogenesis, the development of Leydig cell tumors, and the relative number of sperm produced [109–112]. Additional "uncertainty" factors have been used when extrapolating human toxicity from animal findings for occupational and environmental toxicants (i.e., when determining the benchmark dose or the acceptable daily intake based on the no observed adverse effects level (NOAEL) [113], but these types of studies are not usually employed as part of therapeutic drug testing and would be subject to the same issues described above.

Changes that should be made to the testing and reporting of spermatotoxicity

The most important findings of the present study include the following: only 27% (63/235) of the drugs that had a negative effect in animals reported in the drug label were found to have a documented negative impact on human sperm (in the drug labels or literature). Further, a previous study [3] showed that fewer than half of the drugs with labels indicating that they adversely affected human sperm had similar findings in animals. In addition, for more than half of the drugs found to negatively affect animal spermatogenesis or spermatozoa,

Table 3 Drugs where the animal findings were refuted by PubMed publications

Main indication	Drug name (generic)	Effect(s) in animals	Type of animal(s) affected/tested	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Effect(s) in humans reported in PubMed	PubMed reference
Adrenergic agent	Icatibant acetate[a]	Testicular atrophy/degeneration, reduced sperm counts	Rats and dogs	No		No effect	[74]
Antibacterial agent	Doxycycline/doxycycline hyclate	Reduced motility, velocity and concentration, abnormal morphology	Rats	No		May improve sperm parameters in patients with infections	[75]
	Clarithromycin	Testicular atrophy	Rats and monkeys	No		Improves motility	[76]
Antiepileptic	Pregabalin	Decreased sperm counts and sperm motility, increased sperm abnormalities	Rats	Yes	Epidiymitis	No effect	[77]
Antigout agent	Colchicine/colchicinum	Abnormal sperm morphology and reduced sperm counts in males	Not specified	Yes	Azoospermia, oligospermia	No effect	[78]
Antihyperlipidemic agent	Pravastatin sodium	Sperm abnormalities	Rats	No		No effect	[79]
Antihypertensive agent	Metoprolol	Reversible adverse effects of spermatogenesis (in some studies)	Rats	No		Minimally inhibits motility	[80]
	Pindolol	Testicular atrophy and/or decreased spermatogenesis	Rats	No		No effect	[80]
	Prazosin[a]	Testicular changes consisting of atrophy and necrosis	Rats and dogs	No		No effect	[81]
Anti-infective agent	Griseofulvin[b]	Suppression of spermatogenesis	Rats	No		No effect	[82]
	Minocycline hydrochloride	Reduced sperm cells and motile sperm, increased abnormal sperm, including absent heads, misshapen heads and abnormal flagella	Rats	No		Improves semen parameters in men with infections	[83]
	Tinidazole	Testicular degeneration, spermatogenic effects	Rats	No		Improves sperm parameters as part of treatment for *H. pylori* infections	[76]
Anti-inflammatory agent	Ketoprofen	Abnormal spermatogenesis or inhibition of spermatogenesis	Rats and dogs	No		Treatment may improve male infertility	[84]
	Oxaprozin	Testicular degeneration	Beagle dogs	No		No effect	[85]
Antineoplastic agent	Bicalutamide	Testicular benign interstitial (Leydig) cell tumors	Rats	No		No effect	[86]
	Dasatinib	Reduced size and secretion of seminal vesicles, immature prostate, seminal vesicle, and testis	Rats	No		No effect	[87]
	Epirubicin hydrochloride[c]	Atrophy of the testes and epididymis, reduced spermatogenesis	Mice and rats	No		No effect	[88]
	Fluorouracil[a]	Kills differentiated spermatogonia and spermatocytes	Mice	No		No effect	[89]
	Letrozole	Degeneration of the seminiferous tubular epithelium	Rats	No		Improves sperm parameters as part of treatment for *H. pylori* infections	[90]
	Paclitaxel[c]	Testicular atrophy/degeneration	Rodents	No		No effect	[91]
	Toremifene citrate	Testicular tumors	Mice	No		Improves sperm parameters and hormone levels	[92]
Antiviral agent	Acyclovir	Testicular atrophy and aspermatogenesis	Rats and dogs	No		No effect	[93]
	Miglustat		Rats	No		No effect	[94]

