

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

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Bogotá, D.C.,

Abogado
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ASUNTO	Radicación	10 159 129
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Patente de Invención



Patente de Modelo de Utilidad

Vía Nacional

Vía PCT (Fase Nacional)



Capítulo I



Capítulo II

No. Solicitud Internacional

PCT/KR2009/002636

Fecha de Presentación Internacional

19/Mayo/2009

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 31 a 61	17/Diciembre/2010
Reivindicaciones:	Folios 62 a 63	17/Diciembre/2010
Prioridad:	KR 10-2008-0046199	19/Mayo/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.

3. Objeto de la invención

Título de la solicitud: "Composición farmacéutica para el tratamiento de la eyaculación precoz".

El problema planteado en esta solicitud consiste en proporcionar una composición farmacéutica para el tratamiento de la eyaculación precoz.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica que comprende clomipramina o sales farmacéuticamente aceptables, Sertralina o sales farmacéuticamente aceptables y fluoxetina o sales

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farmacéuticamente aceptables como ingredientes activos.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/55.

4. De la Solicitud de Patente

Titulo

El título es muy general y no define el objeto de de la solicitud, por lo cual se sugiere al solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La Reivindicación 1 no es clara ni concisa, porque no define las cantidades de los principios activos que conforman la composición farmacéutica de interés. Se sugiere definir la composición farmacéutica por sus compuestos y las cantidades de cada uno de los mismos.

Lo anterior aplica para las Reivindicaciones 3 – 8 y 12 – 13.

Las Reivindicaciones 6 y 13 no son concisas ya que por cada grupo de agonistas de serotonina, antagonistas de serotonina, agonistas de adrenérgico, antagonistas de adrenérgico, bloqueadores neuronales de adrenérgico, drogas para el tratamiento de impotencia, inhibidores de fosfodiesterasa 5, inductores de erección y una combinación de los mismos, se encuentra un número ilimitado de sustancias lo que da lugar a un número indefinido de composiciones. Además cuando se dice, por ejemplo, “drogas para el tratamiento de impotencia” se está definiendo el componente de la formulación por su función y no define un componente ni una composición específica como tal. Se sugiere definir la composición farmacéutica por sus compuestos y las cantidades de cada uno de los mismos.

5. Unidad de invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de invención porque se refiere a 2, grupos inventivos.

Los grupos inventivos están definidos por las siguientes características esenciales:

Grupo Inventivo 1 (Reivindicaciones 1 a 5 y 7 a 12): Una composición farmacéutica que comprende clomipramina, sertralina y fluoxetina.

Grupo Inventivo 2 (Reivindicaciones 6 y 13): Composiciones y dosis en forma de unidad oral que contienen clomipramina, sertralina y fluoxetina y un agente adicional seleccionado entre agonistas de serotonina, antagonistas de serotonina, agonistas de adrenérgico, antagonistas de adrenérgico, bloqueadores neuronales de adrenérgico, drogas para el tratamiento de impotencia, inhibidores de fosfodiesterasa 5, inductores de erección y una combinación de los mismos.

El grupo inventivo 1 (composición farmacéutica que comprende clomipramina, sertralina y fluoxetina) se encuentra divulgado en D1.

El problema a ser solucionado en esta invención consiste en suministrar una composición farmacéutica para el tratamiento de la eyaculación precoz. En la solicitud se presentan 2 posibles soluciones correspondientes a los grupos inventivos identificados anteriormente. No se presenta unidad de invención del grupo inventivo

1 con el otro grupo listado, porque en el estado de la técnica, se encuentra una o más características técnicas esenciales que define al otro grupo inventivo en relación con el grupo inventivo 1, por ejemplo clomipramina, sertralina y fluoxetina con drogas para el tratamiento de impotencia. En esta solicitud no se puede identificar la característica técnica esencial que sea común a los grupos inventivos mencionados.

Por lo tanto, esta solicitud carece de unidad de invención, los diferentes grupos no ofrecen un concepto inventivo común. Cada uno de los grupos listados se caracteriza por tener su propia característica técnica esencial. Se sugiere presentar las solicitudes divisionales que considere necesarias, ó limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

Debido a la falta de unidad de invención, el examen de patentabilidad se limita al grupo inventivo 1.

6. 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: Mayo 19 de 2008, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	Artículo ¹	Efficacy and Safety of Fluoxetine, Sertraline and Clomipramine in Patient with Premature Ejaculation: a Double-Blind, Placebo-Blind, Placebo Controlled study	Febrero/1998

D1: (folios 79 - 81), divulga (folio 79) la combinación de fuoxetina, Sertralina y clomipramina para el tratamiento en pacientes que padecen eyaculación precoz.

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

Grupo inventivo 1:

La Reivindicación 1 consiste en una composición farmacéutica para el tratamiento de la eyaculación precoz que comprende clomipramina o una sal farmacéuticamente aceptable de la misma, sertralina o una sal farmacéuticamente aceptable de la misma, fluoxetina o una sal farmacéuticamente aceptable como ingredientes activos.

La Reivindicación 10 consiste en la dosis en forma de unidad oral de la Reivindicación 7, que comprende 0.7 - 22.5 mg de clomipramina, 1.1 – 33.9 mg de sertralina y 0.5 – 17.7 mg de fluoxetina.

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

Características esenciales	D1
dosis en forma de unidad oral	cápsulas (folio 79, página 425)
Clomipramina 0.7 - 22.5 mg	25 mg de clomipramina (folio 79, página 425)
Sertralina 1.1 – 33.9 mg de	50 mg de Sertralina (folio 79, página

¹ KIM, SAE CHUL ET AL.: 'Efficacy and Safety of Fluoxetine, Sertraline and Clomipramine in Patient with Premature Ejaculation: a Double-Blind, Placebo-Blind, Placebo Controlled study' JOURNAL OF UROLOGY vol. 159, no. 2, February 1998, pages 425 – 427.
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sertralina	425)
Fluoxetina 0.5 – 17.7 mg	20 mg de fluoxetina (folio 79, página 425)

El documento D1 se considera el estado de la técnica cercano a la invención definida en las Reivindicaciones 1 y 10 porque divulga la combinación de clomipramina, sertralina y fluoxetina para el tratamiento en pacientes que padecen eyaculación precoz (folio 79, página 425).

La diferencia entre la invención, definida en las Reivindicaciones 1 y 10 y la dosis en forma de unidad oral de D1 consiste en las cantidades de clomipramina, sertralina y fluoxetina, que son particularmente 0.7 - 22.5 mg, 1.1 – 33.9 mg y 0.5 – 17.7 mg, respectivamente.

Sin embargo, en el arte previo se encontraban registros de la eficacia de cada uno de los principios activos para el tratamiento de la eyaculación precoz de manera separada, que se encuentran en el rango reclamado en la presente invención, es decir, en el caso de clomipramina 20 mg diarias ², en el caso de sertralina dosis de entre 25 – 50 mg ³ y en el caso de fluoxetina en concentraciones variantes desde 10 mg/día en adelante ⁴ (ver folios 82 – 96).

Así las cosas, no se evidencia un nivel inventivo en esta solicitud ya que esta combinación no parece conceder un efecto técnico inesperado o una ventaja de las dosis en forma de unidad oral reclamadas en esta solicitud, pues no parecen presentar propiedades superiores en comparación con la administración separada o la combinación del estado de la técnica cercano.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de dosis en forma de unidad oral que comprendan clomipramina (0.7 - 22.5 mg), sertralina (1.1 – 33.9 mg) y fluoxetina (0.5 – 17.7 mg) (dosis plenamente conocidas en el estado del arte), para el tratamiento de eyaculación precoz, alternativas a las ya conocidas en el estado del arte.

Sin embargo, D1 también divulga diferentes soluciones a este problema técnico, particularmente, la selección y administración de clomipramina (25 mg), sertralina (50 mg) y fluoxetina (20 mg), para el tratamiento en pacientes que padecen eyaculación precoz (folio 79, página 425).

En consecuencia, la persona del oficio normalmente versada en la materia habría podido seleccionar los principios activos clomipramina, sertralina y fluoxetina y modificar la cantidad de cada uno de los principios activos como una alternativa para llegar así al objeto de las Reivindicaciones 1 y 10 de la solicitud. Por lo cual se consideran obvias.

Conclusión:

Las Reivindicaciones 1 y 10 cumplen el requisito de novedad (Art. 16), pero no

² ASSALIAN, PIERRE.: "Clomipramine in the treatment of premature ejaculation". Journal of Sex Research. Enero de 1988, Vol. 24 Issue 1-4, p213-215.

