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DIRECCIÓN DE NUEVAS CREACIONES

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Abogado
JUAN PABLO CADENA SARMIENTO
jcadena@bc.com.co

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 Evento 378
 Actuación 519
 Oficio - - - 18708
 Folios 14

Patente de Invención ☒ Patente de Modelo de Utilidad

Vía Nacional

Vía PCT (Fase Nacional) ☒ Capítulo I ☒ Capítulo II

No. Solicitud Internacional PCT/KR2008/006445

Fecha de Presentación Internacional 31/Octubre/2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 8 a 80	02/Junio/2010
Reivindicaciones:	Folios 81 a 96	02/Junio/2010
Oposiciones:	Folios 117 a 125	Lafrancol 19/Agosto/2011
Prioridad:	KR 10-2007-0111783	02/Noviembre/2007
	KR 10-2008-0105439	27/Octubre/2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

Expediente 10-66630 1er Art 45

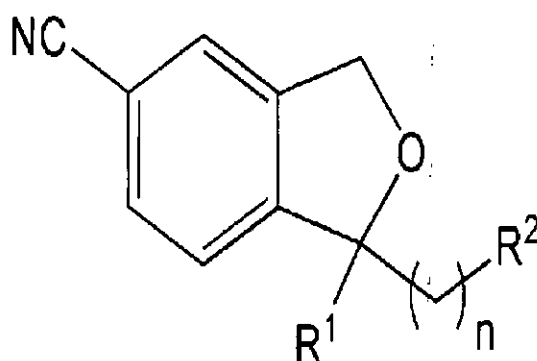
3. Objeto de la invención

Título de la solicitud: "NOVEDOSOS DERIVADOS DE 1,3-DIHIDRO-5-ISOBENZOFURANCARBONITRILLO Y COMPOSICIÓN FARMACÉUTICA DE LOS MISMOS PARA EL TRATAMIENTO DE LA EYACULACIÓN PREMATURA".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una composición farmacéutica para tratar o prevenir la eyaculación prematura, teniendo la composición una vida media corta y un buen efecto para retardar la eyaculación.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto derivado de 1,3- dihidro-5-isobenzofurancarbonitrilo de la fórmula 1, composiciones que lo contienen y un proceso para su preparación

[Formula 1]



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C 07 D 307/87

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de la reivindicación 20 no es patentable de acuerdo con el Art citado.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capítulo reivindicatorio no es conciso porque las definiciones de R¹ y R² conllevan a un número indefinido de compuestos que no encuentran soporte en la descripción. Al revisar en la descripción en los ejemplos se muestra que R¹ corresponde a tienilo, fenilo insustituido o sustituido en la posición 4 por metoxi, metilo, flúor, cloro o dimetilamino; y R² corresponde a dimetilamino, imidazolilo o pirazolilo. Por lo tanto, se sugiere restringir la solicitud a los compuestos y composiciones sustentados en la descripción.

La reivindicación 20 se refiere a un método de tratamiento, lo cual no es patentable según la legislación aplicable. Se sugiere eliminar esta reivindicación del pliego reivindicatorio.

6. Análisis de la Oposición

Argumentaciones de Lafrancol

Afirma el opositor que esta solicitud pretende obtener patente para el uso de composiciones farmacéuticas ya comprendidas en el estado de la técnica argumentando que las composiciones farmacéuticas que comprenden derivados de 1,3-dihidro-5-isobenzofurancarbonitrilo útiles en el tratamiento de la eyaculación prematura son practicas y eventos totalmente conocidos en la industria farmacéutica el estado de la técnica y que no puede existir un beneficio patentario que reivindique composiciones farmacéuticas que comprendan moléculas plenamente identificadas y utilizadas como lo son Citalopram y Escitalopram por lo cual referencia los documentos EP 347066, DE 2657013, US 4136193, US 4943590 y US RE 34712 y anexa copias extractadas de "The Index Merck" referentes a estos principios activos

Respuesta del Examinador Técnico

El opositor presenta documentos patente y copias extractadas de "The Index Merck" que evidencian la existencia de los compuestos Citalopram y Escitalopram, ampliamente conocidos en el estado de la técnica; Dado que la estructura química de estos compuestos cae dentro de la definición de la estructura del compuesto de la formula I reclamado en la solicitud, los documentos presentados por el opositor afectan la novedad de la solicitud.