Table 3 (continued)

Main indication	Drug name (generic)	Effect(s) in animals	Type of animal(s) affected/tested	Human toxicity in DailyMed?	Reported effect(s) in humans (DailyMed)	Effect(s) in humans reported in PubMed	PubMed reference
		Decreased spermatogenesis with altered sperm morphology and motility, decreased fertility, and testicular interstitial cell adenomas					
	Tenofovir	None	Rats	No		Decreased progressive motility	[95]
Bone density conservation agent	Raloxifene hydrochloride	Testicular interstitial cell tumors	Mice			Improves sperm concentration and morphology and increased testosterone in oligospermic med	[96]
Cholinergic agonist	Pilocarpine	Decreased sperm motility, and morphologic evidence of abnormal sperm	Rats	No		No effect	[97]
Dermatological agent	Clobetasol propionate	Increased weights of the seminal vesicles	Rats	No		Treatment of scrotal dermatitis improved the sperm count and motility	[98]
	Isotretinoin	Depression of spermatogenesis	Dogs	No		No effect	[64]
Hypoglycemic agent	Simvastatin	Seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium, testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell	Rats Dogs	No		No effect	[79]
	Lovastatin	Testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, giant cell formation	Dogs	No		No effect	[99]
Opioid antagonist	Naltrexone[a]	Increased testicular mesotheliomas	Rats	No		Increased motility (opposite the effects of morphine)	[100]
	Tadalafil	Degeneration and atrophy of the seminiferous tubular epithelium, decrease in spermatogenesis	Beagle dogs	Yes	Decreased sperm concentration	Improves concentration and motility	[101]

[a] Based on in vitro findings

[b] Based on small studies of < 10 patients, including case studies

[c] Based on studies of combination treatment

the impact in humans is unclear either because no testing or surveillance has been performed, or because the results have not been reported. Even in cases where there was clear reporting of the type of human spermatotoxicity and the number of individuals affected, the data were frequently unclear regarding whether the effects were reversible and how long it took to recover potency. These findings suggest that the current system is not performing well and there is a need for better models, different types of pre-clinical testing, different endpoints, and a better system (and/or different regulations) for reporting data.

It should be noted that most of the general methods used to assess reproductive toxicity were often developed more than 50 years ago, although there have been updates in terms of automation and some of the details (i.e., sub-types of sperm motility) of the analyses. Our data add to the already extensive body of evidence that animal testing (certainly for spermatotoxicity, but also for many other types of toxicity) is not adequate to predict human risk. However, completely retiring the rat is not possible, at least at present. There are currently no other models that provide better predictive value for the various steps of reproduction. Direct testing on human sperm samples is useful and should be implemented whenever possible, but cannot identify changes in hormone levels, reproductive tissues, or germ or support cells. These parameters can only be evaluated in vivo.

While animal testing cannot be avoided at present, there are various steps that should be taken immediately to improve the efficacy and clinical relevance of the testing and reporting of data. First, the general protocol for testing should be reconsidered. The usual one-size-fits-all approach to toxicity testing should be scrapped in favor of integrative studies taking into account the differences in pharmacokinetics/pharmacodynamics of the drug (if known), the intended target population (the age and disease background of the patients may be relevant to the toxicity), the effects of structurally and mechanistically similar drugs, and any information that can be obtained from in silico studies (high-throughput testing of the compound's predicted structure for interactions with characterized receptors and biomacromolecules). It may also be necessary to change the endpoints of studies. Instead of assessing sperm at a single time point (at a pre-specified time after a single dose, or at the end of a chronic study), it would likely be better to collect sperm at several different time points. Collection of multiple samples (including collection on more than 1 day prior to starting treatment) is particularly important for clinical trials given the high variability in human sperm production [111, 114]. Additional testing to confirm recovery would provide helpful information for counseling patients on the long-term adverse effects.

