Review Article

Cannabis and Male Fertility: A Systematic Review

Kelly S. Payne, Daniel J. Mazur, James M. Hotaling and Alexander W. Pastuszak*,†

From the Baylor College of Medicine (KSP), Houston, Texas, Urology Associates (DJM), Englewood, Colorado, and Division of Urology, Department of Surgery, University of Utah School of Medicine (JMH, AWP), Salt Lake City, Utah

Abbreviations and Acronyms

AEA = anandamide
CB1 = cannabinoid receptor 1
CB2 = cannabinoid receptor 2
ED = erectile dysfunction
FSH = follicle stimulating hormone
LH = luteinizing hormone
Met-AEA = methanandamide
THC = Δ-9-tetrahydrocannabinol

Accepted for publication November 14, 2018.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by a National Institutes of Health K08 Scholar Award supported by Mentored Career Development Award K08DK115835-01 from the National Institute of Diabetes and Digestive and Kidney Diseases, and in part by a Urology Care Foundation Rising Stars in Urology Award (AWP).

No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

* Correspondence: Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Room 3B420, Salt Lake City, Utah 84132 (email: alexander.pastuszak@hsc.utah.edu).

† Financial interest and/or other relationship with Endo Pharmaceuticals.

Purpose: With cannabis consumption on the rise and use prominent among males of reproductive age it is essential to understand the potential impact of cannabis on male fertility. We reviewed the literature regarding the effects of cannabis on male fertility.

Materials and Methods: We performed a literature search using PubMed®/MEDLINE® to identify relevant studies of the effects of cannabis on male fertility. Relevant studies were identified and reviewed.

Results: The strongest evidence of cannabis induced alterations in male fertility is in the category of semen parameters. Research supports a role for cannabis in reducing sperm count and concentration, inducing abnormalities in sperm morphology, reducing sperm motility and viability, and inhibiting capacitation and fertilizing capacity. Animal models demonstrate a role for cannabis in testicular atrophy, and reduced libido and sexual function but to our knowledge these results have not yet been replicated in human studies. Studies of hormonal changes suggest inconclusive effects on testosterone levels, lowered luteinizing hormone levels and unchanged follicle-stimulating hormone levels.

Conclusions: Current research suggests that cannabis may negatively impact male fertility. Further studies are needed to validate that robust findings in animal models will carry over into human experience. Clinicians should be aware of these potential effects when prescribing medical marijuana therapies to men of reproductive age, and they should consider the degree of cannabis use as a possible component of a complete male infertility workup.

Key Words: testis; cannabis; infertility, male; spermatozoa; erectile dysfunction

MARIJUANA is a drug derived from the hemp plant *Cannabis sativa* or *Cannabis indica*.[1] Its main psychoactive component is THC, which is linked to altered sensual perception, mood changes and impaired body movement.[1] Sweeping legalization reforms in the United States in the last decade have broadly expanded access to marijuana, such that 8 states have legalized marijuana for recreational use while an additional 19 states permit marijuana for medical purposes.[2]

Cannabis binds to the CB1 and CB2 G protein-coupled cannabinoid receptors, which are the sites of action of endogenous endocannabinoids.[3] This signaling system is involved in a broad array of functions, including energy homeostasis, memory, movement and pain.[4] Exocannabinoids such as cannabis plant derived THC modulate cannabinoid receptors, likely interfering with the balance of downstream endogenous signaling pathways.[5]

Studies to date have broadly demonstrated the presence of cannabinoid

0022-5347/19/2024-0674/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000000248
Vol. 202, 674-681, October 2019
Printed in U.S.A.

receptors on sperm, suggesting that cannabis has the potential to disrupt sperm function.[4,6]

Medical cannabis has been used as an experimental remedy with varying degrees of success in a large number of disorders, including dementia, multiple sclerosis, Parkinson disease, social anxiety disorder, depression, tobacco use disorder and neuropathic pain.[7] Despite its growing popularity in the recreational and medical spheres, considerable research is still needed to understand the potential negative effects of marijuana. Particularly in the area of male fertility cannabis use has been linked to reproductive hormone changes, altered semen parameters and reductions in libido and sexual performance.[8] A detailed review of how marijuana affects male fertility at each point along the fertility axis is needed for clinicians to assess the potential risks that patients incur when using this substance.

