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Original Research

Diagnoses and medications associated with delayed ejaculation

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Abstract

Background: Delayed ejaculation (DE) is a disorder that can cause significant distress for sexually active men. The etiology of DE is largely idiopathic, with even less being known about clinical factors associated with the condition.
Aim: We sought to use data mining techniques to examine a broad group of health conditions and pharmaceutical treatments to identify factors associated with DE.
Methods: Using an insurance claims database, we evaluated all men with a diagnosis of DE and matched them to a cohort (1:1) of men with other male sexual disorders of urologic origin (ie, erectile dysfunction [ED] and Peyronie's disease [PD]). Given the low prevalence of DE, we incorporated the random forest approach for classification of DE vs controls, with a plethora of predictors and cross-validation with the least absolute shrinkage and selection operator (LASSO). We used both a high-performance generalized linear model and a multivariate logistic model. The area under the curve was reported to demonstrate classifier performance, and odds ratios were used to indicate risks of each predictor. We also evaluated for differences in the prevalence of conditions in DE by race/ethnicity.
Outcomes: Clinical factors (ie, diagnoses and medications) associated with DE were identified.
Results: In total, 11 602 men with DE were matched to a cohort of men with PD and ED. We focused on the 20 factors with the strongest association with DE across all models. The factors demonstrating positive associations with DE compared to other disorders of male sexual dysfunction (ie, ED and PD) included male infertility, testicular dysfunction, anxiety, disorders of lipid metabolism, alpha adrenergic blocker use, anemia, antidepressant use, and psychoses such as schizophrenia or schizoaffective disorder. In addition, the prevalence of several conditions varied by race/ethnicity. For example, male infertility was present in 5% of Asian men compared to <2% of men of other races.
Clinical Implications: Several medical conditions and pharmacologic treatments are associated with DE, findings that may provide insight into the etiology of DE and offer treatment options.
Strengths and Limitations: This study is to our knowledge the first to use using data mining techniques to investigate the association between medical conditions/pharmacologic agents and the development of subsequent DE. The generalizability of our findings is limited given that all men were commercially insured.
Conclusion: DE is associated with multiple medical conditions, a finding that may help identify the etiology for this disorder.

Keywords: ejaculation; data mining; erectile dysfunction; Peyronie's disease.

Introduction

Delayed ejaculation (DE), a clinical phenomenon in men that is characterized by difficulty in achieving ejaculation/orgasm, causes personal distress for some men. The International Consultation on Sexual Dysfunction has defined DE as a latency time for intravaginal ejaculation beyond 20-25 minutes of sexual activity that is associated with negative personal feelings such as bother or distress.[1] Other classifications of the disorder, such as in the Diagnostic and Statistical Manual of Mental Disorders and International Classification of Disease, do not require an objective minimum latency time, but rather require the disorder to be present in a majority of sexual encounters and occur persistently over several months.[1,2] Delayed ejaculation affects 2%-6% of men and may be increasingly prevalent in older populations.[3,4] Delayed ejaculation has known associations with medical conditions, such as chronic prostatitis, depression, and testosterone deficiency, and with medications such as selective serotonin reuptake inhibitors (SSRIs).[5-7] However, most cases of DE are idiopathic. Identification of novel clinical factors associated with DE may increase our insight into the etiology of DE, which may lead to improved treatment options.

Data mining, an analytical method that allows for the discovery and extraction of process patterns by using large amounts of data, is being increasingly utilized in healthcare to develop predictive models that can be applied clinically.[8,9] There are a variety of ways in which data mining is performed. Machine learning is a type of data mining in which a large focused set of data points called features are applied to various algorithms in an attempt to identify any predictive and associative patterns relative to an end point (ie, the likelihood of having/developing a medical diagnosis).[10] Data

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mining approaches applied to large sets of healthcare data are helpful in identifying patterns and associations that may not otherwise be detectable by standard statistical methods.[10]

With the goal of improving care for men with DE, we used data mining methods to examine a broad group of health conditions and pharmaceutical treatments to identify associations with DE. We hypothesized that the use of these techniques can enable identification of patient clinical factors that may be significantly associated with the future development of DE. In doing so, we hoped to identify novel relationships that can provide insight into factors that may increase the risk of DE. In addition, we hypothesized that the conditions associated with DE may vary by race and ethnicity.