Los documentos EP347066 (perteneciente a la misma familia de patentes de los documentos US 4943590 y US RE 34712) y US 4136193 (perteneciente a la misma familia de patentes del documento DE 2657013) serán tenidos en cuenta en el examen de patentabilidad

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: Noviembre 02 de 2007, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	EP347066	New Enantiomers and their Isolation.	14/Junio/1988
D2	US4136193	Anti-Depressive Substituted 1-Dimethylaminopropyl-1-Phenyl Phthalans	23/Enero/1979
D3	WO2003042202	Isobenzofuran Derivatives	22/Mayo/2003
D4	WO9819511	Method for The Preparation of Citalopram	14/Mayo/1998

D5	International Journal of Impotence Research (2002) 14, 502-505 Atmaca et al "The Efficacy of Citalopram in The Treatment of Premature Ejaculation: A Placebo-Controlled Study"	The Efficacy of Citalopram in The Treatment of Premature Ejaculation: A Placebo-Controlled Study	01/Junio/2002
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D1
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=0347066A1&KC=A1&FT=D&ND=3&date=19891220&DB=worldwide.espacenet.com&locale=en_EP divulga (página 2 línea 1 a página 3 línea 30, página 10 líneas 20 a 56, reivindicaciones 1 a 8) compuestos correspondientes a enantiómeros de citalopram

D2
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=4136193A&KC=A&FT=D&ND=3&date=19790123&DB=worldwide.espacenet.com&locale=en_EP divulga (columna 1, línea 51 a columna 4 línea 6) un compuesto derivado de benzofurano

D3
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=03042202A1&KC=A1&FT=D&ND=3&date=20030522&DB=worldwide.espacenet.com&locale=en_EP divulga (página 4 línea 5 a página 7 línea 30) compuestos derivados de isobenzofurano

D4
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=9819511A2&KC=A2&FT=D&ND=4&date=19980514&DB=worldwide.espacenet.com&locale=en_EP divulga (página 2 línea 25 a página 7 línea 21) un proceso de preparación de citalopram

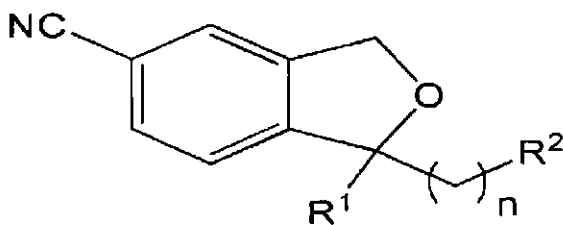
D5
<http://www.sinab.unal.edu.co:2108/ehost/detail?vid=4&hid=15&sid=bff02fcc-7a64-4e68-bc02-a481c2df2f31%40sessionmgr11&bdata=Jmxhbm9ZXMmc2l0ZT1laG9zdC1saXZl#db=a9h&AN=8897046> divulga (páginas 502 a 505) (Ver folios 145 a 148) el efecto del citalopram en el tratamiento de la eyaculación prematura

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en un derivado representado por la Fórmula 1 o una sal farmacéuticamente aceptable del mismo:

[Formula 1]



(Ver folio 81)

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

Características esenciales	D1
[Formula 1]	
Anillo de benzofurano	Anillo de benzofurano
CN	CN
R ¹ Fenilo sustituido	Fenilo sustituido por flúor
-(CH ₂) _n - n es un número entero de 1 a 3	-(CH ₂) ₃ -
R ² Dialquilamino C ₁ – C ₆	Dimetilamino

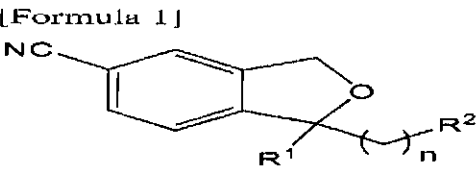
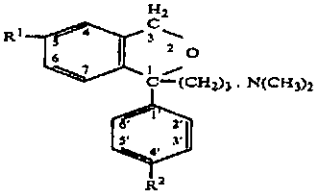
Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D1, el cual da a conocer compuestos correspondientes a enantiómeros de citalopram (página 2 línea 1 a página 3 línea 30, página 10 líneas 20 a 56, reivindicaciones 1 a 8)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D1.