Perhaps the most important changes would be those made to the reporting of the findings. Although the FDA receives the full results of the pre-clinical toxicity studies and clinical safety studies, including the numbers of animals used for pre-clinical testing (or patients included in a clinical trial), this information is frequently lacking from the drug labels in DailyMed. A clear statement of the number of individuals evaluated and the number or percentage of these affected by each adverse effect would help to interpret the findings. It would also be useful for this information to specify the extent of the adverse impact, such as the exact percentages of sperm with abnormal morphology, rather than a blanket statement indicating that there were morphological changes. This information would not need to appear on the main drug label included with the packaging of each drug, but should be linked online (with the link included in the printed information) so that the full details of the study are readily available from DailyMed.

Another point that is commonly lacking in both the DailyMed labels and the data in journal articles is the reversibility of the spermatotoxicity and time to recovery (if recovery is possible). This information is frequently missing for pre-clinical studies, largely because sperm are usually collected at a single time point, sometimes at necropsy. Although clinical trials are more likely to assess the long-term effects of a drug, the long-term reproductive outcomes are often not evaluated. This is partly because such endpoints are difficult to add to standard surveillance protocols because the collection of semen is more invasive and potentially associated with ethical concerns, compared to physical examinations and blood collection.

Finally, computing power has been rapidly increasing during the past few decades, and research studies are helping to illuminate the molecular basis of various physiological processes. Therefore, efforts should be made to better understand the signaling and cellular interactions involved in normal fertility to permit in silico modeling of possible interference by investigational drugs. This would inform confirmatory studies to be performed in vitro on human sperm or iPSC-derived or other sources of germ cells, could suggest biomarkers to allow for more sensitive detection of effects in vivo (in animals and/or humans), and would predict the toxicity likely to be encountered. As in silico modeling continues to improve, it may become possible to evaluate the interactions of various agents and various pathways simultaneously and to combine such findings with those from in vitro and limited in vivo studies for an integrated approach, more accurately predicting the effects in humans [115, 116].

Until toxicity testing is optimized, it is necessary to consider that there is a potential for human risk whenever there is a positive finding of spermatotoxicity in non-clinical or pre-clinical studies for one or more endpoints. The details of the findings and the level of evidence should be included to help physicians and/or pharmacists inform their patients of the risks of specific treatments to their fertility.

Conclusion

Our present findings illustrate the status of male reproductive toxicity testing and provide a useful reference about the FDA-approved drugs known to affect animal spermatogenesis and how these findings correlate with the human clinical setting. These findings emphasize the need for a better understanding of basic sperm biology to allow for the prediction of spermatotoxicity based on a drug's effects (both targeted and nonspecific). A greater understanding of the normal variations in the sperm of men of various ages and different health status would also help to understand what should be considered abnormal during clinical trials and long-term surveillance. In addition, since the predictive value of animal testing is so low, there is a need for a more comprehensive evaluation of the effects on human sperm in vitro and continued development of in silico and alternative in vitro studies so that potential changes can be estimated before the initiation of human clinical trials. Such an understanding could be used to determine whether the normal observations carried out during clinical trials should be increased or altered to better detect changes.

There are several limitations to this review that should be noted. First, only single-ingredient, FDA-approved drugs indicated for human use that were included in the DailyMed database were analyzed in this study. Although this database is the largest of its type, there are still a few drugs for which information is missing. In addition, all over-the-counter medications, including vitamins, supplements, and herbal/alternative medications, were excluded because the toxicity information on these agents is typically lacking. However, these excluded agents may be associated with spermatotoxicity, either when taken alone or by potentiating the effects of other drugs. The present investigation also focused on the direct effects of drugs on spermatozoa, which represents only a small aspect of male fertility. In addition, there may have been some reporting or publication bias for the databases. However, whenever possible, only large and well-designed clinical trials were included for the PubMed data, and it is noted whenever small-scale studies or case reports are cited in the tables. For the DailyMed database, the data sources are often unclear, so the accuracy of the data is also unclear.

Despite these limitations, the present data are useful in that they provide a comprehensive overview of the prescription drugs that affect animal spermatogenesis, as well as an illustration of the relatively poor performance of animal testing for predicting spermatotoxicity. Several suggestions have been made which might improve the testing and reporting of the data, hopefully leading to better patient care.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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