To examine whether cannabis alters male fertility we systematically reviewed current literature comparing hormone levels, semen parameters, gonadal size and sexual function between subjects using cannabis and noncannabis using controls.

MATERIALS AND METHODS

We systematically reviewed the literature to identify relevant studies of how cannabis affects male fertility. We performed a PubMed®/MEDLINE® search in May 2018 using certain MeSH terms in combination with cannabis and in combination with marijuana, including cannabinoid receptors, CB1, CB2, sperm count, sperm concentration, sperm morphology, sperm motility, sperm energy metabolism, sperm viability, sperm fertilization capacity, sperm capacitation reaction, sperm acrosome reaction, follicle stimulating hormone, luteinizing hormone, testosterone, estrogen, testicular size, testicular weight, sexual drive and erectile dysfunction. These search terms were chosen to reflect the various points of male sexual dysfunction which may contribute to infertility. The literature search was limited to English publications or publications translated into English and databases were searched from the date of inception to May 2018.

We included animal and human studies in which primary data were gathered or retrospective analyses were done. Reviews, meta-analyses and unpublished material were excluded from analysis. Article titles and abstracts were reviewed in an unblinded manner to determine eligibility and relevance, and 48 selected studies were included.

Information was extracted from each study based on 1) study participant characteristics, including human or animal status and the previous level of cannabis exposure; 2) intervention type, including acute or chronic marijuana administration and prospective vs retrospective analysis; and 3) outcome measure type, including sperm viability, sperm motility, gonadal size and mating behaviors. Supplementary Appendix 1 (https://www.jurology.com) provides summary data on all surveyed literature regarding sperm parameters. Supplementary Appendix 2 (https://www.jurology.com) provides summary data on all surveyed literature regarding changes to the hormonal axis.

CANNABIS EFFECTS ON SPERM PARAMETERS

Count and Concentration

Cannabis use is strongly associated with reductions in sperm count and concentration in animal and human studies. Decreased epididymal sperm concentrations were observed in mature male rats exposed to 16 puffs per day of marijuana, comparable to the recreational level in humans, for 75 days.[9] This effect was replicated in a study in which 3 to 6 mg/kg of the *Cannabis sativa* derivative bhang was administered in adult male mice, which demonstrated a significantly depressed sperm count ($p < 0.05$).[10] Echoing these observations in rodents, daily administration of cannabis at a rate of 12.5 mg/kg for 30 days in dogs was associated with complete spermatogenesis arrest.[11]

Human studies have shown similar findings. In 20 chronic marijuana users who smoked marijuana at least 4 days per week for 6 months those who smoked 10 or more times per week had a significantly lower average $\pm$ SD sperm count than men who smoked 5 to 9 marijuana cigarettes per week (26.6 ± 7.3 vs 67.9 ± 6.3 million per ml, $p < 0.01$).[12] This suggests an inverse relationship between marijuana use and sperm count. A Danish cohort study on marijuana use in 1,215 participants revealed similar changes.[13] Men who reported using marijuana more than once per week had a 28% lower sperm concentration and a 29% lower sperm count than men who had never used marijuana. In a study in which 16 chronic marijuana smokers were exposed to 4 weeks of high dose marijuana the time to a reduced sperm count was 5 to 6 weeks after initiating marijuana use.[14] In human and animal models cannabis has shown strong links to reduced sperm count and concentration which may be linked to arrested spermatogenesis. Future work is needed to elucidate causal mechanisms.

Morphology

Cannabis use also appears to induce considerable morphological changes in sperm. In a 1978 study Zimmerman et al treated male mice for 5 consecutive days with intraperitoneal injections of the marijuana components THC, cannabinoid or cannabinol.[15] On microscopy 35 days after exposure mice treated with THC and cannabinol had a significantly higher incidence of abnormal morphology than the control group, such as banana-shaped, amorphous, folded or hookless heads. In another study rats given inhaled marijuana demonstrated similar changes in sperm with increased detachment of sperm heads from

tails.[9] These findings were expanded by a prospective, 1,700 unmatched case reference study of men in the United Kingdom presenting at a total of 14 fertility clinics.[16] Men who had used cannabis in the 3 months prior to collection of a semen sample and were younger than 30 years were more likely to be in the category of abnormal sperm morphology, defined as less than 4% normal sperm morphology (OR 1.94, 95% CI 1.05–3.60).