³ KWON, O ET AL.: "Effects of sertraline on brain current source of the high beta frequency band: analysis of electroencephalography during audiovisual erotic stimulation in males with premature ejaculation". International Journal of Impotence Research. Sep/Oct2011, Vol. 23 Issue 5, p213-219.

⁴ ABDOLLAHIAN, EBRAHIM ET AL.: "Study of the Efficacy of Fluoxetine and Clomipramine in the Treatment of Premature Ejaculation after Opioid Detoxification". American Journal on Addictions. Jan/Feb2006, Vol. 15 Issue 1, p100-104.

cumplen con el requisito de nivel inventivo (Art. 18).

Puesto que las Reivindicaciones dependientes 2 – 5, 7 – 9, 11 y 12 no mencionan características inventivas adicionales tampoco se puede considerar inventivas.

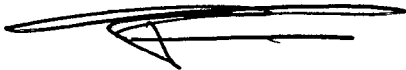
8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	KIM, SAE CHUL ET AL	1 – 5 y 7 – 12	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 13 0 OCT. 2012

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EFFICACY AND SAFETY OF FLUOXETINE, SERTRALINE AND CLOMIPRAMINE IN PATIENTS WITH PREMATURE EJACULATION: A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

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ABSTRACT

Purpose: We compared the efficacy and safety of fluoxetine, sertraline, clomipramine and placebo for the oral pharmacotherapy of premature ejaculation.

Materials and Methods: The study included 36 men (mean age 44 years) who had intravaginal ejaculation latency of less than 2 minutes. Patients took each of 3 drugs and the placebo consecutively during a 4-week period per each agent. Efficacy and side effects data were obtained by a self-reported patient questionnaire that rated intravaginal ejaculation latency, sexual satisfaction of patient and partner, and possible side effects.

Results: After 4 weeks of treatment with placebo, fluoxetine, sertraline and clomipramine the mean intravaginal ejaculation latency time was significantly increased from 46 seconds to 2.27 minutes, 2.30 minutes, 4.27 minutes and 5.75 minutes, respectively (all $p < 0.01$). However, treatment with clomipramine or sertraline caused a greater increase in mean intravaginal ejaculation latency time than fluoxetine or placebo ($p < 0.01$). Patient sexual satisfaction rate after treatment with clomipramine was significantly higher ($p < 0.05$) than with sertraline, fluoxetine or placebo. Partner sexual satisfaction rate was also higher with clomipramine than with sertraline or fluoxetine but no statistical difference was found. The incidence of side effects with clomipramine was significantly higher ($p < 0.05$) compared to that of fluoxetine, sertraline and placebo, while no significant difference among sertraline, fluoxetine and placebo was noted.

Conclusions: In men with premature ejaculation clomipramine was the most useful drug in terms of efficacy. Treatment with sertraline was nearly as effective and had a lower incidence of side effects.

KEY WORDS: ejaculation, fluoxetine, clomipramine, placebos, questionnaire

MATERIALS AND METHODS

Behavioral therapy, such as the Semans pause maneuver, the Masters and Johnson pause-squeeze technique or the Kaplan stop-start method, is considered the gold standard for the treatment of premature ejaculation.¹ While these techniques are harmless and usually a painless treatment modality, and have been fairly successful at rates of 60 to 95%,^{1,2} they require partner cooperation. Most patients who noted improvement in ejaculatory latency with these treatments fail to maintain the gains for the long term.^{3,4} As a result oral pharmacotherapy using tricyclic antidepressants (clomipramine) or selective serotonin re-uptake inhibitor drugs (fluoxetine, sertraline and paroxetine) have been commonly used as alternatives to behavioral therapy, especially in patients for whom psychological treatment has failed and who have rejected psychological treatment, or whose partners were unwilling to cooperate in treatment.^{5,6}

Open label and controlled studies have reported that clomipramine increases intravaginal ejaculatory latency effectively without bothersome side effects in patients with premature ejaculation.^{7,8} Similar findings have been reported in double-blind studies with fluoxetine, sertraline or paroxetine.⁹⁻¹¹ Sexual satisfaction of patients and partners also improved significantly in studies of clomipramine or sertraline.^{10,12} However, there are no studies comparing these drugs in men with premature ejaculation. Therefore, we studied placebo, fluoxetine, sertraline and clomipramine to compare efficacy and safety in such men.

Subjects. A total of 53 heterosexual men with premature ejaculation were enrolled in this study. Premature ejaculation was defined as intravaginal ejaculation latency time of less than 2 minutes that occurred in more than 50% of sexual intercourse. Inclusion criteria were married or living in a stable relationship with a female sexual partner for at least 1 year and possible sexual intercourse at least once per week. Exclusion criteria were presence of major psychiatric disorders, concurrent erectile dysfunction, urethritis or chronic prostatitis, presence of significant medical illness, history of alcoholism or other substance abuse and use of any drug that may affect sexual function. Microscopic examinations on initial voided urine, expressed prostatic secretions and urine voided after prostatic massage were performed to rule out urethritis or chronic prostatitis in all patients.

Study design. We used 40 mg. fluoxetine, 100 mg. sertraline, 50 mg. clomipramine and digestive placebo (40 mg. pancreatin and 95 mg. simethicone). Each patient was informed that he would be given 4 different drugs of identical action to ascertain which of the 4 was most useful. Verbal informed consent was obtained from all patients before the study. Capsules were identical, with each capsule containing 20 mg. fluoxetine, 50 mg. sertraline and 25 mg. clomipramine or placebo. All patients took each drug and the placebo during a 4-week period per each agent with a washout period of at least 1 week between agents. Patients took 1 capsule daily for the first week, then 2 daily for the remaining 3 weeks of the experimental period for that agent. There were 24 possible permutations of drug sequence, all of which were used by at least 1 patient.

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Analysis of efficacy and safety. All measurements were obtained before treatment, after each washout period and after the final experimental phase. Efficacy and side effects were obtained using a patient self-reported questionnaire that consisted of 3 items asking the average intravaginal ejaculation latency time for the last 2 consecutive experiences of intercourse, sexual satisfaction scores of patient and partner, and potential side effects. Time to ejaculation as reported by patients was based on subjective measurement. Side effects were rated on a scale from 0 (none) to 3 (severe).

Statistical analysis. A paired t test was used for the evaluation of intravaginal ejaculation latency time between baseline and after treatment with each drug. A chi-square test was used to compare the sexual satisfaction rate of each patient and partner, and for comparison of the incidence of side effects among placebo, fluoxetine, sertraline and clomipramine. Analysis of variance with multiple comparisons by Duncan's method was used for the comparison of intravaginal ejaculation latency by placebo, fluoxetine, sertraline and clomipramine. Findings were considered significant at $p < 0.05$.

RESULTS

Of 53 original participants 37 (69.8%) with a mean age of 44 years (range 30 to 60) completed the entire study. Of the 37 patients 1 reported delayed ejaculation of more than 30 minutes after treatment with sertraline or clomipramine and therefore we excluded this subject from the data analysis. The 16 patients who dropped out of the study took between 1 and 4 agents (mean 1.6). Reasons for dropout included lost to followup (5 patients), no efficacy (fluoxetine 3, placebo 1, sertraline 1), side effects (clomipramine 3, sertraline 1, placebo 1), and no efficacy plus side effects (clomipramine 1).

After 4 weeks of treatment with placebo, fluoxetine, sertraline and clomipramine the mean intravaginal ejaculation latency time was significantly increased from the pretreatment mean of 46 ± 41 seconds to 2.27 ± 3.78 minutes, 2.30 ± 2.08 minutes, 4.27 ± 5.68 minutes, and 5.75 ± 6.68 minutes, respectively (all $p < 0.01$). According to analysis of variance with multiple comparisons, treatment with clomipramine or sertraline caused a greater increase in mean intravaginal ejaculation latency time than fluoxetine or placebo ($p < 0.01$), while no significant difference was found between sertraline and clomipramine or between placebo and fluoxetine. The most effective drug in the prolongation of intravaginal ejaculation latency time was clomipramine in 25 patients (69.4%), followed by sertraline (33.3%) and fluoxetine (13.9%).

Patient sexual satisfaction rates after treatment with clomipramine, sertraline, fluoxetine and placebo were 52.8, 41.7, 25.0 and 19.4%, respectively. Differences among these drugs in satisfaction rates were statistically significant ($p < 0.05$) (table 1). Partner sexual satisfaction was also higher (38.9%) with clomipramine than sertraline (30.6%) or fluoxetine (19.4%), but no statistical difference was found (table 1).