Puesto que las reivindicaciones 2, 3, 17 y 19 no mencionan características nuevas adicionales tampoco se pueden considerar nuevas.

Los compuestos de la fórmula Markush reclamada en la solicitud son ya conocidos en el estado de la técnica. El hecho de presentar un nuevo efecto terapéutico no le

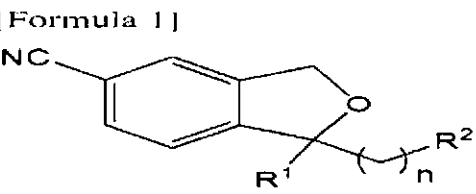
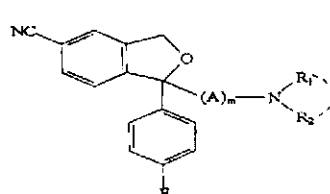
otorga novedad a dichos compuestos.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D2
[Formula 1] 	 (columna 10 línea 66 a columna 11 línea 18 reivindicación 1)
Anillo de benzofurano	Anillo de benzofurano
CN	R ¹ CN
R ¹ Fenilo sustituido	Fenilo sustituido por R ² el cual se seleccionado de halógeno, trifluorometilo, ciano o un grupo R-CO- siendo R un C ₁ – C ₄ alquilo
-(CH ₂) _n - n es un número entero de 1 a 3	-(CH ₂) ₃ -
R ² Dialquilamino C ₁ – C ₆	Dimetilamino

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D2, el cual da a conocer un compuesto derivado de benzofurano (columna 1, línea 51 a columna 4 línea 6)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D2.

Puesto que las reivindicaciones 2, 3, 17 y 19 no mencionan características nuevas adicionales tampoco se pueden considerar nuevas.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D3
[Formula 1] 	 (página 4 línea 5 a página 7 línea 30)

Anillo de benzofurano	Anillo de benzofurano
CN	CN
R ¹	
Fenilo sustituido	Fenilo sustituido por flúor
-(CH ₂) _n - n es un número entero de 1 a 3	-(A) _m - A es un grupo -CH ₂ - m es un entero de 2 a 6
R ² Heterociclilo sustituido o insustituido seleccionado de piridinilo, isoxazolilo, tiazolilo, pirimidinilo, indanilo, benzatiazolilo, pirazolilo, tiadiazolilo, oxazolilo, piperidinilo, morfolinilo, imidazolilo, pirrolidinilo, tienilo, triazolilo, pirrolilo y furilo	N(R ₁)(R ₂) R ₁ y R ₂ junto con el átomo de nitrógeno representan un anillo de cinco o seis miembros que puede estar sustituido con uno o dos heteroátomos seleccionados de oxígeno, azufre y nitrógeno

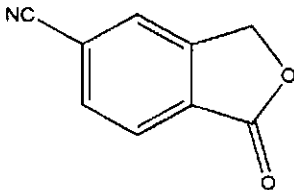
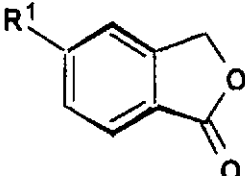
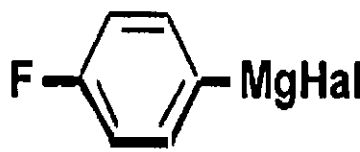
Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D3, el cual da a conocer compuestos derivados de isobenzofurano (página 4 línea 5 a página 7 línea 30)