Despite morphological changes the research suggests that cannabis does not induce chromosome breakage in sperm. Generoso et al administered 50 mg/kg THC 5 times per week for 6 weeks in 498 male mice.[17] After mating them with females no increase was observed in fetal dominant lethal mutations or heritable translocations over those in controls. These findings were supported by a study by Berryman et al, who found no THC induced increase in pre-implantation loss, fetal mortality or the mutation index in fetuses fathered by male mice chronically dosed with THC.[18] In animal and human models evidence suggests that cannabis induces morphological changes in sperm while genetic material is preserved.

Motility and Energy Metabolism

The most extensive body of evidence for cannabis related alterations to sperm is for sperm motility. Whan et al noted spermatotoxic effects of THC by incubating sperm with THC at therapeutic doses, similar to concentrations shown to relieve pain or reduce spasticity in humans with multiple sclerosis (0.032 μM) and recreational concentrations (4.8 and 0.32 μM) for 3 hours, and then measuring motility by computer assisted semen analysis.[19] The sperm were divided into fractions of 90% with the best fertilizing potential and 45% with a poorer subpopulation. Compared to controls the 45% fraction showed 28% reduced motility at 0.032 μM THC ($p=0.004$) and 56% reduced motility at 4.8 μM THC ($p=0.01$). The 90% fraction showed no significant difference in motility at 0.032 μM ($p=0.80$) but a 28% decrease in motility at 4.8 μM ($p<0.001$). Therapeutic and recreational THC concentrations also resulted in reduced straight line velocity. A similar decrease in sperm motility was seen in an analysis of semen samples from 16 healthy, chronic marijuana users after 4 weeks of high dose marijuana.[14]

Barbonetti et al elucidated the mechanism of these findings by establishing a link between CB1 and sperm mitochondrial activity.[20] In sperm incubated with the CB1 receptor agonist Met-AEA a significant reduction was observed in mitochondrial transmembrane potential. When the sperm were placed under glycolysis blockade, causing them to switch oxidative phosphorylation, the introduction of Met-AEA abolished sperm motility.

The link between cannabis and sperm mitochondrial dysfunction was furthered by Badawy et al, who added THC to semen and measured the oxygen concentration as a marker of respiration.[21] Upon the addition of THC mitochondrial respiration immediately declined and was concentration dependent in effect. The results were much more pronounced in washed sperm than in neat semen, suggesting that seminal plasma contains some protective factors.

These various investigations suggest that through the action of cannabis on the CB1 receptor the mitochondrial activity of sperm is reduced and as a result motility is significantly impaired. Although Met-AEA and THC administration in the laboratory has helped map potential pathways, to our knowledge it is not known whether these effects are fully replicated in the male testes. Future testing should be done to explore whether mitochondrial impairment is present in the semen of chronic cannabis users.

Viability

Cannabis also has a detrimental effect on sperm viability. Rossato et al incubated semen samples with the endocannabinoid AEA at varying concentrations and found that viability was decreased in a dose dependent manner at supraphysiological AEA concentrations.[22]

Reduced sperm viability related to cannabis has also been investigated using the highly specific CB1 receptor antagonist rimonabant (SR141716). Cobellis et al found that adding a micromolar concentration of rimonabant induced a small but significant increase in the number of viable spermatozoa.[23] Aquila et al reported similar findings with 1 and 10 nM concentrations of rimonabant increasing sperm viability with no further viability changes observed at higher concentrations.[4] While the cannabinoid system has clear links to sperm viability, future work should be done to confirm these findings with exogenous cannabinoids as well as in the in vivo setting.

Fertilization Capacity

Research suggests that the cannabinoid signaling pathway may be involved in inhibiting sperm capacitation and activation. Using high performance liquid chromatography Schuel et al observed that high levels of AEA are present in seminal plasma and in progressively decreasing amounts in oviductal and follicular fluid, indicating that sperm are exposed to progressively decreasing AEA levels along the entire fertilization path.[24,25] The authors speculated that high AEA levels maintain sperm in a quiescent state and the decrease in AEA levels which occurs in the

fertilization environment enables sperm to become activated. These data suggest that increases in cannabinoid levels may interfere with sperm activation and may be especially pertinent in the female reproductive tract, which the sperm depend on for tightly regulated AEA levels to maintain proper function.