Materials and methods

Subject population

The Optum Clinformatics Data Mart (CDM) database is a deidentified database derived from a large adjudicated claims data warehouse. The CDM database comprises administrative health claims for members of a large national managed care company affiliated with Optum. These claims are submitted for payment by providers and pharmacies and then verified, adjudicated, adjusted, and deidentified.The database includes roughly 83 million patients over an 18-year period, only those with both medical and prescription drug coverage. Data regarding member enrollment, medical claims, outpatient pharmacy, social economics, and laboratory values are included. Using CDM version 3.0 (socioeconomic status view), we evaluated all men with a diagnosis of DE (according to the ICD codes ICD-10, N53.11, and ICD-9, 608.87) and matched them to a cohort of men (age 18 years and older) with other urologic male sexual disorders with (ie, PD, ICD-9 607.85 and ICD-10 N48.6; and ED, ICD-9 607.84, 302.72, 302.70, and 608.89 and ICD-10 N52.9, N52, F52.1, R37, and N53.9). Because the ideal comparison subject for a man with DE is not certain, we chose two control groups with sexual dysfunction disorders. Men with DE treated from 2003 to 2019 in two separate control groups of sexual dysfunction, PD and ED, were separately 1:1 matched on age at onset of disease, start and end year of enrollment, and race. Demographic data were obtained. All medical diagnoses (inpatient and outpatient) and medications prescribed in the 6 months prior to initial diagnosis (ie, DE, ED, or PD) were examined. We identified prevalent diseases using ICD codes (Supplemental Table S1). Men with DE were further stratified by race to identify any racial differences in the prevalence of factors associated with DE. Per the Stanford University protocol and given the use of deidentified data, an institutional board review waiver was applied for this project.

Procedures

Given the low prevalence of DE and to overcome class imbalance, we used 1:1 propensity score matching and then incorporated random forest analysis for classification of DE patients vs controls with a plethora of predictors.

We incorporated random forest methods to discover conditions associated with DE. Random forest is a technique in which the final output is based on the majority predictions of many decision trees.[11] This method randomly chooses underlying predictors with a highly informative node. With repeated steps of splitting the trees, the resulting forest pattern comprises multiple trees. The final prediction is constructed by averaging all trees and outputting the most representative class of individual trees. This methodology was used to describe overall patient characteristics and suggest unknown underlying conditions causing DE. We also validated our results using another high-performance generalized linear model for implementing multiple steps of variable selections and removals, the least absolute shrinkage and selection operator (LASSO) method. This procedure provides final models based on the Schwarz information criterion.

Measures and statistics

We identified all diagnoses and medications given within 6 months of the DE, ED, or PD diagnosis. Results from random forest analysis were summarized using multivariable logistic regression. We used a high-performance generalized linear model with LASSO for cross validation. The results were also summarized by use of multivariable logistic regression. Areas under the curve were calculated to demonstrate classifier performance, and odds ratios (ORs) were used to indicate the risks of each predictor. SAS software version 9.4 (SAS Institute Inc, Cary, NC, United States) or R 4.1.1 (R Foundation for Statistical Computing, 2021, Vienna, Austria) was used.

Results

A total of 11 602 men with DE werematched (1:1) to a cohort of men with PD, and 11 719 men were matched to an ED cohort (Table 1). The mean age of all men in the cohort was 52.5 years. A majority of men were White (>65%). More than 70% of men had an educational status classified as less than a college degree. Men with DE had more annual healthcare visits than their PD or ED counterparts (P <.0001).

We identified the clinical diagnoses and medications associated with DE in models comparing men with DE to those with ED or with PD. Given the two comparison groups, we focused on factors identified across both models. We then examined the 20 factors with the strongest associations as assessed using point estimates (Table 2). Compared to PD and ED, clinical factors such as male infertility (PD: OR, 4.14, 95% CI, 3.03-5.66; ED: OR, 4.04, 95% CI 2.96-5.50), use of alpha adrenergic blocking agents (PD: OR, 1.95, 95% CI, 1.73-2.19; ED: OR, 1.60, 95% CI, 1.42-1.80) and psychoses (PD: OR, 1.92, 95% CI, 1.48-2.49; ED: OR 1.61, 95% CI, 1.26-2.06) were the conditions demonstrating the highest associations with DE (P < .00001 for all) when using random forest analysis (Table 2). Disorders with psychoses included diagnoses such as schizophrenia or schizoaffective disorder. When using LASSO to identify conditions associated with DE, similar factors were identified (Table S1).

The two models showed similar associations with DE. Sensitivity and specificity were 56.3% and 67.9% and 53.5% and 62.9% for comparisons to PD and ED, respectively, when the identified diagnoses and medications were used. The area under the curve for DE vs PD was slightly higher than that of DE vs ED (0.659 vs 0603).

