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OPOSICION A:

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|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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**SOLICITUD
PUBLICADA**

Número del expediente: 07 104.245
Solicitante: TAKEDA PHARMACEUTICALS COMPANY LIMITED
Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo:
**AGENTE PROFILÁCTICO O TERAPÉUTICO PARA TRASTORNO DE
CONDUCTA NOCTURNO ASOCIADO CON DEMENCIA.**
Gaceta: 591 de 30 de Abril de 2008, número de publicación 244.

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: Lafranco S.A. ✓ Dirección: Carrera 1 No. 46-84 Teléfono: (092) 449.30.51 Fax: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 301 463 -8
	REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar ✓ Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: 621.26.31 E-mail: info@reyes-abogados.com Fax: 621.25.42 Domicilio: Bogotá, D.C.

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) y 20 literal d).

Justificación: VER ANEXO

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Comprobante de pago No. 08-60.877(Oposición) Fecha
(Prórroga) FechaJulio 30 de 2008

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Anexos:



Comprobante de pago de la tasa



Poderes, si fuere el caso



Pruebas de los fundamentos de la oposición



Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas



Documentos que acrediten el legítimo interés, si fuere el caso



Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA:

C.C.No. 79.152.473 T.P. No. 44655

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

Expediente 07-104-245

TÍTULO SOLICITADO: "AGENTE PROFILÁCTICO O TERAPÉUTICO PARA
TRANSTORNO DE CONDUCTA NOCTURNO
ASOCIADO CON DEMENCIA"

PUBLICACIÓN:

Gaceta 591 de 30 de Abril de 2008, número de
publicación 244.

PRIORIDAD:

JP 2005-107673 de 04/04/2005

SOLICITANTE:

TAKEDA PHARMACEUTICALS COMPANY LIMITED

APODERADO:

EMILIO FERRERO

TRÁMITE:

PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al
pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655
del Consejo Superior de la Judicatura, actuando como agente oficioso, en nombre
de la sociedad LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A., de
conformidad con la caución prestada, y estando dentro del plazo establecido por el
artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular
la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente 07-104-245,
por no cumplir con los requisitos de patentabilidad a que se refieren los artículos
14, 18 y 20 literal d) de la Decisión 486 de la Comunidad Andina de Naciones, con
base en los fundamentos de hecho y de derecho que me permito exponer a
continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A. – LAFRANCOL S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

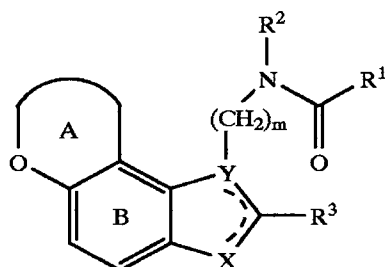
III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite, referida a una composición farmacéutica para prevención o tratamiento de trastornos de conducta nocturnos asociados a demencia que comprende Ramelteon y que puede estar combinado con otros fármacos como inhibidores de acetilcolinesterasa y antagonistas del receptor ácido N-metil-D-aspartico, incumple los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

3.1. Se pretende patentar un nuevo uso de la sustancia (S)-N-[2 (1,6,7,8-tetrahidro-2H-indeno[5,4-b]furan-8-il)etil]propionamida (Ramelteon), empleado ahora en el tratamiento o profilaxis de trastornos de conducta nocturnos asociados con demencia.

Primero que todo, es de suma importancia resaltar que la sustancia (S)-N-[2 (1,6,7,8-tetrahidro-2H-indeno [5,4-b] furan-8-il)etil] propionamida (Ramelteon) reivindicada en la solicitud colombiana en trámite corresponde a un fármaco en primera instancia útil en el tratamiento de trastornos del sueño (insomnio), tal y como lo demuestra la patente americana US 6,034,239 publicada el 07 de Marzo de 2000 y titulada "TRYCICLIC COMPOUNDS, THEIR PRODUCTION AND USE", veamos:

A compound of the formula:



wherein R^1 is an optionally substituted hydrocarbon, amino or heterocyclic group; R^2 is H or an optionally substituted hydrocarbon group; R^3 is H or an optionally substituted hydrocarbon or heterocyclic group; X is CHR^4 , NR^4 , O or S in which R^4 is H or an optionally substituted hydrocarbon group; Y is C, CH or N; ring A is optionally substituted 5- to 7-membered ring; ring B is an optionally substituted benzene ring; and m is 1 to 4, or a salt thereof, a process for producing it, an intermediate for the production and a pharmaceutical composition comprising it are provided. (...)

34. A pharmaceutical composition which comprises a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

35. A composition as claimed in claim 34 wherein said compound or said pharmaceutically acceptable salt has a binding affinity for melatonin receptor.

36. Method for treating or preventing diseases related to the action of melatonin in mammals which comprises administering to a subject in need thereof a therapeutically effective amount of a composition as claimed in claim 35.

