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The adverse association between stimulant use for attention deficit hyperactivity disorder (ADHD) and semen parameters

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Abstract

This study examined the relationship between stimulant medications used for the treatment of attention deficit hyperactivity disorder and semen parameters. We performed a retrospective cohort study at a large, academic institution between 2002 and 2020. We included men with a semen analysis without prior spermatotoxic medication use, empiric medical therapy exposure or confounding medical diagnoses (varicocele, Klinefelter's syndrome, cryptorchidism, cystic fibrosis, diabetes, cancer or cancer-related treatment, and azoospermia). Men were stratified by stimulant exposure (methylphenidate or amphetamines). A multivariable linear regression was fit to assess the association between individual semen parameters, age, stimulant exposure and non-stimulant medication use. Of 8,861 men identified, 106 men had active prescriptions for stimulants within 90 days prior to semen testing. After controlling for age and exposure to non-stimulant medications, stimulant use was associated with decreased total motile sperm count (β: −18.00 mil/ejaculate and standard error: 8.44, $p = 0.033$) in the setting of decreased semen volume (β: −0.35 ml, and standard error: 0.16, $p = 0.035$), but not sperm concentration, motility and morphology. These findings suggest a role for reproductive physicians and mental health providers to consider counselling men on the potential negative impact of stimulants prescribed for attention deficit hyperactivity disorder on semen volume during fertility planning.

Keywords

amphetamine; attention deficit hyperactivity disorder; fertility; methylphenidate; semen quality

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

1 | INTRODUCTION

Semen parameters are affected by a broad range of medications. Whereas certain medications such as selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) can lead to improvement in semen parameters (American Urological Association American Society for Reproductive Medicine, 2020; Chua et al., 2013; Omar et al., 2019), many others can negatively affect semen volume, sperm concentration and sperm motility (Samplaski & Nangia, 2015). Unfortunately, the potential impact of commonly used drugs on fertility is often under-studied. While the US Food and Drug Administration (FDA) does provide guidance for evaluation of testicular toxicity during drug development, the suggested protocols do not require universal study of testicular toxicity in human clinical trials (Food & Drug Administration, 2018). Consequently, many drugs are brought to market and widely used in clinical practice without consideration of the potential fertility implications.

Medications for the treatment of attention deficit hyperactivity disorder (ADHD) are ubiquitous, and men taking these medications are at peak developmental and reproductive years. ADHD is a neurodevelopmental disorder that is typically diagnosed during early childhood with persistence into adulthood, and as a result, medications treating ADHD are often initiated at a young age and continued throughout the primary developmental and reproductive periods of a man's life (Girand et al., 2020; Neurodevelopmental Disorders, 2014; Wolraich et al., 2019). One major class of medications used to treat ADHD is stimulants, which include methylphenidate, amphetamine and amphetamine-based derivatives. Among children and adults 2–24 years of age, stimulant prescription for treatment of ADHD has been steadily increasing, most recently estimated to be prescribed to 7.8% of the population (Girand et al., 2020). Moreover, stimulant misuse, that is not directed by a physician, is estimated to be present in 5.8% of young adults, rendering this an increasingly prevalent drug among men of reproductive age (Substance Abuse & Mental Health Services Administration, 2020).

Despite the widespread use of medications for the treatment of ADHD in adolescent and young adult men, the impact of these drugs on semen parameters and male fertility is poorly studied. Animal studies have suggested that these agents may have a possible gonadotoxic impact (Mattison et al., 2011; Nudmamud-Thanoi & Thanoi, 2011), but clinical evidence, while raising concern, has been limited (Patel et al., 2016; Ramasamy et al., 2014). Therefore, we sought to evaluate the relationship between stimulants and semen parameters among men undergoing fertility evaluation, hypothesizing that stimulant exposure was associated with deleterious changes to semen quality.

2. | MATERIAL AND METHODS

2.1 | Data source

We queried the Northwestern Enterprise Data Warehouse (EDW), an electronic data repository, to identify all adult men who underwent semen analysis across a large, integrated academic healthcare system between March 2002 and October 2020. For each patient, we

extracted data related to demographic characteristics, comorbidities, medications and semen parameters. The Institutional Review Board for Northwestern University Feinberg School of Medicine reviewed and exempted this study from requiring approval.