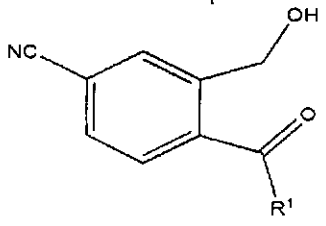
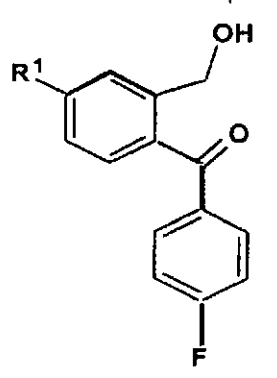
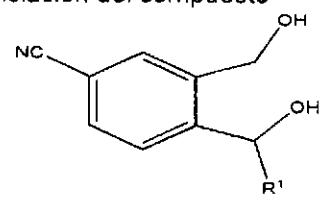
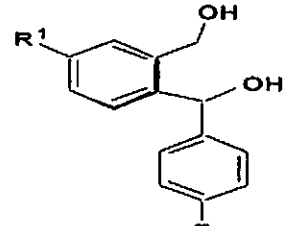
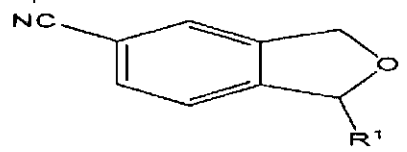
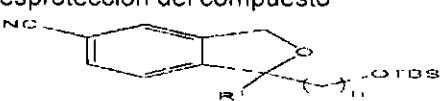
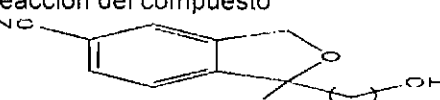
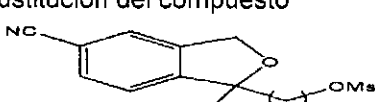
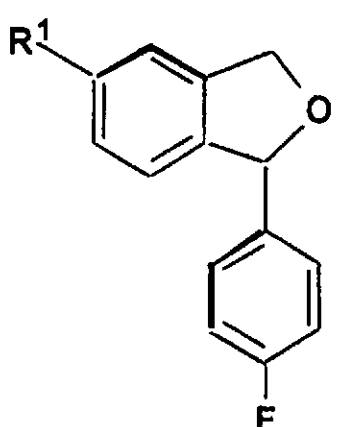
En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D3.

Puesto que las reivindicaciones 2, 3, 9, 15 - 17 y 19 no mencionan características nuevas adicionales tampoco se pueden considerar nuevas.

La reivindicación 21 consiste en un proceso para preparar el derivado como se reivindica en cualquiera de las reivindicaciones 1 a 18 (Ver folios 94 a 96)

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

Características esenciales	D4
Reacción de la 5-cianoftalimida del compuesto  R¹ es fenilo sustituido con R¹MgBr	Reacción de  R¹ es CN con  (página 6 líneas 1 a 3)

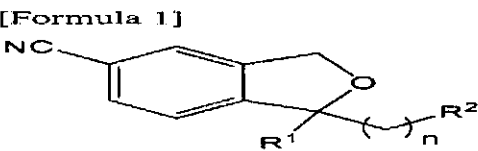
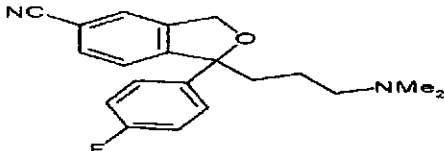
Reducción del compuesto 	Reducción del compuesto  (página 3 líneas 1 a 4)
Ciclación del compuesto 	Ciclación del compuesto  (página 3 líneas 5 a 10)
Introducción del grupo alquilo en posición 1 del compuesto  Desprotección del compuesto  Reacción del compuesto  con metanosulfonilcloruro Sustitución del compuesto  con un grupo R² y reacción por clorinación para obtener el compuesto de fórmula 1	Alquilación del compuesto  para obtener el compuesto de Fórmula I (página 3 línea 9 a página 4 línea 4)

Las características esenciales del proceso de la reivindicación 21 habían sido divulgadas previamente en D4, el cual da a conocer un proceso de preparación de citalopram (página 2 línea 25 a página 7 línea 21)

En consecuencia, la reivindicación 21 no es nueva ó carece de novedad, según lo divulgado en el documento D4.