Table 2 presents overall incidences and types of reported side effects for each drug. The most common side effects of

TABLE 2. Side effects with placebo, fluoxetine, sertraline and clomipramine

	Placebo	Fluoxetine	Sertraline	Clomipramine
No. pts. with side effects (%)	7 (19.4)	13 (36.1)	12 (33.3)	23 (63.9)
p Value*	<0.001	0.034	0.018	
No. side effects:				
Drowsiness	2	6	7	8
Dry mouth		2	4	12
Reduced potency	3	3	3	5
Nausea	1	4	2	3
Vomiting				2
Others	3	3		2

* Compared to incidence of side effect with clomipramine.

each drug were dry mouth (33%) with clomipramine, drowsiness (19%) with sertraline, drowsiness (17%) with fluoxetine and decreased erectile potency (8%) with placebo. The incidence of side effects with clomipramine was significantly higher ($p < 0.05$) compared to that of fluoxetine, sertraline and placebo, while no significant differences were noted among sertraline, fluoxetine and placebo.

DISCUSSION

The neurophysiology of ejaculation is not well understood. It has been suggested that the serotonergic system has an inhibitory influence on ejaculation, whereas the dopaminergic system facilitates male sexual behavior at the level of the brain. Ejaculation also seems to be mediated by α -1 receptor activation, presumably at a peripheral level, with cholinergic fibers having a modulatory role.^{13,14} Recent studies in which administration of tricyclic antidepressants or selective serotonin re-uptake inhibitors caused remarkable increase in ejaculatory latency in patients with premature ejaculation provide additional evidence for the role of serotonergic mechanisms in delaying ejaculation.^{7-11,15,16} Our prospective, randomized, placebo controlled, double-blind study was designed to compare the efficacy and side effects of fluoxetine, sertraline and clomipramine in the same patient with premature ejaculation.

We found that all 3 medications and the placebo caused a significant increase in intravaginal ejaculation latency that was estimated by patient self-report based on subjective measurement. However, the most efficacious drug in terms of prolongation of intravaginal ejaculation latency and improvement in sexual satisfaction of patients and partners was clomipramine, followed by sertraline and fluoxetine. Low efficacy of fluoxetine compared with sertraline in our study might be related to differences in potency of serotonin re-uptake inhibition. It has been reported that sertraline was a more potent inhibitor of serotonin re-uptake than fluoxetine.^{17,18}

The mechanism of action of tricyclic antidepressants or selective serotonin re-uptake inhibitors in delaying ejaculation is unclear. Increased inhibition of serotonin uptake has been suggested as a mechanism by which a number of antidepressants prolong ejaculation.^{1,8} Although sertraline has been reported to be more potent for the serotonin re-uptake inhibition than clomipramine, efficacy of clomipramine in our patients was better than that of sertraline.^{17,18} Experimental and clinical studies have demonstrated that clomipramine administration induced uptake inhibition of dopamine and norepinephrine as well as serotonin, which suggests that the mechanism of clomipramine action may be more complicated than simple inhibition of serotonin uptake.^{1,6,17,18}

There were 2 major problems in our study, including measurement of ejaculatory latency in men with premature ejaculation. We obtained intravaginal ejaculatory latency by patient self-report. Estimation of the usual intromission time, which was based on verbal information and collected at the beginning of the study, could be given roughly by the patients

TABLE 1. Sexual satisfaction rate of 36 patients and partners

	% Satisfied		% Moderate		% Dissatisfied	
	Pts.*	Partners	Pts.	Partners	Pts.	Partners
Baseline				22.2	100	77.8
Placebo	19.4	11.1	27.8	36.1	52.8	52.8
Fluoxetine	25.0	19.4	38.9	38.9	36.1	41.7
Sertraline	41.7	30.6	36.1	38.9	22.2	30.6
Clomipramine	52.8	38.9	25.0	27.8	22.2	33.3

* There were significant differences ($p < 0.05$) among drugs in satisfaction rates of patients.

and could be different from subsequent visits to the clinic. Then patients were asked to report specifically on the last 2 consecutive experiences of intercourse. During the drug phase the subjects were likely to report more accurately intromission times because they specifically paid attention to it. This factor might explain why there was a striking placebo effect. On the other hand, being aware of intromission time during intercourse may induce or aggravate premature ejaculation because it may make patients more nervous. A psychogenic effect of the placebo, when it was used, could be another explanation of the delayed intromission time. The second problem was the washout period between drug administrations. It has been reported that fluoxetine forms a long half-life metabolite norfluoxetine, and the combined half-lives of fluoxetine and norfluoxetine are approximately 10 days, whereas the mean half-lives of sertraline and clomipramine are about 26 and 24 hours, respectively.¹⁷⁻¹⁹ Therefore, the combined effects of these drugs may result in false results, especially in our patients who took fluoxetine and then took the next ordered sertraline or clomipramine. However, since our patients took these drugs and the placebo according to a randomized administration order following at least 1 week of washout time between each agent, and we evaluated efficacy and side effects at least 3 weeks after administration of the previously ordered drug, statistical error should be minimized.

It is known that selective serotonin re-uptake inhibitors have a more favorable side effect profile than clomipramine because of their selective inhibition of serotonin uptake and minimal effect on other monoamines.^{6,9-11} Similar findings were noted in this study. Incidence of side effects with clomipramine was significantly higher than fluoxetine and sertraline. The most commonly reported side effect with sertraline and fluoxetine was drowsiness, and that of clomipramine was dry mouth. The side effects of tricyclic antidepressants and selective serotonin re-uptake inhibitors were dose related.^{1,6} High incidence of side effects with clomipramine (64%) in our patients might be related to relatively high dosages. Therefore, we think that a lower dose of clomipramine or taking it as needed also may be alternative treatment in patients with premature ejaculation, particularly when side effects are of concern.

CONCLUSIONS

Clomipramine was the most efficacious drug for oral pharmacotherapy of premature ejaculation. Treatment with sertraline was nearly as effective, with a lower incidence of side effects. Thus, clomipramine is recommended as regimen of choice for the treatment of premature ejaculation. When the side effects of clomipramine are of concern, sertraline could be an alternative.

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CLOMIPRAMINE IN THE TREATMENT OF PREMATURE EJACULATION

Pierre Assalian

Interference with ejaculation has been reported for a number of drugs: thioridazine (Shader, 1964), chlorpromazine (Greenberg, 1971), chlorprothixene (Ditman, 1964), and chlordiazepoxide (Hughes, 1964).

Blair and Simpson (1965) emphasized the widespread disorders of emission and ejaculation occurring with a wide variety of psychoactive drugs, particularly perphenazine, trifluoperazine, reserpine, and butyrophenones. Shader (1970), reviewing the subject of ejaculation disorders, pointed out that these have been reported with monoamine oxidase inhibitors and that this is known to occur with drugs such as guanethidine and phenoxybenzamine.

More recently, reports of sexual side effects of clomipramine¹ have also begun to surface (Ananth, Pecknold, Van Den Stern, & Engelsmann, 1979; Yassa, 1982). The principle complaint is delayed ejaculation. Complete failure to ejaculate and erectile impotence have also been reported but appear to be much rarer complaints. Ejaculatory disturbances appear to be dose related with delay occurring at low doses and failure occurring at higher doses (Beaumont, 1973). Here I report five cases of how the clomipramine side effect of delayed ejaculation was used in the treatment of premature ejaculation.

Case 1

The patient was a 42-year-old married man, diagnosed as having primary premature ejaculation. Ejaculation occurred very rapidly after penetration. The history was not similar to what Masters and Johnson (1970) described in the initial sexual experience of the premature ejaculator: often involving a prostitute who wished him to "finish off" as fast as possible, or with a girlfriend in settings where the fear of discovery motivated rapid sexual functioning.

Sensate focus, stop-start technique, as well as relaxation exercises administered by a competent sex therapist were of no benefit.

Clomipramine was begun at 25 mg ingested orally at bedtime. One week later the patient reported excellent results in his capacity to control ejacula-

¹Although available in Great Britain and Canada, clomipramine (anafranil) is still under study in the United States. It is not listed in the PDR and will not be available for some time.

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tion. Improvement persists at a dose of 20 mg nightly. The patient is unwilling to discontinue medication for fear of relapse. Follow-up with this patient for 18 months revealed effective ejaculatory control.

Case 2

The patient was a 52-year-old divorced, athletic man living with a 41-year-old woman. He was diagnosed as having secondary premature ejaculation for which no psychological causes were elicited. Clomipramine treatment (25 mg orally) was begun. The patient was irregularly compliant, taking the medication when the companion was present and sexual activity was anticipated, discontinuing when she was out of town, and restarting on the eve of her return. Improved control was reported whenever the drug was taken.

