

STUDY OF THE DOPAMINE TRANSPORTER GENE (*DAT1*) POLYMORPHISM AND SEROTONIN TRANSPORTER PROMOTER GENE IN PATIENTS WITH LIFELONG PREMATURE EJACULATION AND ITS RELATION TO THE RESPONSE TO SSRIs

By

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ABSTRACT

Background: Dopamine and serotonin transporter genes play an important role in the control of the mechanism of ejaculation.

Objectives: Evaluation of the role of serotonin transporter gene promoter and dopamine transporter gene polymorphisms in lifelong premature ejaculation and their role in determining the response to paroxetine and escitalopram.

Patients and Methods: Eighty consecutive patients and controls were recruited. Forty of them suffered lifelong premature ejaculation. They were divided into two equal groups: One group received paroxetine (20 mg daily) for 1 month, and the other one received escitalopram (20 mg daily) for 1 month. Their wives were instructed to measure the intravaginal ejaculation latency time using stopwatch. Five ml blood was withdrawn from patients and controls for PCR.

Results: The present study revealed that the majority of the patients were SL and SS genotypes of the serotonin transporter gene promoter polymorphism. Also, this study revealed that the majority of the patients were (10R/10R) genotypes of the dopamine transporter gene polymorphism. Both of paroxetine and escitalopram significantly delayed ejaculation in the responders.

Conclusion: The study revealed significant association between such response and dopamine transporter gene polymorphism. The present study augmented the significant effect of both paroxetine and escitalopram in delaying ejaculation in the responders.

Key words: Lifelong premature ejaculation (LPE), serotonergic transporter gene promoter polymorphism (5-HTTLPR), dopamine transporter gene polymorphism (DAT1), paroxetine and escitalopram.

INTRODUCTION

ISSM unanimously agreed that the constructs that are necessary to define premature ejaculation are time from penetration to ejaculation, inability to delay ejaculation, and negative personal consequences from premature ejaculation. The committee also agreed that the 1-

minute intravaginal ejaculatory latency time cutoff point should not be applied in the most absolute sense, as about 10% of men seeking treatment for lifelong premature ejaculation have intravaginal ejaculatory latency time of 1–2 minutes with negative personal consequences, such as distress, bother, frustration, and/or

the avoidance of sexual intimacy (McMahon *et al.*, 2008). A role of genetic factors in the etiopathogenesis of premature ejaculation has been claimed, particularly, genotypes of the serotonin transporter gene in patients with premature ejaculation were the main interest of our study and dopamine transporter gene and their relation to response to SSRIs. We aimed in this work to evaluate role of both paroxetine and escitalopram in patients with lifelong premature ejaculation and polymorphisms of both serotonin transporter and dopamine transporter genes (Safarinejad, 2009).

PATIENTS AND METHODS

A total of 80 consecutive potent men were recruited from Andrology and Dermatology Outpatient Clinics, Al-Azhar University Hospitals. Sixty patients suffered from inability to delay ejaculation for more than 1 minute since their first sexual experience were recruited from The Andrology Clinic. Twenty cases were control and recruited from Dermatology Clinic (normally potent men). They were recruited from May 2014 up to June 2015. Approval of the local ethical committee which conforms with the declaration of Helsinki was obtained, after getting writing informed consents from the patients and controls including the purpose of the study and the need to withdraw blood sample (5 ml) from each patient for genotyping at the end of the study.

The age of patients included in our study was between 25-50 years with a stable and continuous marital relationship

for at least one year, being unable to satisfy their partners with intravaginal ejaculation latency time < 1 minute since their first sexual experience on all or nearly all vaginal penetrations with negative personal consequences on him, and his partner and subsequent avoidance of sexual intimacy, with no history of psychosexual counseling before.

We excluded the patients who suffered from erectile dysfunction (ED) of International Index of Erectile Function (score < 21), reduced sexual desire or inhibited male orgasm. Also, patients with history of urinary tract infection, mental disorders, dermatological lesions and chronic physical illnesses affecting ejaculatory function, abusers of alcohol or recreational drug, and patients who received psychotropic medications that may affect response to selective serotonin reuptake inhibitors (SSRIs) or any medical treatment for premature ejaculation in the last 6 months.