Nivel Inventivo (Art18 D486)

La reivindicación 4 consiste en el derivado representado por la Fórmula 1 o la sal farmacéuticamente aceptable del mismo, de acuerdo con la reivindicación 1, en donde R¹ es fenilo sustituido con alquiloxi C₁-C₆

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
SOLICITUD	D5
[Formula 1] 	Citalopram  (páginas 502 a 505) (Ver folios 145 a 148)
Anillo de benzofurano	Anillo de benzofurano
CN	CN
R ¹	
Fenilo sustituido con alquiloxi C ₁ -C ₆	Fenilo sustituido con flúor
-(CH ₂) _n -	-(CH ₂) ₃ -
n es un número entero de 1 a 3	
R ²	Dimetilamino
Dialquilamino C ₁ – C ₆	

El documento D5 divulga la utilización del citalopram en el tratamiento de la eyaculación prematura (páginas 502 a 505)

La diferencia entre la invención, definida en la reivindicación 4 y el compuesto de D5 consiste en que D5 no divulga la sustitución del anillo de fenilo con alquiloxi C₁-C₆

El efecto que logra el incluir el grupo alquiloxi C₁-C₆ sustituyendo el anillo de fenilo es que proporciona un compuesto alternativo para el tratamiento de la eyaculación prematura.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el compuesto conocido en D5 para proporcionar un compuesto alternativo para el tratamiento de la eyaculación prematura".

Sin embargo, la persona del oficio normalmente versada en la materia, fácilmente podría inferir sin mucho esfuerzo de su parte, realizar modificaciones sobre el grupo

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farmacofórico principal de la estructura de D5 esperándose el efecto eficaz en tratamiento de eyaculación prematura sugerido en D5 para llegar así al objeto de la reivindicación 4 de la solicitud. Por lo cual se considera obvia.

En conclusión la reivindicación 4 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 5 – 8, 10 – 14 y 18 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP347066	1 – 3, 17, 19	Novedad
D2	US4136193	1 – 3, 17, 19	Novedad
D3	WO2003042202	1 – 3, 9, 15 – 17, 19	Novedad
D4	WO9819511	21	Novedad
D5	The Efficacy of Citalopram in The Treatment of Premature Ejaculation: A Placebo-Controlled Study	4 – 8, 10 – 14, 18	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
 Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 OCT. 2012

Elaborado por: Rodolfo Cadena Amaya. *oxt*
 Revisado por: Gloria Jacqueline Alfonso.



The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study

M Atmaca^{1*}, M Kuloglu¹, E Tezcan¹ and A Semercioz²

¹Firat University, School of Medicine, Department of Psychiatry, Elazig, Turkey; and ²Firat University, School of Medicine, Department of Urology, Elazig, Turkey

Background: Despite the limited number of available study comparing of their efficacy, selective serotonin re-uptake inhibitors (SSRI) have been thought to have beneficial effects for the patients with premature ejaculation. In the present study, we decided to examine the efficacy of citalopram, an SSRI, in the treatment of premature ejaculation.

Method: The study was consisted of 26 married patients diagnosed with premature ejaculation according to Diagnostic and Statistical Manual of Mental Disorders Third Revised Version (DSM-III-R). The patients were randomly assigned to two groups, citalopram (group I) and placebo (group II), each consisting of 13 patients. The effects of drug on the ejaculatory function were assessed by the intravaginal ejaculation latency time. Additionally, all patients were screened by using Clinical Global Impression-Improvement Scale (CGI-I) and Yonsei Sexual Function Inventory-II (YSFI-II).

Results: The increase in the intravaginal ejaculation latency time in the citalopram group was statistically significant than that of placebo group. In addition, with respect to the subscales of the YSFI-II scale, similar overall significant improvements were seen in the patients given citalopram compared to those given placebo. Of group I patients, five (38.5%) were considered as 'very much improved' and four (30.8%) 'much improved' by CGI-I and only one of group II patients (7.7%) showed 'much improved'.

Conclusion: The patients treated with citalopram showed significantly greater improvement compared to the patients receiving placebo.