Case 3

This patient was a 43-year-old man with primary premature ejaculation. No psychological causes were elicited, and his first sexual experience was not with a prostitute, nor under hurried conditions. Erectile capacity was unimpaired.

The patient was started on 25 mg of clomipramine nightly, and he reported noticeable improvement 2 days later. Ejaculation was delayed and also perceived as being more intense. Sleepiness during the daytime was the cause for decrease in the dose to 10 mg. A concurrent decrease in ejaculatory control was noted, and the patient was replaced on the initial dose with the return of the desired effects. A 12-month follow-up revealed good control.

Case 4

The patient was a 35-year-old man suffering from a primary premature ejaculation, married for 3 years, seemingly a good relationship. He had been in sex therapy twice before his marriage and also after 1 year of marriage. There is no history of a hurried initial sexual experience. He was put on 25 mg of clomipramine at night. Good control was achieved within 48 hours.

Case 5

The patient was a 26-year-old married man with primary premature ejaculation. His initial sexual experience was not hurried. He was put on 25 mg clomipramine ingested orally at bedtime. The patient reported developing control over his ejaculation on the second day. Because of the impossibility of having sexual intercourse with the wife during weekdays, he decided to take the dose on Friday, Saturday, and Sunday nights when sexual intercourse was possible. He is able to have ejaculatory control on those nights.

Discussion

Clomipramine appears to be effective in the treatment of premature ejaculation. In the five reported cases, patients reported significant delay and heightened control of ejaculation with a small night-time dose, which was accompanied in some cases (cases 2 and 5) by minor side effects like sedation during the daytime, a dry mouth, and tendency to constipation. The desired ejaculatory control effect was noticeable as early as on the second day of treatment and persisted as long as the drug was taken.

Ejaculation is dependent primarily upon the integrity of the sympathetic component of the autonomic nervous system (Kaplan, 1974, 1983). Clomipramine's effectiveness results from its ability to inhibit adrenergic receptors of this peripheral sympathetic system. Of the five patients, two had undergone sex therapy unsuccessfully. All five reported no erectile dysfunction, atypical histories of premature ejaculation compared to those as described by Masters and Johnson (1970), and the inability to differentiate between the feeling of ejaculation and the point of no return.

I propose that these patients may represent a subcategory of premature ejaculators possessing a constitutionally hypersensitive sympathetic nervous system preventing them from differentiating between ejaculation and its inevitability and/or once the sympathetic nervous system is triggered, it has to discharge. These individuals would, therefore, be inappropriate for standard (behavioral) sex therapy techniques and may, in fact, be candidates for pharmacological treatment with clomipramine.

Further studies need to be done using a double-blind procedure with a placebo control group to rule out the placebo effect.

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ORIGINAL ARTICLE

Effects of sertraline on brain current source of the high beta frequency band: analysis of electroencephalography during audiovisual erotic stimulation in males with premature ejaculation

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To identify the effects of sertraline, a selective serotonin reuptake inhibitor, for the treatment of premature ejaculation (PE), changes in brain current-source density (CSD) of the high beta frequency band (22–30 Hz) induced by sertraline administration were investigated during audiovisual erotic stimulation. Eleven patients with PE (36.9 ± 7.8 yrs) and 11 male volunteers (24.2 ± 1.9 years) were enrolled. Scalp electroencephalography (EEG) was conducted twice: once before sertraline administration and then again 4 h after the administration of 50 mg sertraline. Statistical non-parametric maps were obtained using the EEG segments to detect the current-density differences in the high beta frequency bands (beta-3, 22–30 Hz) between the EEGs before and after sertraline administration in the patient group and between the patient group and controls after the administration of sertraline during the erotic video sessions. Comparing between before and after sertraline administration in the patients with PE, the CSD of the high beta frequency band at 4 h after sertraline administration increased significantly in both superior frontal gyri and the right medial frontal gyrus ($P < 0.01$). The CSD of the beta-3 band of the patients with PE were less activated significantly in the middle and superior temporal gyrus, lingual and fusiform gyrus, inferior occipital gyrus and cuneus of the right cerebral hemisphere compared with the normal volunteers 4 h after sertraline administration ($P < 0.01$). In conclusion, sertraline administration increased the CSD in both the superior frontal and right middle temporal gyrus in patients with PE. The results suggest that the increased neural activity in these particular cerebral regions after sertraline administration may be associated with inhibitory effects on ejaculation in patients with PE. *International Journal of Impotence Research* (2011) 23, 213–219; doi:10.1038/ijir.2011.30; published online 23 June 2011

Keywords: current-source analysis; electroencephalography; erotic stimulation; premature ejaculation; SSRI

Introduction

The mechanism(s) and cause(s) of premature ejaculation (PE) remain poorly understood despite its high prevalence. In early studies, PE was believed to be primarily a psychological condition. However, the evidence supporting this assumption is scant, and pharmacological and neurobiological studies in human and animals strongly indicate that PE is a neurobiological dysfunction. Both serotonergic and dopaminergic neurons in the central nervous system

(CNS) have a primary role, with secondary influences from several other neurotransmitters.¹ It has been hypothesized that altered levels of serotonin or serotonin receptor sensitivity in the ejaculatory modulating centers of the CNS constitute the pathophysiological basis of ejaculatory disorders.² The selective serotonin reuptake inhibitors (SSRIs) block serotonin (5-hydroxytryptamine; 5-HT) reuptake, resulting in increased 5-HT neurotransmission and activation of postsynaptic 5-HT receptors. SSRI-induced delayed ejaculation and anorgasmia are probably related to increased central 5-HT neurotransmission and activation of postsynaptic 5-HT receptors.

Current-source analysis of electroencephalography (EEG) is an electrographic functional imaging method to identify the current source of brain neuronal activity. It is a computational and mathematical algorithm that analyzes digital EEG

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data. The discrete model of current-source analysis is a method to determine the exact location of current-source dipoles with strength and orientation data. The distributed model is a method to identify the location and extent of current-source distribution. Low-resolution electromagnetic tomography (LORETA) is a distributed model of current-source analysis.^{3,4}

Studies of neurocognitive function using EEG data have focused on the frequency band >20 Hz. Human EEG studies have demonstrated that cortical high-frequency activity is typically enhanced during various cognitive processes.⁵ Complex cognitive tasks ignite neuronal cell assemblies and activate neuronal network loops. During language processing, a loop between Broca's region and Wernicke's region is activated.⁶ When PE patients were sexually aroused, the neuronal activity in the right precentral gyrus, the right insula and the superior parietal lobules of both cerebral hemispheres may be suppressed.⁷ The neuronal oscillation is equivalent to a circulating frequency of 25–30 Hz. In contrast, higher-frequency oscillatory cortical activity, in the range of 40–60 Hz, is seen in less widely dispersed cell assemblies.⁸ The highest frequency band can be analyzed by LORETA as a high-frequency beta band (22–30 Hz). The analysis of this frequency band can be helpful when evaluating neurocognitive functions during various situations.

On the basis of the role of 5-HT neurotransmission in the physiology of ejaculatory control and possibly in the pathogenesis of PE, and because SSRI antidepressants have the well-established side-effect of delaying ejaculation when used to treat depressed patients, currently marketed SSRIs such as paroxetine, fluoxetine, and sertraline, which increase synaptic 5-HT concentration via blockade of 5-HT transporters, have been investigated in numerous clinical studies for managing PE.⁹ Paroxetine and sertraline have provided significant benefits in patients with PE, either via daily administration or on-demand use before intercourse, and fluoxetine has shown some efficacy for PE as continuously dosed therapy.^{10,11} Sertraline achieves peak plasma levels within 4–6 h and has a relatively long half-life of 26 h, allowing on-demand and once-daily dosing, and is highly potent.¹² In addition, it has a higher selectivity than fluoxetine and paroxetine for blocking the reuptake of 5-HT.¹³

To identify the effects of the SSRI sertraline for treating PE, changes in brain current-source density (CSD) of high-frequency beta bands (22–30 Hz) induced by sertraline administration were investigated during audiovisual erotic stimulation.

Materials and methods

Subjects

This protocol was approved by the local ethics committee of our university hospital. Before the

study, the participants were interviewed to assess their motivation for participating in the study and to exclude anyone with a major medical disorder or history of drug abuse, psychiatric disorder or erectile dysfunction. All subjects received a detailed explanation of the study design and gave written informed consent. Eleven right-handed patients with PE (36.9 ± 7.8 years) and 11 right-handed healthy volunteers (24.2 ± 1.9 years) were enrolled. The PE diagnoses were based on an intravaginal ejaculatory latency time of <1 min and a self-report of low or absent control over ejaculation, resulting in distress for the participants, their sexual partners or both. The mean intravaginal ejaculatory latency time of patients with PE and controls, estimated by the patients and controls, was 45 ± 6 s and 8.2 ± 4.3 min, respectively. All patients with PE and the controls had normal erectile function (International Index of Erectile Function EF domain score ≥ 25). Five patients had lifelong (primary) PE, and six had acquired (secondary) PE.