2.2 | Study cohort and patient population

We included patients ages 18 years or older with semen analyses provided for fertility-related care. We excluded patients who were prescribed any of the following medications with potential adverse or enhancing effects on semen or hormone parameters prior to their first semen analysis: testosterone, anti-neoplastic agents, 5-alpha reductase inhibitors (5-ARI), anastrozole, clomiphene citrate and human chorionic gonadotropin (hCG) (Samplaski & Nangia, 2015). We also excluded men with a known diagnosis of varicoceles, cryptorchidism, Klinefelter's syndrome, cystic fibrosis and diabetes mellitus. Men with a prior history of cancer, anti-neoplastic therapy, radiotherapy and azoospermia were also excluded. The patient exclusion criteria and generation of the analysed cohort are outlined in Figure S1.

2.3 | Exposure definition and measurement

The primary exposure was stimulant exposure. This was defined as an active outpatient stimulant prescription within 90 days prior to any semen analysis. The following stimulant medications and their brand name equivalents were included: methylphenidate, dexmethylphenidate, amphetamine, levoamphetamine, dextroamphetamine, lisdexamfetamine and methamphetamine. All patients without stimulant exposure comprised the non-exposure group. For brevity, amphetamine and amphetamine-based derivatives will be referred to as amphetamines in this report.

2.4 | Outcome definition and measurement

The primary outcome was total motile sperm count (TMSC). Secondary outcomes included semen volume, sperm concentration, sperm motility and sperm morphology. For patients with 2 or more semen analyses, we considered the mean of their semen analysis results within a 90-day window following the index semen test. For men in either group who began taking spermatotoxic medications or empirical medical treatment after their initial semen analysis, all semen analyses following this confounding exposure were excluded.

2.5 | Covariates

We adjusted for patient age on the day of the index semen analysis. Additionally, to control for potential confounding effects of non-stimulant medications that were not considered spermatotoxic medications or empirical medical therapies, we identified all outpatient medication orders listed for each patient in the electronic medical record, including supplements and over-the-counter medications. These non-stimulant medication exposures were dichotomized into a binary variable of any versus none. Non-stimulant medication exposures were considered when they were documented during the semen testing windows described above. Index follicular-stimulating hormone (FSH) and morning testosterone (prior to 11 a.m.) levels were compared between groups.

2.6 | Statistical analyses

Descriptive statistics with proportions, medians and interquartile ranges were generated. Chi-squared testing was used to assess for differences in categorical variables unless subgroups had less than 5 patients, in which case Fisher's exact test was used. The Wilcoxon rank sum test was used to assess for differences in continuous variables. Observations with missing values for a given semen parameter were excluded from their respective analyses. Univariable and multivariable linear regression models were created to assess the association between stimulant exposure and semen parameters, adjusting for age and the use of non-stimulant medications. While a standard abstinence period is recommended for 2–3 days prior to all semen analyses, we performed a sensitivity analysis post hoc using a linear regression model to ensure that there were no differences in days of abstinence between the exposed and non-exposed groups. Statistical significance was defined as a p-value ≤0.05. Analyses were performed using Stata 16.1 software (College Station, Texas).

3 | RESULTS

We identified 8,861 men who underwent semen testing and met inclusion criteria between 2002 and 2020. Of these, 106 patients (1.2%) provided semen analyses during known exposure to stimulants while 8,755 had no known exposure during semen testing. The demographic characteristics of our cohort are presented in Table 1. Patients prescribed stimulants were younger and more likely to be Caucasian, take non-stimulant medications and have private insurance compared with non-exposed patients. A larger proportion of stimulant-exposed patients were prescribed amphetamines than methylphenidate (86.7% vs. 16.9%, respectively). Exposures to methylphenidate and amphetamines were not mutually exclusive, and 3.8% of stimulant-exposed patients were prescribed both medication types. No differences in FSH and testosterone levels were identified among men evaluated for endocrine parameters.

Table 2 summarizes median semen parameters between the two exposure groups. Median semen volume was lower in patients exposed to stimulants (2.70 ml vs. 3.00 ml, $p = 0.025$). We found no significant differences in sperm concentration, sperm motility, total motile sperm count or morphology between groups.