We examined differences in conditions associated with DE across different races and ethnicities (Table S2). When stratified by race, certain conditions were more common in one race compared to others. For example, male infertility was

Table 1. Cohort demographics.

Demographic	PD	DE control	Total	*P*	ED	DE control	Total	*P*
No. of patients	11 602	11 602	23 204		11 719	11 719	23 438	
Mean age, years	52.4	52.6		.55	52.	52.4		.9
Age range, years, No. (%)								
18-24	344 (3.0)	289 (2.5)	633	.53	292 (2.5)	295 (2.5)	587	.99
25-34	995 (8.6)	1083 (9.3)	2078		1109 (9.5)	1114 (9.5)	2223	
35-44	1767 (15.2)	2006 (17.3)	3773		2049 (17.5)	2043 (17.4)	4092	
45-54	3104 (26.8)	2937 (25.3)	6041		2957 (25.2)	2962 (25.3)	5919	
55-64	3091 (26.6)	2758 (23.8)	5849		2768 (23.6)	2773 (23.7)	5541	
65+	2301 (19.8)	2529 (21.8)	4830		2544 (21.7)	2532 (21.6)	5076	
Year of enrollment								
2003-2006	4295 (37.0)	4251 (36.6)	8546	.74	4367 (37.3)	4367 (37.3)	8734	.99
2007-2010	3064 (26.4)	3101 (26.7)	6165		3099 (26.4)	3102 (26.5)	6201	
2011-2013	2082 (18.0)	2072 (17.9)	4154		2083 (17.8)	2072 (17.7)	4155	
2014-2017	1898 (16.4)	1925 (16.6)	3823		1917 (16.4)	1925 (16.4)	3842	
2018-2019	263 (2.3)	253 (2.2)	516		253 (2.2)	253 (2.2)	506	
Race, No. (%)								
Asian	258 (2.2)	286 (2.5)	544	.005	300 (2.6)	293 (2.5)	593	.99
Black	1017 (8.8)	1074 (9.3)	2091		1093 (9.3)	1095 (9.3)	2188	
Hispanic	1084 (9.3)	1187 (10.2)	2271		1207 (10.3)	1209 (10.3)	2416	
White	8025 (69.2)	7846 (67.6)	15 871		7898 (67.4)	7895 (67.4)	15 793	
Unknown	1218 (10.5)	1209 (10.4)	2427		1221 (10.4)	1227 (10.5)	2448	
Education								
Less than college	8173 (76.4)	8468 (78.9)	16 641	<.001	8696 (74.2)	8557 (73.0)	17 253	.039
College	2529 (23.6)	2262 (21.1)	4791		2121 (18.1)	2273 (19.4)	4394	
Unknown	900 (7.8)	872 (7.5)	1772		902 (7.7)	889 (7.6)	1791	
US region at diagnosis, No. (%)								
Northeast	1020 (8.8)	1028 (8.9)	2048	.007	1117 (9.5)	1034 (8.8)	2151	<.0001
North Central	2563 (22.1)	2562 (22.1)	5125		2833 (24.2)	2594 (22.1)	5427	
South	5878 (50.7)	5511 (47.5)	11 389		5691 (48.6)	5574 (47.6)	11 265	
West	2128 (18.3)	2476 (21.3)	4604		2070+ (17.7)	2492 (21.3)	4563	
Unknown	13 (0.11)	25 (0.22)	38		<11 (0.06)	20+ (0.21)	32	
No. of visits, median (IQR)	3.0 (2.0-5.0)	3.0 (2.0-6.0)			3.0 (1.0-5.0)	3.0 (2.0-6.0)		

Abbreviations: DE, delayed ejaculation; ED, erectile disfunction; PD, Peyronie's disease.

diagnosed in 5% of Asian men with DE compared to <2% of men of other races. Selective serotonin reuptake inhibitors were prescribed in 11% of white men with DE compared to <8% of Black, Asian, or Hispanic men.