EEG recording

The EEGs were recorded in a comfortable and closed room. A male technician attended each patient to monitor the EEG recordings and mark each of the time points for the experiments. Most of the patients feel discomfort under study conditions. This kind of problem can occur in almost all investigations using EEG, functional magnetic resonance imaging or positron emission tomography (PET). So, we tried to set comfort condition for this study.

All EEGs were recorded using 21 channels (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, T1 and T2) at a sampling rate of 400 Hz based on the international 10–20 system. A scalp EEG was conducted twice, once before sertraline administration and again 4 h after the administration of 50 mg sertraline in each patient or volunteer, as mean peak plasma concentrations (C_{max}) of sertraline occur between 4 and 6 h after administration. The EEGs were obtained during a 5-min segment of watching an erotic video excerpt. The visual angles of the monitor used to display the visual stimuli were 30.5° horizontally, 23° vertically and 38° diagonally. Immediately after the EEG recording session, the participants subjectively graded their level of arousal by estimating erection hardness on a four-point scale.

Cross-spectral analysis using LORETA

After recomputing to the average referential montage, five 5-s artifact-free segments were selected from each EEG recording (filter: 1.6–70 Hz) made while watching the erotic video excerpt. We used the data review and processing module of the brain electrical source analysis to obtain the data. These segments were then subjected to a cross-

spectral analysis. Frequency-domain analysis in the 22–30 Hz frequency band was applied to selected 5-s artifact-free segments. LORETA-KEY (KEY Institute for Brain–Mind Research, Switzerland) was used to calculate the intracerebral current density in a cross-spectral analysis of the segments. LORETA powers were calculated using the software.^{3,14} Our version of LORETA used a three-shell spherical head model, registered to the Talairach human brain atlas and available as digitized magnetic resonance images from the Brain Imaging Center of the Montreal Neurologic Institute.¹⁵ The registration between the spherical and Talairach head geometries used the realistic EEG electrode coordinates reported by Towle *et al.*¹⁶ The LORETA solution space was restricted to the cortical gray matter and hippocampus in the Talairach atlas, as defined by the corresponding digitized probability atlas available from the Brain Imaging Center of the Montreal Neurologic Institute. A total of 2394 voxels was produced at a spatial resolution of 7 mm under this neuroanatomical constraint.³

Statistical analysis

In each patient, five segments of 5-s epochs were selected from the EEG recordings made while watching an erotic video excerpt before and 4 h after sertraline administration. Thus, 110 EEG data pairs (22 subjects $\times$ 5 epochs) were obtained. Paired sample *t*-tests were computed for the log transformed LORETA power at each voxel in the high beta frequency band (22–30/s) to evaluate differences between the EEGs before and after sertraline administration in the patient group. Similarly, independent sample *t*-tests were computed to evaluate differences in the responses to sexual arousal between the patient group and controls during the erotic video session after sertraline administration. Statistical significance was set at $P < 0.01$ for all analyses. The voxel-by-voxel *t*-values were displayed as statistical non-parametric maps. Talairach coordinates, Brodmann areas and anatomical locations of areas and significant current density changes in music video and sexual arousal were obtained using the statistical non-parametric map.

Results

Erection responses to audiovisual erotic stimulation

After the EEG was completed, the participants subjectively graded the level of sexual arousal felt in response to the audiovisual erotic stimulation according to an erection hardness grading scale ranging from I to IV: grade I = increase in size but not hardness, grade II = hard but not hard enough for penetration, grade III = hard enough for penetration but not completely hard and grade IV = completely

hard and fully rigid.¹⁵ In the patients with PE, eight and three patients graded themselves as III and IV, respectively, before the drug was administered at the first EEG, and seven and four patients graded themselves as III and IV, respectively, at the second EEG (4 h after drug administration). In the normal controls, nine and two males graded themselves as III and IV, respectively, at the first EEG (before drug administration), and one, nine and one males graded themselves as II, III and IV, respectively, at the second EEG (4 h after drug administration). The results of the McNemar test showed that the erection response to audiovisual erotic stimulation was not significantly different between the groups ($P = 1.000$).

Effects of sertraline on CSD of high beta frequency band in patients with PE

Comparing between before and after sertraline administration in the patients with PE, the CSD of the high beta frequency band at 4 h after sertraline administration increased significantly in both superior frontal gyri and the right medial frontal gyrus (CSD of PE group with sexual stimuli after sertraline administration – CSD of PE group with sexual stimuli before sertraline administration = difference in CSD between before and after sertraline administration in the patients with PE; *t*-threshold = 3.5385, $P < 0.01$; Figure 1 and Table 1).

Difference in CSD of the high beta frequency band between the two groups after sertraline administration

After sertraline administration, the CSD of the high beta frequency band of the patients with PE were less activated significantly in the middle and superior temporal gyrus, lingual and fusiform gyrus, inferior occipital gyrus and cuneus of the right cerebral hemisphere compared with the normal volunteers (CSD of PE group with sexual stimuli after sertraline administration – CSD of control group with sexual stimuli after sertraline administration = difference in CSD between the two groups; *t*-threshold = –3.2335, $P < 0.01$; Figure 2 and Table 2).

Discussion

Although the control of ejaculation by the CNS is difficult to study in both humans and animals, numerous studies on the role of the CNS in ejaculation have been conducted in animals. However, physiological and behavioral differences between animals and humans make it difficult to directly apply the results to humans. Of the few

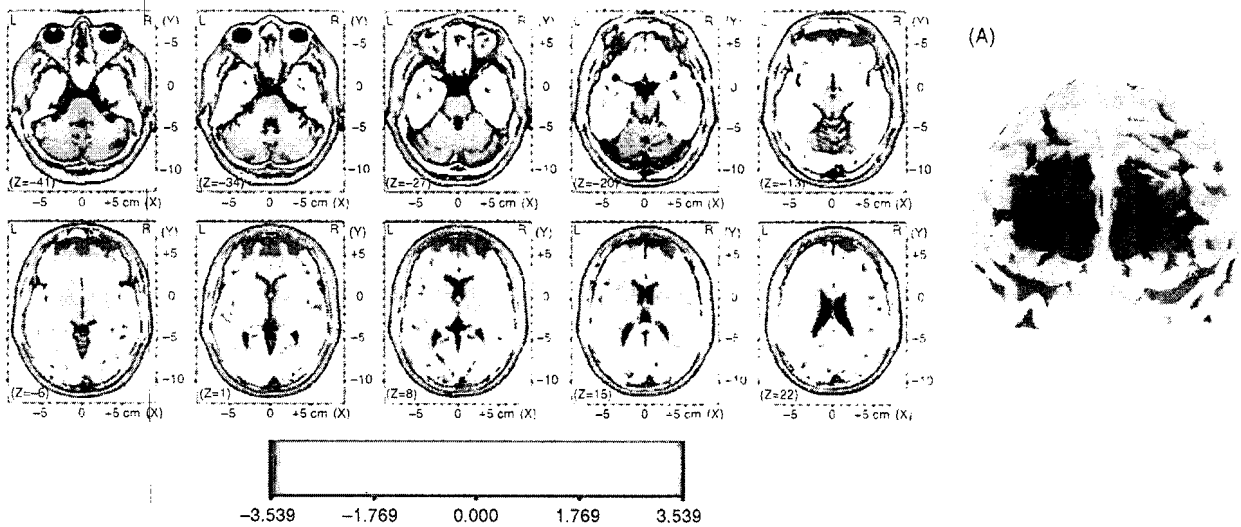


Figure 1 Statistical nonparametric maps of the high frequency band (beta-3, 22–30 Hz) in EEGs during erotic video sessions of patients with premature ejaculation ($n = 11$) compared between before and after sertraline administration. The current-source density at 4 h after sertraline administration increased in both the superior frontal and right medial frontal gyrus of the brain compared with before sertraline administration ($P < 0.01$). (A) Frontal view of 3-dimensional brain. EEG, electroencephalography.