Rossato et al reported that AEA inhibits the capacitation induced acrosome reaction of human sperm after incubation in capacitating medium.[22] Using boar sperm Maccarrone et al found that Met-AEA reduced sperm capacitation in a time dependent manner.[26] They also noted that this effect was mediated by the CB1 receptor since when rimonabant, which blocks CB1, was added, Met-AEA produced no change in capacitation.

Schuel et al used the cannabinoid agonist AM-365 to identify concentration dependent stimulation and inhibition of sperm hyperactivated motility, which is a state needed for sperm to reach the egg surface and which assists with penetration of the zona pellucida.[25] In addition, they found that AM-365 administration completely inhibited the acrosomal modifications needed to prepare for zona pellucida binding and AM-365 decreased tight binding of sperm to the zona pellucida, which is needed for fertilization, by 49% ($p < 0.001$). Whan et al used THC with similar results.[19] They reported that for sperm undergoing artificial induction of the acrosome reaction THC resulted in 57% inhibition of the acrosome reaction ($p < 0.001$).

Current work suggests that the endocannabinoid system is intimately linked to the fertilization process in the male and female reproductive tracts. Given the well described inhibitory effects, cannabis is likely to have negative impacts on fertilizing potential.

CANNABIS EFFECTS ON REPRODUCTIVE HORMONES

Follicle Stimulating Hormone

Relatively few studies have focused on cannabis and FSH levels, and most have observed no effect. Cone et al found no significant change in FSH levels in 4 healthy males with a history of frequent marijuana use before and after 2 marijuana cigarettes per day for 3 consecutive days.[27] This finding was replicated by Wenger et al, who injected THC in the third cerebral ventricle of adult male rats and subsequently observed no alteration in serum FSH levels with time.[28] Vescovi et al observed that cannabis did not alter the response of FSH to gonadotropin-releasing hormone in 10 male chronic marijuana users given gonadotropin-releasing hormone intravenously.[29] A depression in FSH levels was observed only by Kolodny et al, who compared plasma hormone levels among 11 men who used 5 to 9 marijuana cigarettes per week, 9 who used 10 or more marijuana cigarettes per week and normal controls.[12] The group using 10 or more cigarettes per week had significantly lower FSH ($p < 0.01$).

Based on current studies, FSH may not be affected by cannabis except perhaps in the limited case of heavy chronic use. Human studies to date have been limited in suggestive power due to the small cohort sizes, leaving considerable room for further validation with larger sample size investigations.

Luteinizing Hormone

In human and animal models LH is consistently lowered by cannabis.[27–30] In the single exception Kolodny et al did not observe any significant difference in plasma LH levels between men who smoked 5 to 9 marijuana cigarettes per week and men who smoked 10 or more per week.[12] However, the variation in marijuana use levels in this study may have been insufficient to induce LH variations.

The relationship between cannabis and LH was strengthened in a study by Wenger et al, who used polyclonal antibodies against CB1 and CB2 to localize individual cells expressing cannabinoid receptors.[31] The CB1 receptor was found in the anterior pituitary in LH secreting gonadotrophic cells. Wenger et al reaffirmed these results after administering AEA to wild-type and CB1 knockout mice, which revealed decreased LH secretion in the wild-type mice but unchanged LH levels in the CB1 knockout mice.[32] As is the case with FSH related investigations, understanding how cannabis impacts LH would be improved by larger randomized, controlled trials in human subjects.

Testosterone

The reported effect of cannabis on serum testosterone levels is widely variable across current studies. In an early work in 20 chronic marijuana users Kolodny et al found a significant reduction in testosterone levels between chronic and never marijuana users ($p < 0.001$).[12] The average plasma testosterone level in the control group was 742 ± 29 ng/ml, while levels were 503 ± 40 and 309 ± 34 ng/ml in the 5 to 9 and the 10 or more marijuana cigarettes a week groups, respectively ($p < 0.005$). Serum testosterone reduction in the setting of cannabis use has also been observed in several animal models.[10,32] In rats dosed acutely with THC at 10 mg/kg, a significant depression in testicular testosterone synthesis was observed. An even larger effect on testicular testosterone synthesis was observed in rats dosed chronically with THC at 2 mg/kg.[33]