37. A method as claimed in claim 36 which regulates circadian rhythm.

38. A method as claimed in claim 36 which regulates sleep-awake rhythm.

39. A method as claimed in claim 36 which regulates time zone change syndrome.

40. A method as claimed in claim 36 which treats or prevents sleep disorders.

41. A process of manufacturing a pharmaceutical composition comprising the steps of selecting a compound or pharmaceutically acceptable salt of claim 1 and admixing said compound or salt with a pharmaceutically acceptable carrier.

Por ello resulta inaceptable que la presente solicitud busque atribuirse patente sobre un nuevo uso de tales agentes, y en especial de Ramelteon, como

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integrante de una composición para el tratamiento o profilaxis de trastornos de conducta nocturnos asociados con demencia.

Lo dicho se demuestra, sin más, con algunas publicaciones de carácter científico que pueden sustentar y enfocar el uso de Ramelteon en este tipo de trastornos nocturnos, especialmente si se tiene en cuenta que dicho compuesto se reconoce como un agonista del receptor de melatonina, veamos:

Melatonin, Sleep, And Circadian Rhythms: Rationale For Development Of Specific Melatonin Agonists¹.

Abstract: *Circadian rhythm sleep disorders (CRSDs), whether chronic or transient, affect a broad range of individuals, including many elderly, those with severe visual impairments, shift workers, and jet travelers moving rapidly across many time zones. In addition, various forms of insomnia affect another large sector of the population. A feature common among CRSDs and some forms of insomnia is sensitivity to the hormone melatonin, which is secreted by the pineal gland. Accumulating evidence suggests that melatonin may regulate the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although the light-dark cycle is the primary signal that entrains the circadian clock to environmental cycles, exogenous melatonin has been shown to entrain the clock in individuals with no light perception and free-running circadian rhythms. Furthermore, studies have reported beneficial effects of melatonin for treatment of certain insomnias. Together, these studies suggest that melatonin may be useful for treating some insomnias and CRSDs. In these contexts, use of melatonin as a supplement has been popular in the United States. Unfortunately, the therapeutic potential of melatonin has been difficult to realize in clinical trials, possibly owing to non-specific actions of the agent and its unfavorable pharmacokinetic properties when administered orally. In an attempt to take advantage of the therapeutic opportunities available through the brain's melatonin system, researchers have developed several melatonin agonists with improved properties in comparison to melatonin. Some of these agents are now in clinical trials for treatment of insomnia or CRSDs.*

Synthesis Of A Novel Series Of Tricyclic Indan Derivatives As Melatonin Receptor Agonists².

Abstract: *To develop a new therapeutic agent for sleep disorders, we synthesized a novel series of tricyclic indan derivatives and evaluated them for their binding affinity to melatonin receptors. In our previous paper, we proposed a conformation of the methoxy group favorable for the binding of the MT(1) receptor. To fix the methoxy group in an active conformation, we decided to synthesize conformationally restricted tricyclic indan analogues with the oxygen atom in the 6-position incorporated into a furan, 1,3-dioxane, oxazole, pyran, morpholine, or 1,4-dioxane ring system. Among these compounds, indeno[5,4-b]furan analogues were found to be the most potent and*

¹ Turek FW, Gillette MU. Sleep Med. 2004 Nov;5(6):523-32.

² Uchikawa O, Fukatsu K, Tokunoh R, Kawada M, Matsumoto K, Imai Y, Hinuma S, Kato K, Nishikawa H, Hirai K, Miyamoto M, Ohkawa S. J Med Chem. 2002 Sep 12;45(19):4222-39.

selective MT(1) receptor ligands and to have superior metabolic stability. The optimization of substituents led to (S)-(-)-22b, which showed very strong affinity for human MT(1) ($K(i) = 0.014$ nM), but no significant affinity for hamster MT(3)($K(i) = 2600$ nM) or other neurotransmitter receptors. The pharmacological effects of (S)-(-)-22b were studied in experimental animals, and it was found that a dose of 0.1 mg/kg, po promoted a sleep in freely moving cats, as demonstrated by a decrease in wakefulness and increases in slow wave sleep and rapid eye movement sleep, which lasted for 6 h after administration. Melatonin (1 mg/kg, po) also had a sleep-promoting effect, though it lasted only 2 h. A new chiral method for the synthesis of (S)-(-)-22b starting from 60, which was prepared from 59 employing asymmetric hydrogenation with the (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-Ru complex, was developed. (S)-(-)-22b (TAK-375) is currently under clinical trial for the treatment of insomnia and circadian rhythm disorders.

Therapeutic Perspectives For Melatonin Agonists And Antagonists³.