International Journal of Impotence Research (2002) 14, 502–505. doi:10.1038/sj.ijir.3900918

Keywords: SSRI; citalopram; placebo; premature ejaculation

Introduction

Premature ejaculation has been defined as uncontrolled ejaculation whose essential feature is the recurrent or persistent orgasm with minimal sexual stimulation before, on, or after penetration and before the person desires it. The majority of men experienced premature ejaculation can have delay ejaculation and orgasm during self-masturbation for a considerably longer time compared to during coitus.¹ Different treatment approaches have been used for the treatment of premature ejaculation

including local anaesthetic sprays, vascular surgery, propranolol and serotonin reuptake inhibitors.

Sexual side effects, eg decreased libido, orgasm inhibition, erectile dysfunction and priapismus, related to use of antidepressant drugs have been reported. Sexual dysfunction is a common side effect reported by most of the available antidepressant drugs. Studies that were not specifically designed to determine antidepressant-associated sexual side effects reported 5–10% sexual dysfunction in the patients using tricyclic antidepressants (TCAs), while this rate was 10–30% in those using SSRI.^{2–4} On the other hand, despite the limited number of available study comparing of their efficacy, SSRIs; fluoxetine, paroxetine have been thought to have beneficial effects for the patients with premature ejaculation.^{5–7} In the patients with depression, sertraline has been reported to cause retarded ejaculation.⁸ However, to the best of our knowledge, so far, citalopram, an SSRI, has not been systematically

*Correspondence: M Atmaca, Firat (Euphrates) Üniversitesi, Firat Tıp Merkezi, Psikiyatri Anabilim Dalı, 23119 Elazig, Turkey.

E-mail: matmaca_p@yahoo.com

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studied for the treatment of the premature ejaculation. Citalopram shows an effective antidepressant activity without an important cardiotoxic, anticholinergic and sedating effects.⁹

In the present study, we decided to examine the efficacy of citalopram in the treatment of premature ejaculation and hypothesized that it might have beneficial effects on this condition.

Method

Twenty six married male patients (aged 24–46 y) were studied. They applied to Firat University School of Medicine Departments of Psychiatry and Urology and were diagnosed with premature ejaculation according to DSM-III-R¹⁰ and met the study admission criteria. After complete description of the study to the subjects, the written informed consent was obtained from each patient. The study was approved by Local Ethics Committee of the Firat University School of Medicine. Each patient underwent diagnostic evaluation by one trained psychiatrist by using Structured Clinical Interview for DSM-III-R outpatient form (SCID-OP).¹¹ According to SCID-OP, one patient was diagnosed with comorbid major depressive disorder (MDD) and one with obsessive compulsive disorder (OCD). To be able to exclude the organic sexual dysfunctions, the fasting glucose level, urine analysis, complete blood count, sex hormones and prolactin levels were obtained. Exclusion criteria included the presence of erectile dysfunction and inhibited male orgasm, a severe physical illness, the history of alcohol and any substance abuse or dependence, the presence of any endocrinological state and treatment with any psychotropic medication within last 2 weeks. All patients were heterosexual.

The patients were randomly assigned to either citalopram (group I) ($n=13$) or placebo (group II) ($n=13$) treatment in the double-blind design. The drugs were taken after breakfast. In group I, the patients initially received 20 mg citalopram per day. Titration up to 60 mg per day was permitted according to the patient's tolerability and clinical response, with increase of one tablet within the period of two weeks. In group II, the patients received initially identical one placebo tablet per day and placebo was titrated to three capsules according to the clinical response, with increase of one tablet in two weeks' period. The use of concomitant medications was prohibited, with the exception of benzodiazepine. However, no patient required additional drug throughout the study including benzodiazepine. The intravaginal ejaculation latency time was defined as the duration between vaginal intromission and ejaculation.¹² The subjects were asked to determine the average