On univariable analysis, the use of stimulants was associated with significantly lower semen volume (β: −0.32 ml, standard error [*SE*]: 0.16, $p = 0.048$; Table 3) but none of the other semen parameters. On multivariable analysis adjusting for use of non-stimulant medications and age, stimulant remained associated with lower semen volume (β: −0.35 ml, *SE*: 0.16, $p = 0.035$) but was also associated with lower TMSC (β: −18.00 mil/ejaculate, *SE*: 8.44, $p = 0.033$; Figure 1). Given these findings, we performed a sensitivity analysis to evaluate for between-group differences in the days of abstinence prior to semen collection. The median days of abstinence were similar between the exposed (3.00 days, interquartile range [IQR]: 2.00–3.50 days) and non-exposed patients (3.00 days, IQR: 2.00–4.00 days). On univariable regression, we found no significant association between the days of abstinence prior to semen testing and the exposure to stimulant medications (β −0.45 days, *SE*: 0.35, $p = 0.20$).

4 | DISCUSSION

Amphetamines and methylphenidate are common medications used to treat ADHD, sometimes beginning at an early age (Wolraich et al., 2019); however, their impact on male fertility and sexual function is unknown. This problem is further complicated by the initiation of these agents often during critical periods of sexual development and their continuation into ages when reproduction is desired. Properly counselling patients about the reproductive risks of these medications is particularly challenging given the paucity of data to inform meaningful discussions. To this end, we sought to explore the relationship between stimulants and semen parameters in a population of men who had presented for semen analysis at our institution.

Data on the reproductive consequences of amphetamine analogues and methylphenidate are primarily derived from animal studies. Both are sympathomimetic agents that work to increase neurotransmission of dopamine and norepinephrine (Cortese, 2020). Research on amphetamines has primarily focused on methamphetamine, an analogue with increased central nervous system activity. In male rats, methamphetamine induced apoptotic activity in the seminiferous tubules, reduced testicular volume and decreased sperm motility and count (Lin et al., 2014; Nudmamud-Thanoi & Thanoi, 2011; Yamamoto et al., 1999, 2002). Methylphenidate similarly stimulated apoptotic activity in testicular tissue and lowered testicular weight (Cansu et al., 2011). In juvenile rhesus monkeys, methylphenidate treatment initiated during pre-puberty reduced both testicular size and testosterone levels (Mattison et al., 2011). To our knowledge, the link between methylphenidate and human gonadal function is limited to anecdotal case reports, such as that of azoospermia and idiopathic testicular failure following 17 years of methylphenidate use that began prior to 3 years of age (Ramasamy et al., 2014). In light of these findings, we hypothesized that stimulant exposure may exert a detrimental impact on semen parameters.

We found that stimulant use was associated with lower semen volume and TMSC, as a consequence of reduced semen volume as opposed to a spermatoxic effect, but not changes in sperm motility, concentration and morphology. While short-term, intermittent use of stimulants has been used to increase ejaculated semen volume as the treatment for ejaculatory dysfunction and orgasmic dysfunction, our data paradoxically suggest that exposure to stimulants may decrease semen volume (Levine et al., 2020; Lyons et al., 2017). One plausible explanation for this finding is adrenergic desensitization, a well-established phenomenon observed in both pathologic conditions and iatrogenic circumstances (Insel, 1996). Pheochromocytomas, for example, are known to dramatically desensitize α- and β-adrenergic receptors (Zuber et al., 2011). Prolonged sympathomimetic nasal decongestant use also promotes α-agonist tachyphylaxis and rebound congestion (Insel, 1996; Ramey et al., 2006). Although our study design cannot elucidate the precise pathophysiologic mechanisms for our findings, we posit that chronically elevated catecholamines, secondary to regular stimulant use, may promote adrenergic receptor desensitization and downstream impairment of emission and concomitant bladder neck closure. These two factors would reduce seminal fluid deposition in the prostatic urethra and impair antegrade ejaculatory function.