Abstract: Melatonin is a neurohormone synthesized in the pineal gland during the dark period in all species, including humans. The diversity and differences in melatonin receptor distribution in the brain and extracerebral organs suggest multiple functional roles for melatonin. Administration of melatonin agonists reduces neophobia and treatment with a melatonin antagonist during the dark period reverses the anxiolytic-like effect of endogenous melatonin. Chronic treatment with agonists prevents various perturbations induced by chronic mild stress. Melatonin in vivo directly constricts cerebral arterioles in rats and decreases the lower limit of cerebral blood flow autoregulation, suggesting that melatonin may diminish the risk of hypoperfusion-induced cerebral ischemia. At the extracerebral level, melatonin regulates intestinal motility in rats. The intestinal postprandial motor response is shorter in the dark phase than in the light phase and this reduction is reversed in animals pretreated with a melatonin antagonist. Moreover, melatonin reduces the duration of cholecystokinin excitomotor effect. Endogenous melatonin may modulate intestinal motility to coordinate intestinal functions such as digestion and transit and control the metabolism of the animal. An adipocyte melatonin binding site may also participate in this control. Melatonin is involved in a wide range of physiological functions. The question remains as to whether evolution, adaptation and diurnal life have modified the physiological role of melatonin in humans. Moreover, the functional role of each of the receptor subtypes has to be characterized to design selective ligands to treat specific diseases.

Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia⁴.

Abstract

Previously, we reported that morning bright light therapy improved sleep time and cognitive function in Alzheimer type of dementia. We conducted a double blind study to examine the effects of melatonin on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type of dementia. The subjects were 9 persons given a placebo (PLA), and 11 given melatonin (3 mg)(MLT). The mean age was 79.2 $\pm$ 6.4 (17 females and 3 males). The drugs were given at 20:30 each day for 4 weeks. We checked sleep time and activity by Actigraph through one week before and the 4th week after drug administration. Cognitive and non-cognitive functions were evaluated with the clinical dementia rating scale (CDR), and Mini Mental State Examination (MMSE), and the Alzheimer's Disease Assessment Scale (ADAS). We successfully recorded Actigraph data from 18 patients (PLA8, MLT10). The mean sleep time

³ Delagrangé P, Atkinson J, Boutin JA, Casteilla L, Lesieur D, Misslin R, Pellissier S, Pénicaud L, Renard P. J Neuroendocrinol. 2003 Apr;15(4):442-8.

⁴ Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S. J Nippon Med Sch. 2003 Aug;70(4):334-41.

change ratio and SD of the administration of PLA in the night was $-0.2 \pm 13.7\%$, and MLT was $33.2 \pm 37.6\%$. The mean activity counts and SD of the administration of PLA in the night was $29.8 \pm 77.0\%$; in MLT it was $44.9 \pm 21.9\%$. Melatonin significantly prolonged the sleep time ($p=0.017$) and decreased activity ($p=0.014$) in the night (21:00-6:00) in the MLT group, although no significant difference in sleep time or activity in the daytime (6:00-21:00) was recognized between the two groups. In comparison with ADAS cognition score changes, the mean change and SD in the PLA was 0.3 ± 3.7 ; in MLT it was -4.3 ± 3.6 points. In comparison with ADAS non-cognition score, the mean change and SD in the PLA group was -0.8 ± 1.0 , in the MLT group it was -4.1 ± 2.2 points. There were also significant differences between the PLA and the MLT groups in the comparison with the score improvement of ADAS cognition ($p=0.017$) and non-cognition ($p=0.002$), otherwise there was no significant difference in improvement of MMSE between both groups. Melatonin administration had effect to improve sleep time and night activity, but no significant effect to improve daytime naps and activity. Although melatonin administration might has less strong effect on circadian rhythm than morning bright light therapy we previously reported, cognitive and non-cognitive functions were improved. Melatonin seemed to be useful for care of the Alzheimer type of dementia patients.

Effects of melatonin in two individuals with Alzheimer's disease⁵.

Abstract

Dementia has been associated with circadian rhythm disturbances expressed in several dimensions including body temperature, hormonal concentrations, sleep and wakefulness patterns, and rest-activity cycles. These disturbances may be the result of a dampening in the amplitude of the circadian rhythm. One of the symptoms associated with the aging process has been a decline in the amplitude of the melatonin rhythm. Here, the results of melatonin administration to two patients with Alzheimer's disease are presented. Melatonin administration enhanced and stabilized the circadian rest-activity rhythm in one of the patients along with some reduction of daytime sleepiness and an improvement in mood. The other patient, who was characterized by less cognitive impairment, showed no significant changes associated with melatonin ingestion. Interestingly, the acrophase of rest-activity was delayed for about one hour in both patients. These results suggest that melatonin may have beneficial effects in some patients with Alzheimer's disease.