Table 1 Brain areas with significant increases in current-source density of the high beta frequency band in response to audiovisual sexual stimulation compared between before and 4 h after sertraline administration in the patients with premature ejaculation ($n = 11$; $P < 0.01$)

Brodmann area	Anatomical region	t-value
10	Superior frontal gyrus, both	4.4152
10, 11	Medial frontal gyrus, right	4.4152

studies in humans, most have used PET or functional magnetic resonance imaging,^{17–19} measuring changes in cerebral blood flow or changes in oxygen concentration in blood flow to indirectly reflect neuronal activity. These methods are widely accepted, but their limitations must be considered. The current source of localization of EEG activity directly measures cerebral neuronal activity and may be better than PET or functional magnetic resonance imaging for detecting neuronal activity. There was a study in which digital EEG data were analyzed by LORETA to identify the active brain regions associated emotional processing.²⁰ Our study also adopted the analytic methods of EEG.

To know the effects of SSRI on PE, investigation of EEG changes in ejaculation (or orgasm) state is more appropriate than in erection state. But, because EEG is a very sensitive study, it is difficult to analyze the EEG change in ejaculation (orgasm) state. In particular, too many signals (muscle contraction, eye movement, fantasy and so on) are recorded in orgasm occurred within 2–3 s; interpretation of these signals may cause another question and debate.

Hence, EEGs were not recorded in orgasm state but erection state. To record the EEG in erection state, audiovisual erotic stimulation was used in this study. To support the reliability of this study, we did the erection hardness grading scale.²¹ Using the scale, all the patients and controls subjectively graded the level of sexual arousal felt in response to the erotic stimulation. All of them graded their response to grade III or IV (grade III = hard enough for penetration but not completely hard and grade IV = completely hard and fully rigid) during the EEG taken before the sertraline intake. All of them except one graded their response to grade III or IV during the EEG taken after the sertraline intake. Just one of the normal controls graded as grade II (hard but not hard enough for penetration) after the sertraline intake. Duration of erection without penetration (without direct stimulation to the penis) and intravaginal ejaculatory latency time in PE patient are different from each other. Erection without penetration under the ejaculation threshold can be sustained for a long time. Although extremely severe cases of PE patients sometimes could not endure over 1 min, to get the good results, the patient who ejaculated in <5 min by audiovisual erotic stimulation were excluded from this study.

The most widely used SSRIs are fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline. They all act similarly by blocking 5-HT transporters, thereby preventing 5-HT reuptake from the synaptic cleft into the presynaptic serotonergic neuron. This leads to elevated extracellular 5-HT levels within the synaptic cleft. On the basis of studies of patients with depression who were given an SSRI, ejaculatory disorders have been incidentally reported as

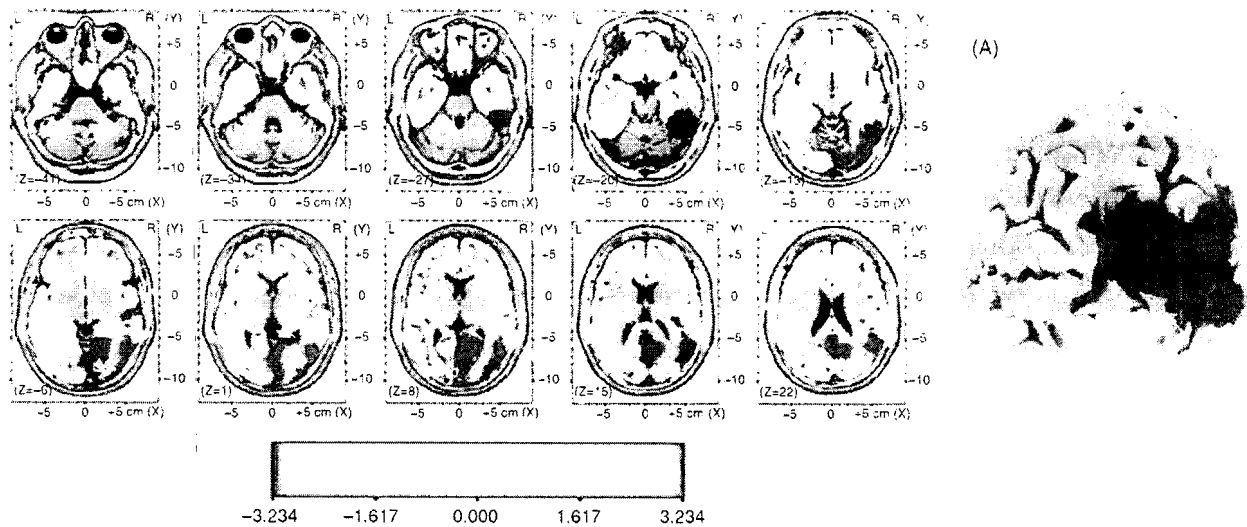


Figure 2 Statistical nonparametric maps of the high frequency band (beta-3, 22–30 Hz) in EEGs after sertraline administration during the erotic video sessions compared between patients with premature ejaculation ($n = 11$) and the controls ($n = 11$). The current-source density of the patients at 4 h after sertraline administration decreased in the middle and superior temporal gyri, inferior occipital gyrus, fusiform gyrus, lingual gyrus, and cuneus of the right cerebral hemisphere compared with the controls ($P < 0.01$). (A) Occipital view of the 3-dimensional brain. EEG, electroencephalography.

Table 2 Brain areas with significant decreases in current-source density of the high beta frequency band in response to audiovisual sexual stimulation compared between the patients with premature ejaculation ($n = 11$) and the controls ($n = 11$) at 4 h after sertraline administration ($P < 0.01$)

Brodmann area	Anatomical region	t-value
21	Middle temporal gyrus, right	-3.3536
21, 13	Superior temporal gyrus, right	-3.3536
17	Cuneus, occipital lobe, right	-3.4193
30	Posterior cingulate gyrus, right	-3.5837
18	Lingual gyrus, occipital lobe, right	-3.7152
37	Fusiform gyrus, temporal lobe, right	-3.7152
19	Inferior occipital gyrus, right	-3.7481
19	Fusiform gyrus, occipital lobe, right	-3.7481
19	Inferior occipital gyrus, right	-3.7481
18	Fusiform gyrus, occipital lobe, right	-4.1756

side effects, and SSRIs have been used to treat PE. Since the first publications reporting the use of clomipramine²² and paroxetine²³ for the treatment of PE, numerous other studies have confirmed the efficacy of SSRIs and clomipramine for treating lifelong PE.^{24–26}

Sertraline at daily doses of 25–50 mg has been repeatedly reported to improve not only the ejaculation latency time in men with PE but also the control over ejaculation and sexual satisfaction, as evidenced by open-label and controlled studies that reported subsequent increased frequency of intercourse.^{27–29} Similar to other types of SSRIs, sertraline reaches C_{max} within 4–6 h following administration. On the basis of these findings, the current study used EEG to examine the effects of

50 mg sertraline on cerebral activation 4 h after its administration.^{30,31}

Little is known about the mechanisms by which serotonin controls ejaculation in the cerebrum. However, according to animal experiments, serotonin concentration increases or decreases in a specific area of the cerebrum, and this delays or accelerates ejaculation. Little is known about the specific mechanisms of how SSRIs affect ejaculation. In our previous study using EEG in patients with PE,⁷ we observed decreased neuronal activity in the precentral gyrus, insula of the right cerebral hemisphere and both superior parietal lobules during sexual arousal induced by an erotic video. In addition, the neuronal activity of patients with PE decreased in the right parahippocampal gyrus and left middle temporal gyrus compared with normal controls. These findings suggest that the inhibitory control of ejaculation in the CNS may be impaired in patients with PE.

In the current study, we observed a similar functional decline in the brain as that shown in our previous study. Neuronal activity of patients with PE decreased in the middle and superior temporal gyrus, lingual and fusiform gyrus, inferior occipital gyrus and cuneus of the right cerebral hemisphere compared with controls. Thus, central control of the temporo-occipital area of the right hemisphere for ejaculation may be disordered in patients with PE. In a previous study concerning the ejaculatory control center of the brain using PET, neocortical activity increased in the inferior and superior frontal gyrus, inferior parietal lobule, inferior temporal gyrus and precuneus in the right cerebral hemisphere during ejaculation.³²

According to our results, sertraline may not act in the disordered brain areas of patients with PE, but in different areas, and may increase neuronal activity in both the superior frontal and right medial frontal areas of the brain. The prefrontal cortex is crucial for cognitive control.³³ In particular, the dorsolateral prefrontal cortex is important for the inhibitory control of desire.³⁴ Taken together, both frontal areas may also be a part of the inhibitory ejaculatory control center of the cerebral neocortex, and sertraline may be associated with the cortically acting and inhibiting effects of sexual processing in patients with PE. The functional sites may be in both the superior frontal and right medial frontal areas of the brain.