Discussion

This is to our knowledge the first reported study utilizing a data agnostic approach to identify clinical factors associated with a diagnosis of DE with respect to other diagnoses of sexual dysfunction. Our analyses suggest that DE is associated with male factor infertility, anxiety, or depression. Data mining is an emerging method of identifying clinical factors and helping to develop predictive models that may enhance medical decision making.[9] Zhou et al describe the current practice of medicine transitioning to that of "precise medicine" and data mining analyses playing an important role in contributing to this transition.[9] There has been an increasing utilization of data mining methodology in recent years, with the number of yearly publications more than doubling between 2013 and 2019.[12] These methods have been increasingly utilized in the urological literature as well. Data mining has been used to identify predictive factors associated with various urologic conditions, such as urinary tract injury during surgery, reproductive outcomes following varicocele embolization, and treatment response for benign prostatic hyperplasia.[13,14] Our data suggest that data mining is an efficient and accurate way of identifying clinical factors related to conditions of sexual dysfunction in large cohorts of men. While basing clinical practice on statistical methodology can be problematic, it is reassuring that our model showed reasonable accuracy in predicting eventual DE as well as confirmed several known factors (eg, depression). Indeed, the presence of identified diagnoses (eg, male infertility, anxiety, depression) or subsequent treatments may predict the development of DE.

The diagnoses and medications associated with DE in our study are consistent with those identified in prior reports. Mulhall et al reported a 42% incidence of SSRI use in 206 patients with delayed orgasm.[7] The mechanism of SSRI-induced DE may be multifractional. SSRIs are hypothesized to lead to a hyperprolactinemic state and/or desensitization of oxytocin neurons leading to DE, and men who on SSRI therapy have a seven-fold risk of developing DE.[15-17] Indeed, SSRIs are prescribed for the treatment of rapid ejaculation as a means of prolonging climax.[18] In addition, men with DE have also been shown to have higher depression and anxiety scores.[19] Anxiety in these men may be psychosexual in nature and related to stresses and concerns during sexual relationships, such as hurting their partners or fear of impregnation.[20,21] Our data emphasize the importance of identifying men with anxiety who present with sexual dysfunction and helping to facilitate care to help mitigate the future risk of developing DE.

A majority of men with DE in our cohort had metabolic syndrome, a finding consistent with previous studies which showed a 5% prevalence of DE among men with metabolic syndrome.[22] Through hormonal, vascular, and inflammatory pathways, the metabolic syndrome is associated with impaired

Table 2. Random forest analysis identifying factors associated with DE compared to those associated with PD or ED.

Factor	DE vs PD, No. (%)			DE vs ED, No. (%)		
	PD	DE	OR (95% CI)	ED	DE	OR (95% CI)
Male infertility	53 (0.5)	198 (1.7)	**4.14 (3.03-5.66)**	52 (0.44)	201 (1.7)	**4.04 (2.96-5.50)**
Selective alpha-1-adrenergic block agent	648 (5.6)	994 (8.6)	**1.95 (1.73-2.19)**	612 (5.2)	994 (8.5)	**1.60 (1.42-1.80)**
Other nonorganic psychoses	92 (0.79)	258 (2.2)	**1.92 (1.48-2.49)**	100 (0.85)	259 (2.2)	**1.61 (1.26-2.06)**
Iron deficiency anemia	129 (1.1)	260 (2.2)	**1.89 (1.51-2.37)**	145 (1.2)	260 (2.2)	**1.31 (1.05-1.64)**
Phosphodiesterase inhibitors	564 (4.9)	867 (7.5)	**1.64 (1.47-1.84)**	754 (6.4)	889 (7.6)	**1.29 (1.16-1.43)**
Phosphodiesterase type 5 inhibitors	679 (5.85)	1006 (8.7)	**1.50 (1.35-1.67)**	1194 (10.2)	1006 (8.6)	0.80 (0.73 -.088)
Antidepressants, miscellaneous	264 (2.3)	545 (4.7)	**1.45 (1.23-1.71)**	256 (2.2)	545 (4.7)	**1.47 (1.25-1.73)**
Malaise and fatigue	1096 (9.5)	1723 (14.9)	**1.41 (1.29-1.53)**	1466 (12.5)	1740 (14.9)	1.08 (0.997-1.17)
Depressive disorder	460 (4.0)	917 (7.9)	**1.41 (1.24-1.60)**	556 (4.7)	929 (7.9)	**1.15 (1.02-1.29)**
Selective serotonin reuptake inhibitors	654 (5.6)	1153 (9.9)	**1.39 (1.24-1.56)**	628 (5.4)	1153 (9.8)	**1.50 (1.33-1.68)**
Anxiety	847 (7.3)	1462 (12.6)	**1.37 (1.24-1.52)**	871 (7.4)	1473 (12.6)	**1.33 (1.21-1.47)**
Essential hypertension	3656 (31.5)	4623 (39.9)	**1.33 (1.25-1.41)**	4782 (40.8)	4655 (39.7)	0.93 (0.88 -.0993)
Nutrition symptoms	208 (1.8)	296 (2.6)	1.20 (0.993-1.45)	223 (1.9)	300 (2.6)	**1.21 (1.01-1.45)**
Testicular dysfunction	1046 (9.0)	1435 (12.4)	**1.20 (1.09-1.31)**	907 (7.7)	1444 (12.3)	**1.53 (1.40-1.68)**
Disorder of lipoid metabolism	3442 (29.7)	4074 (35.1)	**1.16 (1.08-1.23)**	4041 (34.5)	4112 (35.1)	**1.08 (1.02-1.15)**
Other back disorder	1297 (11.2)	1566 (13.5)	**1.11 (1.02-1.21)**	1312 (11.2)	1584 (13.5)	**1.11 (1.02-1.20)**
Diabetes mellitus	1318 (11.4)	1658 (14.3)	1.09 (0.999-1.19)	1729 (14.8)	1676 (14.3)	0.994 (0.92-1.08)
Other disorder of the joint	1149 (9.9)	1345 (11.6)	1.06 (0.97-1.17)	1160 (9.9)	1355 (11.6)	**1.13 (1.03-1.23)**
Antidepressants	569 (4.9)	732 (6.3)	1.06 (0.94-1.20)	608 (5.2)	756 (6.5)	1.12 (0.995-1.27)
Respiratory symptoms	1735 (15.0)	2020 (17.4)	1.01 (0.93-1.09)	1950 (16.6)	2040 (17.4)	0.94 (0.87-1.01)
Nonspecific findings on examination of blood	1406 (12.1)	1529 (13.2)	0.98 (0.90-1.06)	1573 (13.4)	1537 (13.1)	0.87 (0.80 -.094)
Other disorders of soft tissues	1490 (12.8)	1695 (14.6)	0.97 (0.89-1.05)	1460 (12.5)	1705 (14.6)	1.01 (0.93-1.10)
Urinary symptoms	2107 (18.2)	1992 (17.2)	0.88 (0.82-0.95)	1702 (14.5)	2002 (17.1)	1.04 (0.96-1.12)
HMG-COA reductase inhibitors	2018 (17.4)	2135 (18.4)	0.87 (0.80-0.94)	2076 (17.7)	2135 (18.2)	0.94 (0.87-1.01)
Prostate hyperplasia	2709 (23.4)	2390 (20.6)	0.75 (0.70-0.81)	1993 (17.0)	2397 (20.5)	**1.1 (1.03-1.19)**