Como vemos, estas publicaciones científicas contienen información que puede conllevar a cualquier persona medianamente versada en la materia a utilizar Ramelteon para tratar trastornos del sueño relacionados con trastornos de melatonina; adicionalmente, podría pensarse que, el nivel inventivo de la solicitud colombiana se ve desvirtuado, en el sentido que una persona medianamente versada en la materia deduciría la utilidad de dicho fármaco en los trastornos nocturnos relacionados demencia, si se tiene en cuenta que dichos trastornos nocturnos corresponden a los mismos trastornos del sueño, específicamente los

⁵ Jean-Louis G, Zizi F, von Gizycki H, Taub H. Percept Mot Skills. 1998 Aug;87(1):331-9.

relacionados a cuadros de insomnio y también si se tiene en cuenta que, la melatonina tiene efectos mejorados tanto en el ritmo del sueño como en las funciones cognitivas y no cognitivas en Alzheimer tipo demencia.

Así las cosas, pese a que el solicitante no pretende obtener patente sobre los agentes agonistas del receptor de melatonina como tales, pues todos ellos están comprendidos en el estado de la técnica desde antes de la fecha de prioridad de la solicitud y carecen de protección *per se* en Colombia, es clara su pretensión de obtener exclusiva sobre un nuevo uso, el cual no puede ser objeto de privilegio a la luz de la Decisión 486. La concesión de la solicitud restringiría injustificadamente el empleo de los compuestos agonistas del receptor de Melatonina (Ramelteon), por el simple hecho de revelar para el otra indicación como agente para el tratamiento de trastornos de conductas asociados con la demencia.

3.2. Carencia de Nivel Inventivo de los Usos reivindicados

Ahora bien y si en gracia de discusión fueran patentables los segundos o “nuevos” usos, estos deberían cumplir con los requisitos de novedad y nivel inventivo. Ello no ocurre en el caso que nos ocupa, por obra de lo contenido en algunas publicaciones anteriores a la fecha de prioridad de la solicitud que afectan al menos el nivel inventivo de la solicitud en cuestión, y desde luego, los de la aplicación colombiana equivalente:

Por ejemplo, en relación a la asociación de (S)-N-[2(1,6,7,8-tetrahidro-2H-indeno[5,4-b]furan-8-il)etil]propionamida (Ramelteon) con fármacos inhibidores de acetilcolinesterasa y/o antagonistas de receptor de NMDA (explícitamente donepezilo, galantamina, rivastigmina, tacrina y memantina), existen también publicaciones de carácter científico que demuestran la utilidad de dichos fármacos (inhibidores de acetilcolinesterasa y/o antagonistas de receptor de NMDA) en diversos tipos de demencia, veamos:

Efficacy and Tolerability of Donepezil in Vascular Dementia Positive Results of a 24-Week, Multicenter, International, Randomized, Placebo-Controlled Clinical Trial⁶.

Abstract: *Background and Purpose*—Clinical observations suggest that patients with vascular dementia (VaD) may benefit from treatment with cholinesterase inhibitors. This study evaluated the efficacy and safety of donepezil for relieving symptoms of dementia in VaD. *Methods*—Patients (n=603; mean age, 73.9 years; 55.2% men) with probable (70.5%) or possible (29.5%) VaD, according to criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), were randomized to 24 weeks of treatment with donepezil 5 mg/d (n=198), donepezil 10 mg/d (5 mg/d for first 28 days; n=206), or placebo (n=199). Analyses were based on the intent-to-treat population. *Results*—At week 24, both donepezil groups showed significant improvement in cognition versus placebo on the Alzheimer's Disease Assessment Scale—cognitive subscale (mean change from baseline score effect size: donepezil 5 mg/d, -1.90; P<0.001; donepezil 10 mg/d, -2.33; P<0.001). Significant improvements in patients' global function were seen versus placebo at week 24 (observed cases), on the Clinician's Interview-Based Impression of Change—Plus version only for patients on donepezil 5 mg/d (P=0.014), and on the Sum of the Boxes of the Clinical Dementia Rating only for patients on 10 mg/d (P=0.007). Donepezil-treated patients showed significant benefits in activities of daily living over placebo on the Alzheimer's Disease Functional Assessment and Change Scale (mean change from baseline score effect size at week 24: donepezil 5 mg/d, -1.31, P=0.02; donepezil 10 mg/d, -1.31, P=0.02). Donepezil was well tolerated. Withdrawal rates due to adverse events were relatively low (placebo, 11.1%; donepezil 5 mg/d, 11.1%; donepezil 10 mg/d, 21.8%; P=0.005 versus placebo). *Conclusions*—These data demonstrate that donepezil is an effective and well-tolerated treatment for VaD and show it may have an important place in the management of this condition.

Tacrine Therapy is Associated with Reduced Mortality in Nursing Home Residents with Dementia⁷.