The evidence that cannabis depresses testosterone levels relies heavily on animal studies. In contrast to findings in animals, most human studies

support the conclusion that testosterone levels are not significantly changed by cannabis use. A 1974 study by Mendelson et al in 27 chronic marijuana users who were administered marijuana for 21 days showed no significant changes in plasma testosterone levels.[34] In a 1986 study of 4 male chronic marijuana users given 2 marijuana cigarettes per day depressed free testosterone levels were observed but the levels did not significantly differ from baseline.[27] In a later study free testosterone levels were compared in 41 normal controls and in 66 Pakistani men who smoked cannabis daily or regularly consumed cannabis tea.[35] No significant difference was observed in plasma testosterone levels between the cannabis users and the normal controls. Although sample size was limited in these early human studies, they suggest that cannabis consumption does not significantly alter testosterone levels.

It is only recently that large cohort studies of cannabis users have been possible. To date these studies have continued the trend of presenting conflicting or inconclusive evidence on the link between cannabis use and testosterone levels.

The first large cohort study on the effects of cannabis use was performed by Gundersen et al in 2015 using a registry of 1,215 Danish men undergoing compulsory medical examination to determine fitness for service.[13] Testosterone levels were 7% higher in self-reported marijuana smokers than in nonusers. This was within the same range of testosterone elevation observed in cigarette smokers in the cohort. The authors cautioned that the increased testosterone levels in marijuana users could not be separated from the effect of tobacco smoking alone.

A second major cohort study was done in 2017 by Thistle et al.[36] They used data on 1,577 American men using data from the 2011 to 2012 United States National Health and Nutrition Survey with several novel outcomes. No difference was observed in serum testosterone levels between ever and never users of marijuana. However, serum testosterone levels showed an inverse association with time since the last regular use of marijuana, and since the last marijuana use (p for trend 0.02 and <0.01, respectively). This indicated that recency rather than frequency of use may have the strongest relationship with serum testosterone levels. Additional large, population based samples are needed to clarify currently conflicting reported effects of cannabis on testosterone levels.

TESTICULAR SIZE CHANGES

Current research suggests a link between cannabis and testicular atrophy, although this evidence relies largely on animal models. Studies in mice and rats have recorded significant dose dependent reductions in prostate and seminal vesicle weight.[10,37–39] A study of dogs administered daily cannabis extract (12.5 mg/kg body weight) recorded testicular degeneration and necrosis after only 30 days of exposure.[11]

In a histological examination of the testes of mice exposed to cannabis Mandal and Das found fewer spermatogonia as well as basement membrane damage, scant cytoplasm and shrunken nuclei.[40] They also observed a reduction in seminiferous tubule diameter. Fortunately complete recovery of spermatogenesis and testicular cell function was seen 45 days after ceasing cannabis use, although testicular weight and seminiferous tubule size were not completely restored at that time. The authors speculated that testicular damage may be due to oxidative stress as a result of finding a significant decrease in antioxidant enzymes in affected testicles. This hypothesis was furthered by the work of Alagbonsi et al, who found that testicular damage induced by *Cannabis sativa* in rats was ameliorated by administering an antioxidant combination of melatonin and vitamin C.[41]

Banerjee et al reported that cannabis has direct effects on seminiferous tubule function which is not mediated simply by hormone levels.[10] The seminiferous tubules express LH receptor and fatty acid amide hydrolase, which has a pivotal role in modulating sperm motility, capacitation and the acrosome reaction. Western blot of LH receptor and fatty acid amide hydrolase after low and high dose administration of bhang showed significant reductions in the expression of each protein ($p<0.05$).

Animal models present clear evidence of testicular atrophy after prolonged and consistent exposure to cannabis, an effect which is likely to be largely reversible. Current research indicates that this effect is at least in part due to direct damage to the seminiferous tubules, which may be mediated by oxidative stress. Future work is needed to better understand how these findings carry over into human models, particularly in terms of identifying the quantity and the duration of cannabis exposure which could produce changes equivalent to those observed in animal studies to date.