The patients were divided into 2 equal groups; one group was given 20-mg paroxetine and the other 20-mg escitalopram (once daily for 1 month) to compare efficacy of both drugs in delaying ejaculation in these patients, and the role of the studied genes polymorphisms in determining the response of the patients to such drugs. Patients were supplied with an ejaculatory diary, and were asked to record frequency of coitus, quality of erection, and intravaginal ejaculatory latency time (IELT) using stopwatch handled by patient's wife. The patients' wives were instructed to measure the time taken from vaginal penetration until sense of ejaculation.

The patients were reviewed weekly, and all these measurements before and after treatment were recorded with any potential side effects. We evaluated the potency of the men included in this study using validated Arabic version of International index of erectile function (IIEF) (Shamloul et al., 2004). A responder was defined as an individual who had 2 folds or greater increase in the geometric mean of intra vaginal ejaculation latency times (IELT) compared with base line values after three months of paroxetine and escitalopram therapy. A non-responder was defined as an individual who had a fold increase of the geometric mean of IELT of less than 2. The cutoff was based on the outcome data of a meta-analysis of daily selective serotonin reuptake inhibitors treatment for premature ejaculation, in which placebo response was consistently lower than a twofold increase of the geometric mean of IELT compared with baseline values (Waldinger et al., 2004).

Blood samples were collected into tubes containing EDTA. Genomic DNA was extracted from the whole blood using EZ-10 spin column Blood Genomic DNA Mini preps kit (Biosystems, California, US) and stored at -20°C until genotyping was performed. The insertion/deletion in the *serotonin transporter gene promoter* (*5-HTTLPR*) was assessed only by polymerase chain reaction (PCR) amplification.

The sequences of PCR primers were 5'-CCGCTCTGAATGCCAGCACCTAAC-3' and 5'-AGAGGGACTGAGCTGGACAACCAC-3'. Each PCR contained 10 ng genomic DNA in a final volume of 20 μl reaction which included 10 pmol of

each primer (Operon Biotechnologies, Germany), 1 U Taq DNA polymerase (Promega Corporation, US), 0.1 mM dNTP mix (Promega Corporation, US), 2.0 \times 1 Taq buffer with KCl, and 1.0 mM MgCl₂. PCR was performed on an automated DNA thermal cycle (Piq lab, Biotechnologie) with procedure as follows: initial denaturation at 95 $^{\circ}\text{C}$ for 10 min, 40 cycles of amplification consisting of denaturation at 94 $^{\circ}\text{C}$ for 30 sec, annealing at 66 $^{\circ}\text{C}$ for 45 sec, extension at 72 $^{\circ}\text{C}$ for 45 sec and in the last cycle, extension was prolonged to 7 min. Allele sizes were determined by comparison of bands with size standards after electrophoresis in a 6.5% polyacrylamide gel and silver staining. Amplification of the (*5-HTTLPR*) gene gave two alleles differing by 44 bp (L with 522 bp and S with 478 bp) (Bleich et al., 2007).

The variable number of tandem repeats (VNTR) polymorphism in *DAT1* was genotyped using PCR method (Vandenbergh et al., 1992). Briefly, genomic DNA was isolated from whole blood by mean of a DNA extraction kit (QIAamp[®] kit (QIAGEN, Valencia, CA)). A total of 50 ng of genomic DNA was mixed with 20 pmol of each *DAT1* primer: upstream, TGTGGTGTAGGGAACGGCCTGAGA; downstream, AAATCCAGTGGGGTCCCTTCCTG in a total volume of 25 μl containing 10 mM Tris-hydrochloride, pH 8.3; 50 mM potassium chloride; 2.0 mM magnesium chloride; 0.2 mM each deoxyribonucleotide triphosphate; and 1 U of DNA polymerase. The PCR protocol involving an initial 5-min denaturing step at 95 $^{\circ}\text{C}$, followed by 35 cycles of 94 $^{\circ}\text{C}$ for 45 sec, 67 $^{\circ}\text{C}$ for 60 sec, 72 $^{\circ}\text{C}$ for 30 sec, followed by 74 $^{\circ}\text{C}$ for 10 min for the final extension. The

PCR products were electrophoresed on a 2% agarose gel, and visualized by ethidium bromide staining. Molecular weights of 320, 360, 400, 440, 480 and 520 bp corresponded with the six-, seven-, eight-, nine-, 10- and 11-copy alleles, respectively.