Abstract: *OBJECTIVES:* To investigate the extent to which treatment with tacrine is associated with a reduction in mortality in nursing home residents with dementia. *DESIGN:* We performed a retrospective cohort study using the Systematic Assessment and Geriatric drug use via Epidemiology database, which contains data collected with the Minimum Data Set on a cross-section of over 400,000 nursing home residents in five U.S. states. *SETTING:* Retrospective data analysis of residents in nursing homes. *PARTICIPANTS:* We identified 1,449 users of tacrine and 6,119 nonusers matched on facility, date of tacrine use, level of cognitive function, and dementia diagnosis. *MEASUREMENTS:* Comparisons of the two groups were made for sociodemographic variables, dementia severity, number of medications, and major comorbid illness (heart disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease, malnutrition), and survival over the 3-year study period. *RESULTS:* Based on Cox proportional hazards models, tacrine users showed a significantly lower mortality rate than nonusers. The hazard rate ratio was 0.76 (95% CI 0.70–0.83). After adjusting for

⁶ Sandra Black, FRCP; Gustavo C. Román, MD, FACP, FRSM(Lond); David S. Geldmacher, MD; Stephen Salloway, MD; Jane Hecker, MD; Alistair Burns, MD; Carlos Perdomo, MS; Dinesh Kumar, MS; Raymond Pratt, MD; and the Donepezil 307 Vascular Dementia Study Group. Stroke October 2003. Stroke is available at <http://www.strokeaha.org>

Brian R. Ott, MD, and Kate L. Lapane, PhD. JAGS 50:35–40, 2002. J Am Geriatr Soc 50:35–40, 2002.

the confounding variables of sociodemographic factors, level of function in activities of daily living, cognitive function, number of drugs, and comorbid illnesses, this survival advantage was still significant at 0.85 (95% CI 0.77–0.93). **CONCLUSION:** Treatment of nursing home residents with tacrine is associated with lower mortality. This observation has implications for the socioeconomic impact of cholinesterase inhibitor therapy in those with advanced dementia and for quality of life issues in the nursing home that deserve future investigation.

An Open-Label Extension Trial Of Galantamine In Patients With Probable Vascular Dementia And Mixed Dementia⁸.

Abstract: *Background:* Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia worldwide. Galantamine, an acetylcholinesterase inhibitor and allosteric nicotinic modulator, has shown broad clinical benefits in patients with mild to moderate dementia due to AD, probable VaD, or AD with cerebrovascular disease (CVD)-so-called mixed dementia. *Objective:* The purpose of this study was to evaluate the efficacy and safety profiles of galantamine 24 mg/d in patients with VaD or AD with CVD over the longer term (>6 months). *Methods:* This was an open-label extension of a 6-month double-blind study of galantamine. Patients who had been randomized to receive galantamine 24 mg/d or placebo in the double-blind phase were eligible to continue open-label treatment with galantamine 24 mg/d for 6 months. The primary efficacy end point was change in cognition, based on scores on the 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11). Secondary measures included changes in functional ability (as measured on the Disability Assessment for Dementia [DAD]) and behavior (as measured on the Neuropsychiatric Inventory [NPI]). Safety and tolerability were also monitored. *Results:* Four hundred fifty-nine patients (240 men, 219 women; mean [SE] age, 75.2 [0.33] years) entered the open-label phase. Of these patients, 195 (42.5%) had a diagnosis of probable VaD, and 238 (51.9%) had a diagnosis of AD with CVD; the remainder had an inconclusive diagnosis. At month 12 of the study, improvements from baseline (the start of the double-blind phase) in ADAS-cog/11 scores were observed in both the group that received placebo during the double-blind phase (placebo/galantamine group: -0.3 point; 95% CI, -1.64 to 1.06) and the group that received galantamine during the double-blind phase (galantamine/ galantamine group: -0.9 point; 95% CI, -1.73 to 0.03). Improvement in functional ability was demonstrated by statistically significant mean (SE) changes from baseline in DAD score in both the placebo/galantamine group (-7.4 [1.68]; $P \leq 0.001$) and the galantamine/galantamine group (-3.6 [1.33]; $P \leq 0.01$). There was no significant change in mean (SE) NPI scores in either group (0.2 [0.98] and 0.1 [0.70], respectively). Galantamine treatment was well tolerated. *Conclusions:* In these patients with VaD and AD with CVD, galantamine treatment produced similar sustained benefits in terms of maintenance of or improvement in cognition (ADAS-cog/11), functional ability (DAD), and behavior (NPI) after 12 months.

Memantine For Dementia⁹.

Abstract: *BACKGROUND:* Alzheimer's disease, vascular and mixed dementia are the three commonest forms of dementia affecting older people. There is evidence that the excitatory activity of L-glutamate plays a role in the pathogenesis of Alzheimer's

GAL-INT-6 Study Group, INCONNU ERKINJUNTTI Timo ; KURZ Alexander; SMALL Gary W.; BULLOCK Roger; LILIENFELD Sean ; DAMARAJU C. V.; Clinical therapeutics ISSN 0149-2918. 2003, vol. 25, no6, pp. 1765-1782.

⁹ Areosa SA, Sherriff F. Cochrane Database Syst Rev. 2003;(3):CD003154.