Only one prior study has examined the impact of stimulant use on semen parameters. Patel et al. communicated their preliminary findings from a retrospective review of 86 stimulant users without spermatotoxic medication exposure compared with controls (Patel et al., 2016). They observed no difference in semen volume but identified decreases in concentration (−1.2 million/ml, $p = 0.015$), total progressive motility (−2.8%, $p = 0.012$) and TMSC (−1.3 million/ejaculate, $p = 0.015$). Our results differed both in the types of semen parameters found to be significantly associated with medication use and the magnitude of decrease in TMSC (−1.3 vs. −18.00 mil/ejaculate). Several differences in study design may account for these discrepant findings. First, our study excluded patients with comorbidities associated with infertility in order to minimize confounding, whereas Patel et al. did not. Second, we included men taking non-ADHD medications in both our control and exposure groups, whereas Patel et al. did not. Third, the majority of patients in the current study were prescribed amphetamines rather than methylphenidate (86.7% vs. 16.9%), whereas Patel et al. did not report on this sub-classification.

Despite these differences, the current study expands upon these prior findings to engender a measure of caution when considering stimulant use in men undergoing fertility evaluation. While we did not identify a direct impact of stimulants upon spermatogenic parameters, the detriment to semen volume and, consequentially TMSC, may be pertinent in the appropriate clinical setting. Our work is limited to adult men seeking care for fertility-related purposes, limiting its generalizability to other populations taking stimulant medications, such as paediatric patients being treated using stimulant medications. In men with normal sperm counts and TMSC, these decreases may be minor and of limited clinical significance; however, in those with poor parameters culminating in a low TMSC, these decreases may result in clinically meaningful differences such as downgrading from intrauterine insemination to in vitro fertilization. As such, we suggest that patients with impaired parameters in the setting of stimulant use be properly counselled about the potential risks of these medications and, after weighing the risks and benefits, consider discussing with their mental health providers potential adjustments and/or alternative treatment strategies while seeking paternity.

If a stimulant is held for the purpose of optimizing semen volume, providers should minimize the amount of time these medications are withheld to avoid a detrimental impact on their patient’s mental health. Any effort to withhold stimulants for the purposes of reproduction should be under the guidance of the patient’s mental health provider. Medication half-lives should also be considered: Amphetamine derivatives have half-lives between 10 and 15 h (Markowitz & Patrick, 2017). The half-lives of various methylphenidate formulations range between 4 and 7 h (Jaeschke et al., 2021). It is possible that the effects of stimulants on semen volume may resolve after being discontinued for several days; however, the current study was not able to address this question.

Our findings must be evaluated in the context of several limitations. First, our results are retrospective and rely on diagnostic coding and prescription-level data, which may be subject to unmeasured error in omission and misdiagnosis. Second, medication exposure was determined according to documentation within the electronic medical record, but true medication adherence could not be confirmed, and the duration of exposure was unable to

be accurately determined. Given this, we considered exposure as a binary variable based on the presence of an active prescription from our institution or one identified from an outside institution during the medication reconciliation process. Finally, there may be contamination within the control cohort, as some of these men could have received prescriptions omitted by the electronic health record or may have illicitly used stimulants. We did consider and query all available medication reconciliation data from outside providers, which likely mitigated any contamination that was present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CONFLICT OF INTEREST

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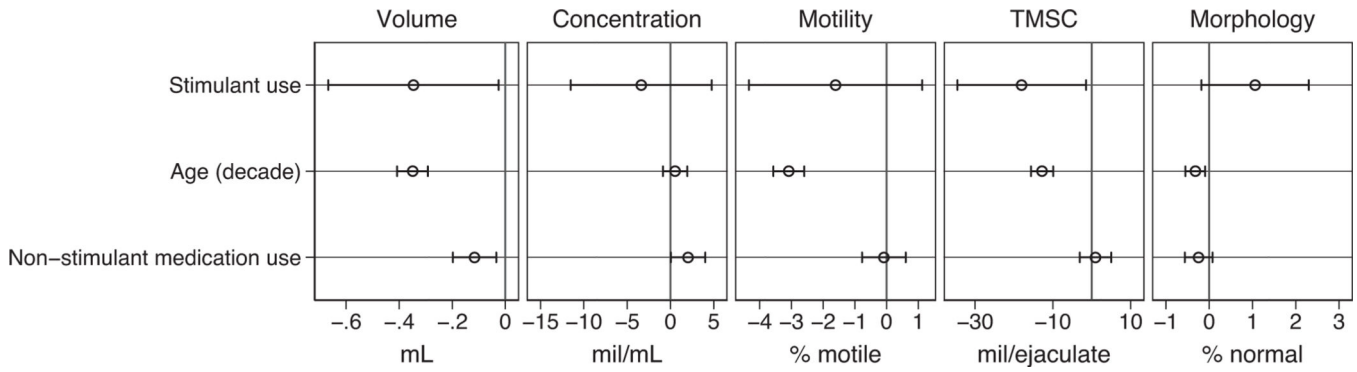

FIGURE 1.