intravaginal ejaculation latency time for three consecutive episodes of coitus verified by both patients and their wives via a chronometer. The patients and their wives were encouraged to engage in coitus twice a week and record intravaginal ejaculation latency time. All patients and their partners were individually interviewed at the beginning of the study and at week 2, 4, 8. All patients were screened by using Clinical Global Impression-Improvement Scale (CGI-I).¹³ Additionally, changes in general sexual function were examined by using Yonsei Sexual Function Inventory-II (YSFI-II).¹⁴ This scale is the self-rating of 7-item 100 mm visual analogue scale which demonstrates performance anxiety for the rapid ejaculation, sexual desire, satisfaction with ejaculation and overall sexual functions. The score ranged from 0 (not at all) to 100 (most ever). On the other hand, in one patient with major depression and one patient with OCD, the psychopathology at each interview was screened by Hamilton Depression Rating Scale (HDRS)¹⁵ and Yale-Brown Obsession Compulsion Scale (Y-BOCS)¹⁶ respectively. Statistical analysis was performed by using chi-square, Student's *t* and repeated measures ANOVA tests.

Results

All patients completed the study. The mean age, age of wives and duration of illness in group I were 32.74 ± 10.54 , 30.34 ± 11.26 and 8.84 ± 5.11 y, respectively whereas those in group II were 31.51 ± 9.88 , 28.94 ± 10.12 and 9.08 ± 4.78 y, respectively ($P > 0.05$). At the end of the study, among group I patients, nine (69.2%) were receiving 20 mg/day, two (15.4%) 40 mg/day, and two (15.4%) 60 mg/day of citalopram. In group II patients, one (7.7%) was receiving two tablets/day, day, and 12 (92.3%) three tablets/day at the end of the study.

At the baseline, the mean intravaginal latency time was 33.46 ± 17.96 in group I and 30.38 ± 14.64 seconds in group II. The difference was not statistically significant ($P > 0.05$). The mean time at last assessment was 283.85 ± 80.50 in group I and 35.77 ± 13.52 seconds in group II ($P < 0.001$). The intravaginal ejaculation latency time considerably increased after 8 weeks of treatment in group I ($P < 0.001$) but not in group II ($P > 0.05$). The difference in the mean intravaginal latency time between groups arrived a statistical significance at the evaluation of week 2 ($P < 0.001$). This separation continued until the end of the trial (Table 1).

With respect to the subscales of the YSFI-II scale, greater significant improvements were seen in group I compared to group II. The mean changes

Table 1 Intravaginal ejaculation latency time (sec) and the mean CGI-I scores

Week	Intravaginal ejaculation latency time (sec)				CGI-I			
	Citalopram (n = 13)	Placebo (n = 13)	t*	P*	Citalopram (n = 13)	Placebo (n = 13)	t*	P*
0	33.46 ± 17.96	30.38 ± 14.64	0.48	0.64	—	—	—	—
2	119.23 ± 42.71	32.69 ± 12.52	7.01	<0.001	4.00 ± 0.71	4.77 ± 1.09	−2.13	<0.05
4	233.46 ± 42.20	35.00 ± 12.08	16.30	<0.001	2.08 ± 0.64	4.46 ± 0.77	−8.54	<0.001
8	283.85 ± 80.50	35.77 ± 13.52	10.96	<0.001	1.38 ± 0.51	4.08 ± 1.04	−8.41	<0.001
0–2**	50.57, <0.001	2.96, 0.11			—	—		
2–4**	162.95, <0.001	3.60, 0.08			105.00, <0.001	3.08, 0.104		
4–8**	10.51, <0.01	0.11, 0.75			15.68, <0.01	4.55, 0.054		

*, Used Student *t*-test.
**, Used repeated measures ANOVA test (given *F* and *P* values, respectively).

from the baseline to the last assessment in group I were significantly higher compared to group II in all subscales: the sexual desire (19.5 mm for citalopram group and 2.8 mm for placebo group; *P* < 0.001); the quality of erection (21.4 mm for citalopram group and 4.2 mm for placebo group; *P* < 0.001); anxiety for rapid ejaculation (−28.3 mm for citalopram group and −5.23 mm for placebo group; *P* < 0.001); the satisfaction with ejaculation (21.4 mm for citalopram group and 6.1 mm for placebo group; *P* < 0.01); the partner's satisfaction with ejaculation (35.8 mm for citalopram group and 8.3 mm for placebo group; *P* < 0.001); the overall sexual satisfaction (29.3 mm for citalopram group and 7.4 mm for placebo group; *P* < 0.001) and the partner's overall satisfaction (31.2 mm for citalopram group and 9.1 mm for placebo group; *P* < 0.01).