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disease and in the damage from an ischaemic stroke. A low affinity antagonist to N-Methyl-D-aspartate (NMDA) type receptors, such as memantine, may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. **OBJECTIVES:** To determine the clinical efficacy and safety of memantine for people with Alzheimer's disease, or vascular or mixed dementia. **SEARCH STRATEGY:** Trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 15 April 2003 using the terms: memantin*, D-145, DMAA, DRG-0267. All major health care databases and trial databases within the scope of the group are searched regularly to keep this Register up to date. **SELECTION CRITERIA:** Double-blind, parallel group, placebo-controlled, randomized and unconfounded trials in which memantine was administered to people with dementia. **DATA COLLECTION AND ANALYSIS:** Data were extracted, pooled where possible, and weighted mean differences, standardized mean differences or odds ratios were estimated. Intention-to-treat (ITT) and observed cases (OC) analyses are reported, where data were available. **MAIN RESULTS:** Effect of memantine in patients with moderate to severe Alzheimer's disease: analysis of the change from baseline at 28 weeks gave statistically significant results in favour of memantine for 20 mg/day on cognition (MD: 6.1, 95% CI 2.99 to 9.21, $P=0.0001$) activities of daily living (MD 2.10, 95% CI 0.46 to 3.74, $p=0.01$) and in the global clinical impression of change measured by the CIBIC-Plus at 28 weeks (MD -0.30, 95% CI -0.58 to -0.02, $p=0.04$), in all cases the analysis was the ITT-LOCF population (Reisberg 2000). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of memantine for the number who suffer agitation. Effect of memantine in patients with mild to moderate vascular dementia: analysis of the change from baseline at 28 weeks gave statistically significant results in favour of memantine (20 mg/day) for cognition (MD -2.19, 95% CI -3.16 to -1.21, $P<0.0001$) but there was no benefit for the clinical impression of change, or for global measures of dementia (MMM300, and MMM500). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of memantine for the number who suffer agitation. Effect of memantine in patients with Alzheimer's disease and vascular dementia at 12 weeks: there was no statistically significant difference between memantine (10 mg/day) and placebo in activities of daily living. There was a benefit in favour of memantine (10 mg/day) compared with placebo at 12 weeks, for the numbers improved in terms of clinical impression of change (60/82 compared with 38/84 - OR 3.30, 95% CI 1.72 to 6.33, $P=0.0003$) (Winblad 1999). Effect of memantine in patients with vascular dementia, Alzheimer's disease and dementia of non-specified type at 6 weeks: there were beneficial effects on cognition (Ditzler 1991), activities of daily living (Ditzler 1991, Pantev 1993), behaviour (Pantev 1993) and global scales (Gortelmeyer 1992; Pantev 1993; Ditzler 1991) and in global impression of change (Gortelmeyer 1992; Ditzler 1991). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of placebo for the number who suffer restlessness. **REVIEWER'S CONCLUSIONS:** There is a beneficial effect of memantine (20 mg/day) for patients with moderate to severe Alzheimer disease on cognition and functional decline but not in the clinical impression of change. For patients with moderate to severe Alzheimer disease on cognition and functional decline but not in the clinical impression of change. Patients with mild to moderate vascular dementia receiving memantine 20 mg/day had less cognitive deterioration at 28 weeks but again this effect was not clinically discernible. There is a possible beneficial effect on cognition, function and global scales for memantine at 6 weeks in mixed populations. The drug is well tolerated and the incidence of adverse effects is low. More studies are needed.

Rivastigmine In Subcortical Vascular Dementia: An Open 22-Month Study¹⁰.

Abstract: Further to recent data indicating that patients with vascular dementia (VaD) show a cholinergic deficit, we aimed to determine whether rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), has any effects on the symptoms of VaD. Patients aged 65-80, with a diagnosis of dementia and probable VaD, received rivastigmine 3-6 mg/day (n=8) or cardioaspirin (n=8) in an open study for 22 months. At 22 months, patients treated with rivastigmine showed significant improvements in executive function and behavioural symptoms (both $p < 0.05$ vs. both baseline and control group), which were reflected in reduced caregiver stress ($p < 0.05$ vs. baseline and controls). Baseline scores of global response, cognition, word fluency and activities of daily living were maintained in patients receiving rivastigmine, and there was no increase in benzodiazepine or neuroleptic intake. In contrast, the control group showed no improvements in any domain, and significant deterioration in global response and executive function (both $p < 0.05$ vs. baseline and rivastigmine group). Side effects in both groups were tolerable and there were no study withdrawals. Long-term rivastigmine treatment appeared to be safe and effective in this patient population. In particular, improvements in domains particularly relevant to this condition were observed. These benefits may reflect the drug's dual inhibitory effects on the cholinergic system, and its particular activity in frontal areas of the brain. A large, double-blind study of rivastigmine in patients with VaD would be worthwhile.