Statistical analysis: Hardy-Weinberg equilibrium (HWE) was determined to check the laboratory efficacy of PCR analysis in the patients and the controls groups by using a chi-square test. Allele and genotype frequencies between patients and controls were compared by using IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). The mean, median, and geometric mean of IELT were calculated for stopwatch-determined

IELTs and percentages when appropriate. Analysis of variance (ANOVA) was performed to determine an association between the genotype in the patient group and the fold increases in the IELT. A p-value less than 0.05 was considered statistically significant.

RESULTS

The minimum age of the patients was 23 years old, and the maximum was 63 years old, while in the controls the minimum was 27 years old and the maximum was 46 years old. This showed a statistically significant difference (p value= 0.023) using **Mann-Whitney test (Table 1)**.

Table (1): Ages of the groups.

Groups Parameters	Control			Patients			P value
	Mean ±SD	Minimum	Maximum	Mean ±SD	Minimum	Maximum	
Age	36.40±5.76	27.00	46.00	41.42±8.96	23.00	63.00	0.023

The frequency of the genotypes and Alleles of serotonin transporter gene promoter among the controls and the patients were as follows: 18 patients were LL (30%), 24 patients were SL (40%) and 18 patients (30%) were SS. In the controls, the genotypes were 10 LL (50%), 6 SL (30%) and 4 SS (20%) respectively. This did not show a statistically significant result (p value= 0.265). The Alleles L and S were present equally in the patients (50% each) while in the controls the Alleles were 26 L (65%) and 14 S (35%). This did not show a statistically significant result (p value= 0.099). The frequency of the

genotypes and Alleles of dopamine transporter gene among the patients and the controls were as follows: 6 patients (10%- 6R/6R), 17 (28.3% - 6R/10R) and 37 patients (61.7% - 10R/10R), and in the controls were 15 (75%- 6R/6R), 4 (20% - 6R/10R) and 1 (5%- 10R/10R). This showed a statistically significant result (p-value= <0.001), and the Alleles of the patients were 29 (24.2%- 6R) and 91 (75.8%- 10R), and of the controls were 34 (6R-85%) and 6 (15%- 10R). This showed a statistically significant result (p-value= <0.001) (**Table 2**).

Table (2): Prevalence of gene polymorphisms of the groups.

Genotypes		Groups		Control (20)		Patients (60)		P value
		Count	%	Count	%			
Genotype 1 LL/SS	LL	10	50.0%	18	30.0%	0.265		
	SL	6	30.0%	24	40.0%			
	SS	4	20.0%	18	30.0%			
	Allele L	26	65%	60	50%	0.099		
	Allele S	14	35%	60	50%			
Genotype 2 6/10	6R/6R	15	75.0%	6	10.0%	<0.001		
	6R/10R	4	20%	17	28.3%			
	10R/10R	1	5.0%	37	61.7%			
	Allele 6R	34	85%	29	24.2%	<0.001		
	Allele 10R	6	15%	91	75.8%			

Both escitalopram and paroxetine showed excellent response with both groups and resulted in statistically significant results (Table 3).

Table (3): Response to escitalopram and paroxetine of patients.

Response		Groups	
		Group I	Group II
IELT PRE (seconds)	Mean	43.46	36.40
	Standard Deviation	14.13	12.87
	Minimum	20.00	10.00
	Maximum	80.00	50.00
IELTPOST (seconds)	Mean	434.42	335.40
	Standard Deviation	638.06	357.75
	Minimum	30.00	15.00
	Maximum	1800.00	1200.00
P VALUE		<0.001	<0.001

There was no statistically significant relation between different genotypes 1 in the terms of fold increase (p-value=0.275) and log FI (p-value= 0.916) and serotonin transporter promoter gene polymorphism, using (Table 4).

Table (4): Relation between the responders and serotonin transporter gene.

Genotype		Genotype 1 LL/SS			P Value
		LL	SL	SS	
Fold increase	Mean	6.18	12.29	7.84	0.275
	Standard Deviation	6.65	14.74	10.66	
	Minimum	1.08	1.25	1.14	
	Maximum	22.50	45.00	40.00	
Log FI	Mean	1.22	1.63	1.34	0.916
	Standard Deviation	1.15	1.43	1.20	
	Minimum	.08	.22	.13	
	Maximum	3.11	3.81	3.69	

There was a statistically significant relation between different genotypes 2 in the terms of fold increase (p-value=0.019), log FI (p-value= 0.010), and dopamine transporter gene polymorphism (Table 5).