SEXUAL FUNCTION

Cannabis, which has been used as an aphrodisiac since ancient times, was anecdotally described to enhance sexual performance and enjoyment.[42] In interview data on 800 chronic cannabis users collected by Kolodny et al 83% reported enhanced sexual pleasure while using cannabis.[43] A recent investigation by Androvicova et al validated these results by showing that cannabis intoxication

increased activation of the right nucleus accumbens upon presentation of erotic stimuli, leading the authors to conclude that cannabis may help in the treatment of hypoactive sexual desire.[44]

In contrast to these findings, animal studies demonstrated reduced libido after acute and chronic cannabis administration. Using 5 mg/kg THC Murphy et al found that 30 minutes after THC injection the percent of male rats showing copulatory behavior with sexually receptive females was significantly diminished.[45] Using 10 mg/kg THC Dhawan and Sharma found that after 30 consecutive days of THC administration male rats showed reduced copulatory and mounting behaviors without decreased motor activity levels overall.[46]

Supporting the findings in animal models, research has also tied cannabis to sexual dysfunction. Aversa et al observed that of 64 men evaluated for ED complaints 78% with organic ED admitted to frequently smoking cannabis in contrast to only 3% with nonorganic ED.[47] The group demonstrated that impaired epithelium dependent vasodilation occurred more frequently in individuals with organic ED, leading to the conclusion that cannabis likely induces ED through early endothelial damage.

Strengthening the evidence that the cannabinoid system is linked to erectile capacity, Succu et al found that the CB1 receptor blocker rimonabant induced erection in rats when injected into the paraventricular nucleus.[48] Melis et al followed up on these results and reported that the mechanism is likely mediated by neuronal nitric oxide synthase activation by rimonabant.[49]

On the whole, current research points to a paradoxical effect of cannabis on sexual function. While short-term libido is augmented, the ability to achieve erection appears to be diminished. Future research is needed to elucidate the causative effects.

CONCLUSIONS

As cannabis increasingly gains legalized status across the United States, the popularity and prevalence of use continue to grow. Although medically it demonstrates therapeutic promise in some areas such as multiple sclerosis and chronic neuropathic pain, the potential adverse effects remain widely under studied.[8]

Because men of reproductive age are the most prevalent users of marijuana, its ability to impact male fertility is of special importance.[50] Current research shows that cannabis likely has negative impacts at several points along the male fertility pathway. Human sperm express cannabinoid receptors, suggesting that they are directly impacted by alterations in the balance of the endocannabinoid system. The effect of cannabis on testosterone levels is largely undetermined while LH levels appear to be lowered and FSH levels are unchanged.

The strongest evidence for the deleterious effects of cannabis on male reproductive capacity is its impact on semen parameters. Studies demonstrate reduced sperm count and concentration, morphological changes, reduced motility and viability, and decreased fertilizing capacity in animals and humans exposed to marijuana or cannabis derivatives. Furthermore, animal studies suggest that cannabis has a role in testicular atrophy. While cannabis may increase libido in the short term, chronic use may diminish erectile function in men.

The evidence presented to date largely relies on animal models, in vitro studies of endogenous cannabinoid compounds and retrospective analyses. The ethical and legal complications of an in vivo, controlled study drive the limited amount of data presented in human subjects, a limitation which is unlikely to abate going forward. Future studies should focus on gathering large cohort data in national surveys, similar to the voluntary, cannabis related data collection done with compulsory military fitness examinations in Denmark.[13] These types of studies are needed to confirm that animal models can be translated to human experience.

Furthermore, the mechanistic underpinnings of cannabis effects on the hormonal axis, libido and erectile function require greater elucidation to move beyond current associational studies. Special attention should be given to determining effect reversibility and establishing a level of cannabis use which would meaningfully decrease fertilizing potential. Until the links between cannabis use and male fertility become more concrete and well described, physicians should consider probing the degree of cannabis use in evaluations of male infertility and they may choose to consider possible complications in reproductive age individuals when evaluating the prescription of medical marijuana.

REFERENCES

1. Sharma P, Murthy P and Bharath MM: Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iran J Psychiatry 2012; **7:** 149.
2. Governing: The States and Localities 2018: State Marijuana Laws in 2018 Map. Available at http://www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html. Accessed November 13, 2018.
3. Pertwee RG: The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008; **153:** 199.
4. Aquila S, Guido C, Santoro A et al: Human sperm anatomy: ultrastructural localization of

the cannabinoid1 receptor and a potential role of anandamide in sperm survival and acrosome reaction. Anat Rec (Hoboken) 2010; **293:** 298.