Abbreviations: DE, delayed ejaculation; ED, erectile disfunction; HMG-CoA, Hydroxymethylglutaryl-CoA. PD, Peyronie's disease. Overall order based on strength of association. Bold OR values denote $P < .005$.

male erectile function.[23] In the current study we also found an association with ejaculatory function, with 26%-53% of men in the cohort having hypertension and approximately 33% with associated lipid dysfunction, findings that are further supportive of an association between ejaculatory function and components of metabolic syndrome.

Delayed ejaculation has also been associated with a diagnosis of male infertility. The incidence of ejaculatory dysfunction among men with infertility is well known, with 1% of infertile men experiencing anejacultion.[24] The cause of this problem may be multifactorial and may be related to coexisting medical conditions and/or pharmacologic therapies, but any direct link between male factor infertility and the development of subsequent ejaculatory dysfunction is an area that requires future research.

Although there are racial differences among men presenting for ejaculatory dysfunction,[25] to the best of our knowledge, our study is the first to compare DE by race in a large cohort of men. We identified different associated conditions and ages of presentation across different races, findings which have important clinical implications.

Several study limitations warrant mention. Pre-existing comorbidities or medication use were not controlled for in this analysis, which may affect the generalizability of these findings. Furthermore, as with any claims-based analysis, the granular etiology of DE was not known (ie, situational or generalized). Next, additional clinical information such as ejaculatory latency time or anxiety/stress levels were not available. The current report relies on coding accuracy, which may vary between providers. Association does not indicate that causation and temporality of the relationships could not be identified. Cohort matching may limit differences based on matching parameters (eg, age, race). The study population comprises men with employer-based insurance and may not be generalizable to all men.

Conclusion

Delayed ejaculation is associated with multiple medical conditions, which may help identify etiology and risk and could eventually lead to novel treatment options that arise from a better understanding of causes of this disorder.

Supplementary material

Supplementary material is available at *Sexual Medicine* online.

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None reported.

Conflicts of interest: Dr. Eisenberg, is an advisor to the companies Dadi, Roman, Sandstone, Hannah and Underdog and also serves as a consultant to Gilead.

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