The limitation of this study is lack of placebo control group. Small sample size is another study limitation. Although it has this limitation, this study represents a first description of action of SSRI in CNS of PE patients. Further studies using functional magnetic resonance imaging or PET are need for comparison with this study.

Conclusion

Sertraline may act in areas of the brain different from the disordered area in patients with PE. Sertraline may increase neuronal activity in both the superior frontal and right medial frontal area of the brain in patients with PE, and this may be associated with the inhibitory effects of ejaculation in such patients. Those areas may also be a part of the ejaculatory control center in the neocortex of the brain.

Conflict of interest

The authors declare no conflict of interest.

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Study of the Efficacy of Fluoxetine and Clomipramine in the Treatment of Premature Ejaculation after Opioid Detoxification

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Premature ejaculation is a common symptom that can provoke relapse in formerly opioid-dependent men after detoxification. The purpose of this study was to compare the efficacy of clomipramine and fluoxetine for the treatment of premature ejaculation in formerly opioid-dependent men after detoxification. Sixty opium-detoxified men with A & B DSM—IV diagnostic criteria for premature ejaculation participated in a prospective two-week descriptive inferential clinical trial after a two-week washout period. The subjects did not consume any other medications but naltrexone for maintenance of an opium-free state. The subjects were randomly divided into two groups of thirty subjects, one group received fluoxetine (10 mg/d for the first and 20 mg/d for the second week), and the other received clomipramine (25 mg/d for the first and 50 mg/d for the second week). Twenty five subjects did not continue the treatment and were lost to follow-up. The severity of the premature ejaculation was graded regarding the subjects' report in weeks 0, 1, and 2. Mann Whitney-U and Wilcoxon non-parametric tests were used for statistical analysis. Fluoxetine (10 mg/d then 20 mg/d) and clomipramine (25 mg/d then 50 mg/d) were both effective in the treatment of premature ejaculation and did not show any difference in efficacy. The severity of premature ejaculation did not show any relation to the subjects' age, education level, opioid type, or route of abuse. Fluoxetine and clomipramine both can be equally used in the treatment of premature ejaculation following opioid detoxification, depending on their side effects and other symptoms in the subjects. (Am J Addict 2006;15:100–104)

Impotence is a common problem during detoxification from opioids.¹ Shortly after detoxification, most male subjects experience symptoms such as premature ejaculation and spontaneous or nocturnal emissions. These symptoms may contribute to the relapse of the subjects who return to

opioid abuse.² This evidence makes the quest for some effective treatment for these symptoms more important. Because the research does not support the permanent efficacy of psychotherapeutic methods such as psychosexual counseling or behavioral therapy, the trend to pharmacological therapies has been increased. Besides, the pathology of premature ejaculation after detoxification is biological, and there are many limitations for the use psychotherapeutic methods in the special group of involved subjects that are in lower social, cultural, and financial situations. These all make the need for pharmacological treatments more prominent for this special problem.

Delay in ejaculation is one of the side effects of serotonin-specific reuptake inhibitors (SSRIs) and TCAs that make them useful in the treatment of premature ejaculation with physiologic rather than physical etiologies.¹ Most of the previous studies examined serotonin reuptake inhibitors, of which clomipramine were often used. Among the SSRIs, fluoxetine has been administered the most, with doses of 20 mg/d, although doses of 40 mg/d and even 60 mg/d were reported. Previous research reported a prominent increase in the time before ejaculation during intercourse and more satisfaction of the sexual partner.² The effect of fluoxetine seems to be due to the increase in the threshold of sensory nerves of the penile skin.³ Clomipramine also increases the latency period before ejaculation, especially if it is taken right before intercourse.⁴ Research has shown that the effect of clomipramine is improved by increasing the dose from 10 to 30 mg/d. These results suggest that the doses can be increased for the subjects who do not respond to the usual doses up to 30 mg daily.⁵

Another study was performed on the contraction responses of the vasa deferens in vitro and in vivo. It was found that the response was decreased after the use of clomipramine in mice because of the increased level

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of epinephrine. The inhibitory effect of clomipramine was 100 times more than the SSRIs. These differences might be related to the different effects of these medications in increasing the latency period before the ejaculation.⁶ Other researchers found clomipramine more effective than sertraline, fluoxetine, and placebo, although the side effects were greater for the clomipramine.⁷

Previous studies on the issue were lacking some important characteristics, such as:

- there were very few studies performed on premature ejaculation during the opioid detoxification period;
- many of the previous studies were done with some medications that are not available or too expensive in Iran, so research on more available data for the region was needed;
- the results of some of the previous studies did not support each other.

The purpose of this study was to assess and compare the efficacy of clomipramine and fluoxetine for the treatment of premature ejaculation in former opioid-dependent men after detoxification.

METHOD

This descriptive, interventional research was a clinical trial in which subjects with the complaint of early ejaculation were randomly divided into two groups and followed in weekly periods for three months. The research was performed in a governmental daily clinic for opioid detoxification, and the subjects visited voluntarily at the clinic.

Subjects Characteristics

A questionnaire covering personal data such as age, level of education, type, and route of opioid or other substance abuse was filled out for every subject. Subjects were asked to grade their ejaculation in five degrees of early and intolerable, early but tolerable, somewhat early, satisfactory, and late. This section of the questionnaire was supposed to be filled out again in the second and the third weeks of the study. Subjects were also asked if they had nocturnal emissions during the detoxification period. Additionally, subjects were not supposed to have any other psychiatric diagnosis other than addiction and premature ejaculation and were not to consume any medications other than naltrexone.

Experimental Protocol

All of the subjects in the clinic were supposed to undergo a two-week period of detoxification and then enter the psychotherapy programs. They were also introduced to the Narcotics Anonymous (NA) society. Urine morphine checks were administered. If the morphine

check was negative, a naltrexone challenge test was administered. If those results were also negative, subjects received naltrexone capsules 50 mg daily.

After the two-week washout period, the subjects would be interviewed by the psychiatrist. The ones who met the DSM—IV A and B criteria (not C) for premature ejaculation would enter the research program. Subjects were then randomly divided into two equal groups, thirty subjects in each.

The first group received 10 mg fluoxetine every morning for the first week and then 20 mg daily. The second group received 25 mg clomipramine every night for the first week and 50 mg for the second week. At the end of the first and the second weeks, all of the subjects were interviewed by the psychiatrist and assessed for the side effects of the medications. They were also asked to rate their ejaculation in the five degrees previously mentioned.

During the course of the research, 25 subjects (twelve from the clomipramine group and thirteen from the fluoxetine group) did not continue the program (ie, they did not attend the follow-up) and were omitted from the research.

The data were analyzed by Mann-Whitney U, Wilcoxon Signed Ranks, and Kruskal-Wallis tests with SPSS-10 software.

RESULTS

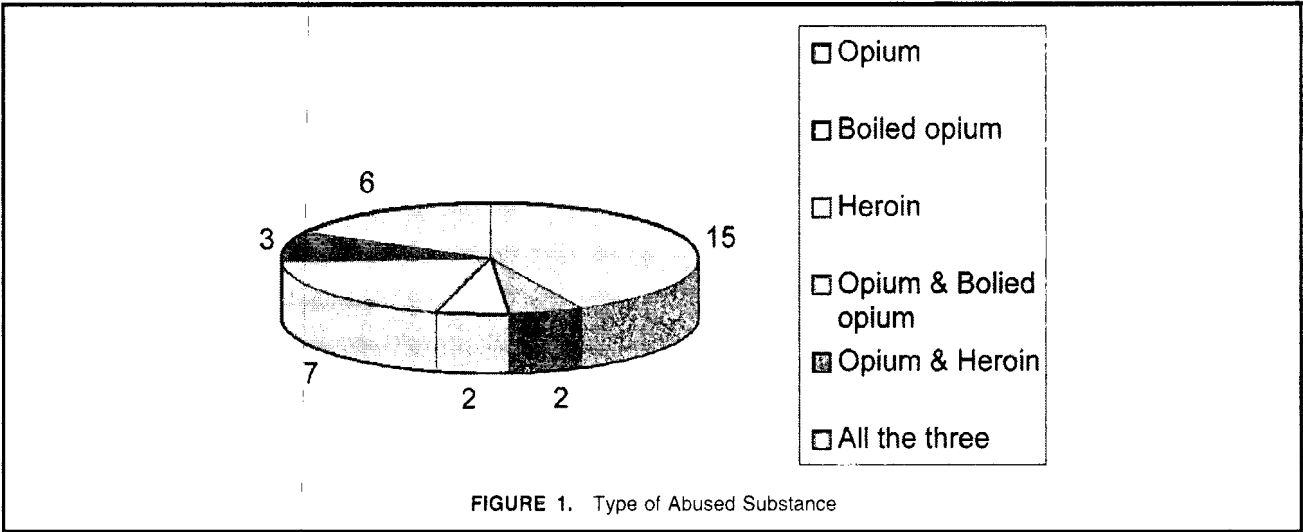
There were 35 subjects in the two groups and the average age was 34.4 (minimum of 22 and maximum of 45). Seventeen subjects (48.6%) received fluoxetine (average age of 35.12 years, SD = 6.48) and eighteen subjects (51.4%) received clomipramine (average age of 33.72 years, SD = 5.98). No statistical relation was found between the age of subjects and the severity of the symptom before and after the treatment (Mann-Whitney >0.05).