5. Jensen B, Chen J, Furnish T et al: Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr Pain Headache Rep 2015; **19:** 50.
6. Agirregoitia E, Carracedo A, Subirán N et al: The CB(2) cannabinoid receptor regulates human sperm cell motility. Fertil Steril 2010; **93:** 1378.
7. Noel C: Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders. Ment Health Clin 2018; **7:** 29.
8. Bari M, Battista N, Pirazzi V et al: The manifold actions of endocannabinoids on female and male reproductive events. Front Biosci (Landmark Ed) 2011; **16:** 498.
9. Huang HF, Nahas GG and Hembree WC 3rd: Effects of marihuana inhalation on spermatogenesis of the rat. Adv Biosci 1978; **22-23:** 419.
10. Banerjee A, Singh A, Srivastava P et al: Effects of chronic bhang (cannabis) administration on the reproductive system of male mice. Birth Defects Res B Dev Reprod Toxicol 2011; **92:** 195.
11. Dixit VP, Gupta CL and Agrawal M: Testicular degeneration and necrosis induced by chronic administration of cannabis extract in dogs. Endokrinologie 1977; **69:** 299.
12. Kolodny RC, Masters WH, Kolodner RM et al: Depression of plasma testosterone levels after chronic intensive marihuana use. N Engl J Med 1974; **290:** 872.
13. Gundersen TD, Jørgensen N, Andersson AM et al: Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. Am J Epidemiol 2015; **182:** 473.
14. Hembree WC 3rd, Nahas GG, Zeidenberg P et al: Changes in human spermatozoa associated with high dose marihuana smoking. Adv Biosci 1978; **22-23:** 429.
15. Zimmerman AM, Zimmerman S and Raj AY: Effects of cannabinoids on spermatogenesis in mice. Adv Biosci 1978; **22-23:** 407.
16. Pacey AA, Povey AC, Clyma JA et al: Modifiable and non-modifiable risk factors for poor sperm morphology. Hum Reprod 2014; **29:** 1629.
17. Generoso WM, Cain KT, Cornett CV et al: Tests for induction of dominant-lethal mutations and heritable translocations with tetrahydrocannabinol in male mice. Mutat Res 1985; **143:** 51.
18. Berryman SH, Anderson RA Jr, Weis J et al: Evaluation of the co-mutagenicity of ethanol and delta 9-tetrahydrocannabinol with Trenimon. Mutat Res 1992; **278:** 47.
19. Whan LB, West MC, McClure N et al: Effects of delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro. Fertil Steril 2006; **85:** 653.
20. Barbonetti A, Vassallo MR, Fortunato D et al: Energetic metabolism and human sperm motility: impact of CB_1 receptor activation. Endocrinology 2010; **151:** 5882.
21. Badawy ZS, Chohan KR, Whyte DA et al: Cannabinoids inhibit the respiration of human sperm. Fertil Steril 2009; **91:** 2471.
22. Rossato M, Ion Popa F, Ferigo M et al: Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function. J Clin Endocrinol Metab 2005; **90:** 984.
23. Cobellis G, Cacciola G, Scarpa D et al: Endocannabinoid system in frog and rodent testis: type-1 cannabinoid receptor and fatty acid amide hydrolase activity in male germ cells. Biol Reprod 2006; **75:** 82.
24. Schuel H and Burkman LJ: A tale of two cells: endocannabinoid-signaling regulates functions of neurons and sperm. Biol Reprod 2005; **73:** 1078.
25. Schuel H, Burkman LJ, Lippes J et al: Evidence that anandamide-signaling regulates human sperm functions required for fertilization. Mol Reprod Dev 2002; **63:** 376.
26. Maccarrone M, Barboni B, Paradisi A et al: Characterization of the endocannabinoid system in boar spermatozoa and implications for sperm capacitation and acrosome reaction. J Cell Sci 2005; **118:** 4393.
27. Cone EJ, Johnson RE, Moore JD et al: Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol Biochem Behav 1986; **24:** 1749.
28. Wenger T, Rettori V, Snyder GD et al: Effects of delta-9-tetrahydrocannabinol on the hypothalamic-pituitary control of luteinizing hormone and follicle-stimulating hormone secretion in adult male rats. Neuroendocrinology 1987; **46:** 488.
29. Vescovi PP, Pedrazzoni M, Michelini M et al: Chronic effects of marihuana smoking on luteinizing hormone, follicle-stimulating hormone and prolactin levels in human males. Drug Alcohol Depend 1992; **30:** 59.