Como se puede apreciar, existe suficiente información que revela la anterioridad en el uso de dichos compuestos en el tratamiento de diversos tipos de demencia, lo que conllevaría a cualquier persona medianamente versada en la materia, teniendo en cuenta además la información disponible para Ramelteon y expuesta anteriormente, a asociar dichos fármacos en una formulación farmacéutica para con esto tratar los trastornos del nocturnos (del sueño) derivados de la sintomatología de diversos tipos de demencia. En otras palabras, si se tiene clara la utilidad de Ramelteon en el tratamiento de trastornos del sueño, y así mismo se tiene clara la utilidad de donepezilo, galantamina, rivastigmina, tacrina y memantina en el tratamiento de demencia, y conociendo además los respectivos mecanismos de acción de los correspondientes compuestos sería evidente que dichos mecanismos de acción fueran complementarios, y pudieran ser útiles en el tratamiento de pacientes dementes con alteraciones del sueño.

3.3. Por ultimo y si estuviéramos ante una revelación textual del uso del compuesto (S)-N-[2(1,6,7,8-tetrahidro-2H-indeno[5,4-b]furan-8-il)etil] propionamida (Ramelteon) en combinación con agentes inhibidores de la acetilcolinesterasa y/o antagonistas del receptor de NMDA (donepezilo, galantamina, rivastigmina, tacrina y memantina) para el tratamiento de demencia y trastornos nocturnos relacionados a la misma, es necesario resaltar que el capítulo reivindicatorio de la solicitud

¹⁰ Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. J Neurol Sci. 2002 Nov 15;203-204:141-6.

colombiana en curso se encuentra dirigido específicamente en sus reivindicaciones 7, 8 y 9, al uso de una combinación farmacológica entre dichos compuestos, lo cual es inaceptable a la luz de la Decisión 486.

En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial.

Aunque a la ausencia de ellos nos hemos referido ya, cabe desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

De la misma manera la Decisión 486 de la Comunidad Andina de Naciones en su aparte d del artículo 20 del capítulo I, acerca de los requisitos de patentabilidad, menciona que no serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos animales; y si tenemos en cuenta que la solicitud en trámite reivindica también un método de contracepción en un mamífero, tal como lo señala explícitamente en sus reivindicaciones 4 y 5, queda claramente expuesta la improcedencia para otorgar el privilegio de patente a esta solicitud.

En conclusión la solicitud colombiana en trámite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, principalmente porque en el estado de la técnica se encuentra suficiente información que permitiría establecer de manera obvia la asociación de los compuestos mencionados en el capítulo reivindicatorio de la misma para fabricar una formulación farmacéutica que permita obtener un medicamento eficiente para

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tratar los trastornos del sueño en pacientes dementes, lo cual desvirtúa su nivel inventivo, y en segundo lugar porque incurre directamente en una improcedencia de patentabilidad al reivindicar un método terapéutico para dichos trastornos.

Por lo expuesto anteriormente, respetuosamente llamo la atención sobre el hecho de que la solicitud de la referencia, en todas sus reivindicaciones, no cumple con los requisitos dispuestos en la Decisión 486 de 2000, por tal razón no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 18 y 20 literal d) (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- US 6,034,239 publicada el 07 de Marzo de 2000 y titulada "TRYCICLIC COMPOUNDS, THEIR PRODUCTION AND USE" capítulo reivindicatorio.
- Abstracts de todas las publicaciones científicas mencionadas en el acápite de fundamentos de la oposición.

VI. ANEXOS

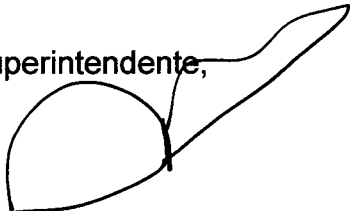
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Lafrancol S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Los mencionados en el acápite de pruebas y en el texto de la oposición.

VII. NOTIFICACIONES

Tanto el suscrito apoderado como mi representada, **LABORATORIO FRANCO COLOMBIANO S.A. – LAFRANCOL S.A.**, las recibiremos en la secretaría de su Despacho o en mi oficina de abogado, localizada en la Carrera 17 No. 88-23, Oficina 207, Fax (1) 621.25.42 de esta ciudad.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.



US006034239A

United States Patent [19]**Ohkawa et al.**[11] **Patent Number:** **6,034,239**[45] **Date of Patent:** **Mar. 7, 2000**[54] **TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE**[75] **Inventors:** **Shigenori Ohkawa**, Osaka; **Osamu Uchikawa**, Hyogo; **Kohji Fukatsu**, Hyogo; **Masaomi Miyamoto**, Hyogo, all of Japan[73] **Assignee:** **Takeda Chemical Industries, Ltd.**, Osaka, Japan[21] **Appl. No.:** **08/812,168**[22] **Filed:** **Mar. 6, 1997****Related U.S. Application Data**

[60] Provisional application No. 60/013,733, Mar. 20, 1996, and provisional application No. 60/023,090, Jul. 25, 1996.