Multivariable linear regression models evaluating the association of stimulant use with individual semen parameters. Abbreviations: TMSC, total motile sperm count

TABLE 1

Demographics of men exposed and not exposed to stimulants

Variable	Exposed (*n* = 106)	Non-exposed (*n* = 8,755)	*p*-value
Age (IQR)	34.00 (31.00 – 34.00)	35.0 (32.00 – 40.00)	0.002
Race/ethnicity (%)			<0.001
White	73 (68.9)	3,932 (44.9)	
Black, non-Hispanic	2 (1.9)	389 (4.4)	
Hispanic	3(2.8)	249 (2.8)	
Other	11 (10.4)	1,715 (19.6)	
Declined/unknown	17 (16.0)	2,470 (28.2)	
Insurance status (%)			<0.001
Private only	102 (96.2)	6,824 (77.9)	
Public or state-based only	0	86 (1.0)	
Public/private combination	0	17 (0.2)	
Self-pay	0	299 (3.4)	
Other/unknown	4(3.8)	1,529 (17.5)	
FSH (IQR) *	4.50 (3.31–6.51)	4.30 (3.00–6.50)	0.542
Testosterone (IQR) †	356(261–463)	327(260–418)	0.378
Non-stimulant medication use (%)	80 (75.5)	2,072 (23.7)	<0.001
Stimulant-type (%) ‡			
Amphetamines	92 (86.7)		
Methylphenidate	18 (16.9)		

Abbreviations: FSH, follicle-stimulating hormone; IQR, interquartile range.

* FSH levels are summarized for 44 men exposed to stimulants and 2,021 men not exposed to stimulants.

† Testosterone levels collected prior to 11 am are summarized for 33 men exposed to stimulants and 1,372 men not exposed to stimulants.

‡ The use of amphetamines and methylphenidate was not mutually exclusive and may occur at separate time points for a given patient.

TABLE 2

Semen parameters of men exposed and not exposed to stimulants

Semen parameter	Exposed	*n* *	Non-exposed	*n* *	*p*-value
Volume (ml)	2.70 (1.90–3.50)	102	3.00 (2.00–4.00)	8,282	0.025
Concentration (mil/ml)	40.50 (21.25–67.12)	92	42.50 (23.80–67.25)	8,203	0.46
Motility (%)	59.00 (52.00–64.00)	99	59.00 (51.00–66.00)	8,246	0.32
TMSC (mil/ejaculate)	71.60 (27.54–106.09)	92	72.49 (32.29–125.46)	8,201	0.19
Normal morphology (%)	6.00 (3.00–11.00)	98	7.00 (4.00–12.50)	7,624	0.39

Note: Values are reported as median (interquartile range).

Abbreviation: TMSC, total motile sperm count.

*Sample sizes differ from the overall cohort sizes after accounting for missing data.

TABLE 3

Univariable and multivariable linear regression for association between stimulant exposure and semen parameters

	Univariable		Multivariable*	
Semen parameter	**Parameter estimate (*SE*)**	***p*-value**	**Parameter estimate (*SE*)**	***p*-value**
Volume (ml)	−0.32 (0.16)	0.048	−0.35 (0.16)	0.035
Concentration (mil/ml)	−2.40 (4.11)	0.56	−3.37 (4.15)	0.42
Motility (%)	−0.88 (1.39)	0.53	−1.61 (1.39)	0.25
TMSC (mil/ejaculate)	−14.44 (8.39)	0.085	−18.0 (8.44)	0.033
Morphology (% normal)	1.00 (0.63)	0.11	1.06 (0.63)	0.094

Abbreviations: *SE*, standard error; TMSC, total motile sperm count.

*All multivariable models were adjusted for use of non-stimulant medications and age.