30. Martín-Calderón JL, Muñoz RM, Villanúa MA et al: Characterization of the acute endocrine actions of (-)-11-hydroxy-delta8-tetrahydrocannabinol-dimethylheptyl (HU-210), a potent synthetic cannabinoid in rats. Eur J Pharmacol 1998; **344:** 77.
31. Wenger T, Fernández-Ruiz JJ and Ramos JA: Immunocytochemical demonstration of CB1 cannabinoid receptors in the anterior lobe of the pituitary gland. J Neuroendocrinol 1999; **11:** 873.
32. Wenger T, Ledent C, Csernus V et al: The central cannabinoid receptor inactivation suppresses endocrine reproductive functions. Biochem Biophys Res Commun 2001; **284:** 363.
33. List A, Nazar B, Nyquist S et al: The effects of delta9-tetrahydrocannabinol and cannabidiol on the metabolism of gonadal steroids in the rat. Drug Metab Dispos 1977; **5:** 268.
34. Mendelson JH, Kuehnle J, Ellingboe J et al: Plasma testosterone levels before, during and after chronic marihuana smoking. N Engl J Med 1974; **291:** 1051.
35. Friedrich G, Nepita W and André T: Serum testosterone concentrations in cannabis and opiate users. Beitr Gerichtl Med 1990; **48:** 57.
36. Thistle JE, Graubard BI, Braunlin M et al: Marijuana use and serum testosterone concentrations among U.S. males. Andrology 2017; **5:** 732.
37. Dixit VP, Sharma VN and Lohiya NK: The effect of chronically administered cannabis extract on the testicular function of mice. Eur J Pharmacol 1974; **26:** 111.
38. Harclerode J: Endocrine effects of marijuana in the male: preclinical studies. NIDA Res Monogr 1984; **44:** 46.
39. Fujimoto GI, Morrill GA, O'Connell ME et al: Effects of cannabinoids given orally and reduced appetite on the male rat reproductive system. Pharmacology 1982; **24:** 303.
40. Mandal TK and Das NS: Testicular toxicity in cannabis extract treated mice: association with oxidative stress and role of antioxidant enzyme systems. Toxicol Ind Health 2010; **26:** 11.
41. Alagbonsi IA, Olayaki LA and Salman TM: Melatonin and vitamin C exacerbate Cannabis sativa-induced testicular damage when administered separately but ameliorate it when combined in rats. J Basic Clin Physiol Pharmacol 2016; **27:** 277.
42. Chopra GS and Jandu BS: Psychoclinical effects of long-term marijuana use in 275 Indian chronic users. A comparative assessment of effects in Indian and USA users. Ann N Y Acad Sci 1976; **282:** 95.
43. Kolodny RC, Masters WH and Johnson VE: Textbook of Sexual Medicine. Boston: Little Brown & Co 1979.
44. Androvicova R, Horacek J, Tintera J et al: Individual prolactin reactivity modulates response of nucleus accumbens to erotic stimuli during acute cannabis intoxication: an fMRI pilot study. Psychopharmacology (Berl) 2017; **234:** 1933.
45. Murphy LL, Gher J, Steger RW et al: Effects of delta 9-tetrahydrocannabinol on copulatory behavior and neuroendocrine responses of male rats to female conspecifics. Pharmacol Biochem Behav 1994; **48:** 1011.
46. Dhawan K and Sharma A: Restoration of chronic-Delta 9-THC-induced decline in sexuality in male rats by a novel benzoflavone moiety from Passiflora incarnata Linn. Br J Pharmacol 2003; **138:** 117.
47. Aversa A, Rossi F, Francomano D et al: Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. Int J Impot Res 2008; **20:** 566.

48. Succu S, Mascia MS, Sanna F et al: The cannabinoid CB1 receptor antagonist SR 141716A induces penile erection by increasing extra-cellular glutamic acid in the paraventricular nucleus of male rats. Behav Brain Res 2006; **169:** 274.

49. Melis MR, Succu S, Mascia MS et al: The cannabinoid receptor antagonist SR-141716A induces penile erection in male rats: involvement of paraventricular glutamic acid and nitric oxide. Neuropharmacology 2006; **50:** 219.

50. Center for Behavioral Health Statistics and Quality: 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville, Maryland: Substance Abuse and Mental Health Services Administration 2017.