At the evaluation of week 2, CGI-I scores were 4.00 ± 0.71 and 4.77 ± 1.09 points in group I and II, compared with 1.38 ± 0.51 and 4.08 ± 1.04 points at the last assessment in group I and II, respectively. Group I separated from group II at the evaluation of week 2 on the CGI-I scale (*P* < 0.05). According to CGI-I, of group I patients, five (38.5%) were considered as very much improved and four (30.8) much improved. Only one of group II patients (7.7%) showed much improved by CGI-I. There was a statistically significant difference between the treatment groups with respect to the treatment response, as determining by CGI-I (*P* < 0.0001) (Table 1).

One patient with MDD and one patient with OCD were randomly assigned to group I. The HDRS score of depressive patient was 30 at the baseline, 28 at the week 2 evaluation, 26 at the week 4 evaluation and 18 at the last assessment. The Y-BOCS score of the patient with OCD was 29 at the baseline, 27 at the week 2 evaluation, 18 at the week 4 evaluation and 12 at the last assessment.

Three patients from group I complained from headache and nausea and one patient from group II experienced sweating. It is worth noting that no patient withdrew from each treatment group because of adverse events.

Discussion

The main findings of our study are as follows: (1) Citalopram is more efficacious than placebo in the treatment of premature ejaculation, (2) the onset of the therapeutic effect seems to occur with citalopram by week 2, (3) citalopram provides also significant improvements on the overall sexual functions of the patients with the premature ejaculation, as determining by YSFI-II scale.

The inhibitory effect of serotonin on libido, ejaculation and orgasm has been attributed to serotonin-induced decrease in dopamine (a neurotransmitter enhancing sexual function) level in central nervous system.^{17,18} Methylene-dioxy-metamphetamine induces serotonin and dopamin release with the central action, and causes increase in libido and sexual satisfaction by dopamin release, while causes delay and prominent inhibition in the ejaculation and orgasm by serotonin activation.¹⁹ Actually, the effect of serotonin in the development of premature ejaculation and other sexual dysfunctions was hypothesized based on the observations that imipramine had more significant sexual dysfunctions compared to the desipramine, and antidepressant-induced orgasm inhibition could be reversed by a non-selective serotonin antagonist, cyproheptadine.^{12,20}

Selective or non-selective serotonin reuptake inhibitors have been demonstrated to be effective for the treatment of premature ejaculation.^{5–7,21} Girgis *et al*²¹ reported that clomipramine, a non-selective serotonin reuptake inhibitor, in low doses was effective in the treatment of premature ejaculation, though high doses could limit its use because of adverse events. In addition, the efficacy of fluoxetine⁶ and paroxetine,⁵ SSRIs, has been shown in the patients with the premature ejaculation. In the present study, the intravaginal ejaculation latency time changed considerably in 69.3% of 13 patients in citalopram treated group, as also supported by CGI-I. Another important finding of

the present study is that significant improvements in all subscales of YSFI-II scale have been seen in group I compared to group II, suggesting that the overall sexual functions of patients with the premature ejaculation including sexual desire and partner's satisfaction have improved. In two patients with comorbid MDD and OCD, the significant improvement in the intravaginal ejaculation latency time, despite not in depressive and obsessive-compulsive symptoms, within two weeks of the treatment is considered that this situation may be associated with the direct effect of the central serotonin reuptake blockage of citalopram, the most selective reuptake inhibitor among all SSRIs.⁹ Although the clinical improvement in MDD and OCD generally results in the improvement of related sexual dysfunctions, this generally appears within after at least three or four weeks of treatment with SSRIs. On the other hand, one can speculate that less dose of citalopram might be enough to postpone ejaculation since more than two third of the patients given citalopram was receiving 20 mg daily at the last assessment.

In summary, our results suggest that citalopram may be effective in treatment of the premature ejaculation with mild side effects. However, further investigations with large sample in which long-term effectivity of this drug is taken into consideration are required.

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