Table (5): Relation between the responders and (DAT) gene.

Genotype		Genotype 2 6/10			P VALUE
		6R/6R	6R/10R	10R/10R	
Fold increase	Mean	1.61	4.21	12.67	0.019
	Standard Deviation	.11	4.87	13.46	
	Minimum	1.50	1.08	1.25	
	Maximum	1.75	12.00	45.00	
Log FI	Mean	.47	.88	1.83	0.010
	Standard Deviation	.07	1.01	1.31	
	Minimum	.41	.08	.22	
	Maximum	.56	2.48	3.81	

DISCUSSION

Lifelong PE as a neurobiological dysfunction with a genetic vulnerability for short IELTs related was postulated to decreased central serotonin (5 hydroxy-tryptamine [5-HT]) neurotransmission and/or 5-HT receptor dysfunction, i.e. a hypofunction of 5-HT_{2C} and/or hyperfunction of 5-HT_{1A} receptors (**Safarinejad, 2009**).

This study showed that the majority of the patient's genotypes as regards 5-HTTLPR gene was SL followed by SS, while in the controls' genotype was mainly LL, despite such difference it was statistically insignificant which may signify that LL was protective against lifelong PE.

As regards DAT1 gene, the majority of the patients was 10R/10R followed by 6R/10R, while in the controls' genotype was mainly 6R/6R, and such difference was statistically significant that 6R/6R was protective against lifelong PE.

The Study demonstrated also that both paroxetine and escitalopram were effective in patients with lifelong PE, and showed statistically significant results where response of patients to both drugs was unrelated to 5-HTTLPR gene polymorphism. Meanwhile, it showed a significant relation with DAT1 gene polymorphism where, to the best of our knowledge, this was the first study to show the response of DAT1 gene to different SSRIs.

Several studies evaluated the role of 5-HTTLPR gene polymorphism in patients with lifelong PE. Some of them were consistent with our findings (**Ozbek et al., 2009, Safarinejad, 2009 and Zhu et al.,**

2013). **Safarinejad (2009)** explained the role of S allele of the serotonin transporter linked promoter region polymorphism in patients with lifelong PE. Patients with the homozygous form might have a higher increase in synaptic 5-HT concentration. Meanwhile, they have reduced transcription activity leading to fewer target molecules for transport into nerve cells. This could result in increased up-regulation of 5-HT_{1A} autoreceptors and thereby result in long-term deactivation of serotonergic transmission.

On the other hand, **Janssen et al. (2009)** showed that men with LL genotypes have statistically shorter IELTs than men with SS and SL genotypes. They attributed that to more (or better) functioning 5-HT transporters that would correspond with lower synaptic serotonin, and consequently lower stimulation of any 5-HT receptor.

Vandenbergh et al. (1992) stated that 10R allele is the most frequent among the DAT1-VNTR polymorphism. The prevalence of the genotypes and allele frequencies were examined in a study performed by **Safarinejad (2011)**. He showed that the patients with PE were more likely to have the 9/10 genotype and 9R allele than the control group, and this was highly consistent with several reports from Asian countries. Studies on Asian populations have shown that more than 90% of the Japanese, Mongolian and Korean populations have the 10R allele (**Kim et al., 2006**).

Several studies evaluated the response of 5-HTTLPR gene to SSRIs and were consistent with our findings (**Janssen et al., 2014 and Ozbek et al., 2014**). Contrary to our finding, **Serretti et al.**

(2007) stated that there is significant association of the 1 variant of 5-HTTLPR and a better response to SSRIs and this effect seemed independent from ethnic differences. The subjects with S/S genotype have difficulties to reach remission and take a long time, over 4 weeks, to respond as well as the subjects with s allele take a long time to respond. **Ozbek et al. (2009)** concluded that further clinical studies are needed to compare the 5-HTTLPR gene polymorphism in primary and secondary PE patients. Genetic polymorphism in the 5-HTT gene might also be investigated to understand the genetic nature of patients' responses to different SSRIs commonly used in the treatment of PE.