Education

The most common level of official education in the subjects (sixteen subjects, 45.7%) was junior high school degree. No significant statistical relation was found between the level of education and the severity of the premature ejaculation before and after the treatment (Kruskal-Wallis >0.05).

Type of Substance

Twenty-three subjects (63%) were not abusing any other substance or medicinal drug, and thirteen (37%) were abusing other substances or drugs, including alcohol (8.5%), cannabis (5.7%), alcohol + cannabis (11.4%), and medicinal drugs (11.4%) (see Fig. 1). No relation was found between the abused substance and the severity of



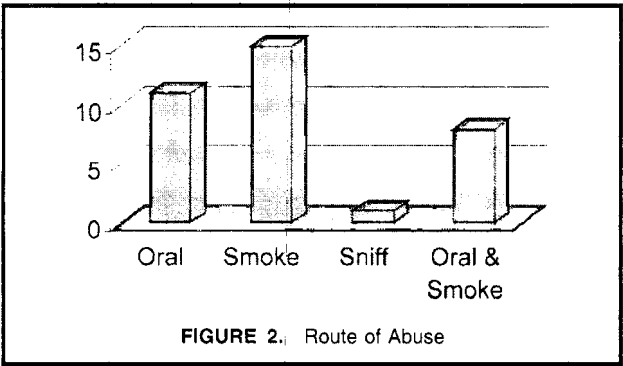
the symptoms before and after the treatment course (Mann-Whitney U, $p > 0.05$). All of the patients were cigarette smokers.

Route of Opioid-Abuse

The most common route of abuse was smoking, or oral (fluoxetine, nine subjects, 53%, clomipramine, thirteen subjects, 72.2%) (see Fig. 2). There was no statistical relation between the route of abuse and the severity of the symptoms before and after the treatment course (Mann-Whitney, $p > 0.05$).

Nocturnal Emissions during the Detoxification Period

Twenty-three subjects had this problem during the detoxification period, but twelve others did not complain about the symptom. The difference in the mean rank severity of the premature ejaculation between the two groups with and without the nocturnal emissions at week 0 was not statistically significant ($p = 0.075 > 0.05$), but it was significant for the end of the first ($p = 0.004 < 0.05$) and the second weeks ($p = 0.017 < 0.05$).



History of Premature Ejaculation before the Addiction

Thirteen subjects (37%) had the problem before their addiction and 63% did not. No significant difference was found between the subjects with and without the history of premature ejaculation before the addiction in severity of premature ejaculation in the weeks 0, 1, and 2 (Mann-Whitney >0.05).

For the clomipramine group, the severity of the premature ejaculation at the end of the first week of the treatment was less than at the beginning of the treatment (Wilcoxon test $p < 0.001$). There was also a significant decrease in the severity of the symptom after the second week in comparison with the first week (Wilcoxon $p < 0.001$).

For the fluoxetine group, the severity of the symptom at the end of the first week was less than at the beginning of the treatment (Wilcoxon $p = 0.004 < 0.05$), and it was also decreased at the end of the second week in comparison to the first week (Wilcoxon $p = 0.001$).

In a comparison between the two groups of fluoxetine and clomipramine in the severity of the premature ejaculation before the treatment and at the ends of weeks 1 and 2, no significant statistical difference was detected (see Table 1). The Mann-Whitney test p values for weeks 0, 1, and 2 were 0.782, 0.443, and 0.525—all bigger than 0.05.

DISCUSSION

Because there was no statistical difference between the two groups of fluoxetine and clomipramine in the mean rank severity of premature ejaculation at the beginning of the research, it was concluded that the two groups have been in the same situation, and it would be proper to further compare the groups after treatment. The mean ages of the two groups also were not statistically different.

TABLE 1. Comparison of the effects of the two drugs at the end of the weeks 1 and 2

Type of drug		N	Mean rank	Sum of ranks
Beginning of the study	Clomipramine	18	17.53	315.50
	Fluoxetine	17	18.50	314.50
	Total	35		
Week 1	Clomipramine	18	16.69	300.50
	Fluoxetine	17	19.38	329.50
	Total	35		
Week 2	Clomipramine	18	16.89	304.00
	Fluoxetine	17	19.18	326.00
	Total	35		

(The average age of the subjects was 34.4 with the minimum of 22 and the maximum of 45).

Both groups manifested a decrease in the severity of symptoms after one week of treatment that shows the efficacy of both drugs. There was also a significant decrease in the severity of symptoms after the second week of the treatment. Because the dosage was doubled for both groups in the second week, it is not clear whether the decrease has been due to the continuation of the treatment or the change in the dosage. Therefore, it can be suggested that if a satisfactory result is not achieved at the beginning of the treatment, the dosage or the duration of the treatment can be increased.

There was also no difference between the efficacy of the two drugs at the end of the first and the second week. According to this finding, both of the medications can be administered for the treatment of premature ejaculation after detoxification in the previously substance-dependent subjects. The choice of the proper medication can be based on the side effects of each one, or on other symptoms of the subject (eg, in a subject with coexisting sleep problems, clomipramine can be the drug of choice).

There was also no relation between the severity of symptoms or the response to the treatment and the age of the subjects, nor was any relation found between the severity of the symptoms and the educational level of the subjects, although it has been claimed that premature ejaculation is more common among men with higher levels of educational because of their interest in the sexual satisfaction of their partner. This might be explained by the fact that premature ejaculation after the substance detoxification is more related to biological etiology rather than psychological etiologies. There was also no relation between the level of response to treatment and the educational level of the subjects.

There was no statistical difference between the type of substance or route of abuse and the severity of the symptoms or the level of response to the treatment.

History of premature ejaculation before the dependency was found in 37% of subjects, but there was no statistical relation between this history and the severity of the symptom after the detoxification or the response to

the treatment. This might again be explained by the different etiology of the symptoms in the two conditions: premature ejaculation after detoxification is more related to biological rather than psychological etiologies.

Because the efficacy of both medications in the treatment of premature ejaculation is equal, the treatment of choice can be selected according to other effects of the medications or their side effects profile. For instance, in the elderly or in people with cardiac disorders, fluoxetine is more suitable than clomipramine, which has alpha adrenergic blocker effects and might induce changes in blood pressure and heart rate. In people who are in detoxification for alcohol or benzodiazepines and thus are more susceptible to convulsion, fluoxetine is also more suitable than clomipramine, which decreases the threshold for seizure. However, there is evidence of increased satisfaction during orgasm in patients who have been consuming clomipramine, and there are also reports of decreased sensitivity of glans penis during the use of clomipramine, which might increase sexual satisfaction. Finally, since the tricyclic antidepressants might increase agitation in people with the diagnosis of borderline personality disorder, it might be better to choose fluoxetine rather than clomipramine for these patients. Fluoxetine seems to be less proper for people who complain about insomnia, while the sedative effects of clomipramine might be helpful to these people. Fluoxetine is also less suitable for people whose appetite is decreased or have experienced weight loss because of its decreasing effects on appetite. However, fluoxetine is more effective in decreasing the craving for opioids and might decrease the chance of relapse.⁸

There were some limitations for this study. The study was not placebo-controlled, so one could not be sure that the results for both fluoxetine and clomipramine groups were better than placebo, and the placebo effect was not assessed. However, patients could not ethically be left without an effective treatment in the placebo group. The absence of an effective treatment for premature ejaculation is very bothersome for patients and could increase the relapse rate of substance abuse. The dropout rate was also high in this study (26 out of forty

patients). This high dropout rate was mostly related to the fact that our patients were mostly of the lower level social group and most of them had also borderline anti-social personality traits/disorders that would decrease their compliance and cooperation with the treatment.

Finally, premature ejaculation after the detoxification period in previously opioid-dependent subjects is a common symptom that is mainly related to the hyperactivity of the afferent nervous system (rather than the psychological etiologies) and responds properly to the biological treatments.

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