A role of dopamine transporter gene polymorphism in premature ejaculation was postulated (**Santtila et al., 2010**). The DA transporter (DAT) is a presynaptic plasma membrane protein expressed solely in DA-synthesizing neurones (**Bannon, 2005**). Therefore, it plays a critical role in ending DA neurotransmission. The gene for the DAT SLC6A3 is located on chromosome 5 at p15.3, and contains 15 exons spanning about 50 kb (**Vandenbergh, 1992**).

Whereas reports on the effects of these polymorphisms on gene expression have been conflicting (**Van Dyck et al., 2005**), functional magnetic resonance imaging and PET studies suggest the 9 allele, as compared to the 10 allele, to be associated with enhanced dopaminergic output (**Brody et al., 2006**), and enhanced activation of brain regions innervated by DA afferents (**Franklin et al., 2009**).

Prompted by the apparent involvement of dopaminergic neurotransmission in

ejaculation, and the important role of the dopamine transporter as a regulator of DA function **Vandenbergh et al. (1992)** stated that 10R allele is the most frequent among the DAT1-VNTR polymorphism.

Also, **Santtila et al. (2010)** demonstrated a significant association between individuals homozygous for the 10R allele and PE. Studies on Asian populations have shown that more than 90% of the Japanese, Mongolian and Korean populations have the 10R allele (**Kim et al., 2006**). Our findings could be seen contradictory to the prevalence of the genotypes and allele frequencies examined in a study performed by **Safarinejad (2011)** which showed that the patients with PE were more likely to have the 9/10 genotype and 9R allele than the control group.

A recent meta-analysis of all drug treatment studies has demonstrated that paroxetine exerts the strongest ejaculation delay (**Malavige and Jayawickrema 2015**).

Safarinijad (2007) stated that oral escitalopram is an effective treatment for PE with long-term benefit for the patient after it is withdrawn. However, another study performed in demonstrated that daily escitalopram treatment effects the semen parameters of patients with lifelong PE (**Koyuncu et al., 2011**).

CONCLUSION

There were excellent responses to both escitalopram and paroxetine in treatment of premature ejaculation. There was a statistically significant relation between the responders and dopamine transporter gene polymorphism that was in contrast to be found in SERT gene.

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دراسة جين ناقل الدوبامين وجين ناقل سيروتونين المحفز في المرضى الذين يعانون من سرعة القذف و علاقته بالإستجابة لمانع إعادة امتصاص سيروتونين الإنتقائي

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خلفية البحث: أثبتت الدراسات علي جين ناقل الدوبامين، و جين ناقل سيروتونين المحفز في المرضى الذين يعانون من القذف المبكر مدي علاقتهم بالاستجابة لمانع إعادة امتصاص سيروتونين الانتقائي، والعلاقة بين تعدد الأشكال الوراثية لجين ناقل سيروتونين و جين ناقل الدوبامين و القذف المبكر.

الهدف من البحث: دراسة جين ناقل الدوبامين وجين ناقل سيروتونين المحفز في المرضى الذين يعانون من سرعة القذف و علاقته بالإستجابة لعقاري الباروكستين والإسيتالوبرام.

المرضي وطرق البحث: شملت هذه الدراسة 60 مريضاً من المترددين على عيادة الأمراض الجلدية والذكورة بمستشفى الحسين الجامعي من مايو 2014 إلي يونيو 2015، والمصابين، ويعانون من القذف المبكر و 20 من الأصحاء كضوابط، و تم تقسيم المرضى إلي مجموعتين : المجموعة الأولى تم إعطائها عقار الباروكستين علي هيئة أقراص (20ملي جرام) والمجموعة الثانية عقار إيسيتالوبرام (20 ملي جرام) يوميا لمدة شهر، وطلب من زوجاتهم قياس الوقت الكمون داخل المهبل باستخدام ساعة إيقاف، و تم سحب عينة 5 ملي من دم المرضى و الضوابط لعمل (PCR).

النتائج: الأغلبية من المرضى كانت تحمل الشكل الجيني (SL)، (SS) لجين ناقل سيروتونين، والشكل الجيني (10R/10R) لجين ناقل دوبامين، فضلاً عن أن هناك علاقة إيجابية بين جين ناقل دوبامين والإستجابة لكلٍ من العقارين.

الإستنتاج: وجود علاقة إيجابية بين إستجابة المرضى لعقاري إيسيتالوبرام وباروكستين، وجين ناقل الدوبامين، و فاعلية كلا العقارين في علاج القذف المبكر.