[30] **Foreign Application Priority Data**

Mar. 8, 1996	[JP]	Japan	8-051491
Jul. 12, 1996	[JP]	Japan	8-183667
Feb. 13, 1997	[JP]	Japan	9-029185

[51] **Int. Cl.⁷** **C07D 413/00**; C07D 493/00; C07D 307/92; C07C 233/00[52] **U.S. Cl.** **544/147**; 544/153; 549/387; 549/458; 564/189[58] **Field of Search** 564/189; 544/387, 544/458, 153, 147[56] **References Cited****U.S. PATENT DOCUMENTS**

5,296,482	3/1994	Peglion et al.	514/213
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5,661,186	8/1997	Takaki et al.	514/630

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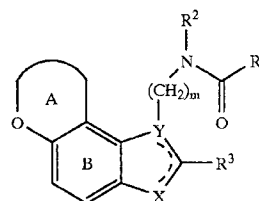
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Macor et al., J. Med. Chem., vol. 35, No. 20 (1992) 3625-32.

Tetrahedron Letters, vol. 36, No. 39 (1995) 7019-7022.

Primary Examiner—John Kight*Assistant Examiner*—Raymond Covington*Attorney, Agent, or Firm*—Fitzpatrick, Cella, Harper & Scinto[57] **ABSTRACT**

A compound of the formula:



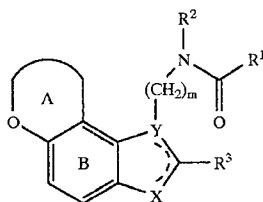
wherein R^1 is an optionally substituted hydrocarbon, amino or heterocyclic group; R^2 is H or an optionally substituted hydrocarbon group; R^3 is H or an optionally substituted hydrocarbon or heterocyclic group; X is CHR^4 , NR^4 , O or S in which R^4 is H or an optionally substituted hydrocarbon group; Y is C, CH or N; ring A is optionally substituted 5- to 7-membered ring; ring B is an optionally substituted benzene ring; and m is 1 to 4, or a salt thereof, a process for producing it, an intermediate for the production and a pharmaceutical composition comprising it are provided.

41 Claims, No Drawings

various disorders associated with melatonin activity in vivo. In addition, the compound (I) of the present invention or a salt thereof has excellent in vivo behavior and have excellent solubility in water.

We claim:

1. A compound of the formula:



wherein R¹ represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;

R² represents a hydrogen atom or an optionally substituted hydrocarbon group;

R³ represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

X represents CHR⁴, NR⁴, O or S in which R⁴ represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y represents C, CH or N, provided that when X is CH₂, Y is C or CH;

..... represents a single bond or a double bond;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring; and

m represents an integer of 1 to 4, or a salt thereof.

2. A compound as claimed in claim 1, wherein R¹ is (i) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkylcarbamoyl, di-C₁₋₆ alkylcarbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino,

(ii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and C₆₋₁₄ aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino, or

(iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkynyl, C₂₋₆ alkenyl, C₇₋₁₁ aralkyl, C₆₋₁₀ aryl, C₁₋₆ alkoxy, C₆₋₁₀ aryloxy, formyl, C₁₋₆

alkyl-carbonyl, C₆₋₁₀ aryl-carbonyl, formyloxy, C₁₋₆ alkyl-carbonyloxy, C₆₋₁₀ aryl-carbonyloxy, carboxyl, C₁₋₆ alkoxy-carbonyl, C₇₋₁₁ aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C₁₋₄ alkyl, oxo, amidino, imino, amino, mono-C₁₋₄ alkylamino, di-C₁₋₄ alkylamino, 3- to 6-membered cyclic amino, C₁₋₃ alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfinio, phosphono, sulfamoyl, mono-C₁₋₆ alkylsulfamoyl, di-C₁₋₆ alkylsulfamoyl, C₁₋₆ alkylthio, C₆₋₁₀ arylthio, C₁₋₆ alkylsulfinyl, C₆₋₁₀ arylsulfinyl, C₁₋₆ alkylsulfonyl and C₆₋₁₀ arylsulfonyl;

R² is (i) a hydrogen atom or (ii) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino;

R³ is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino or (iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkynyl, C₂₋₆ alkenyl, C₇₋₁₁ aralkyl, C₆₋₁₀ aryl, C₁₋₆ alkoxy, C₆₋₁₀ aryloxy, formyl, C₁₋₆ alkyl-carbonyl, C₆₋₁₀ aryl-carbonyl, formyloxy, C₁₋₆ alkyl-carbonyloxy, C₆₋₁₀ aryl-carbonyloxy, carboxyl, C₁₋₆ alkoxy-carbonyl, C₇₋₁₁ aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C₁₋₄ alkyl, oxo, amidino, imino, amino, mono-C₁₋₄ alkylamino, di-C₁₋₄ alkylamino, 3- to 6-membered cyclic amino, C₁₋₃ alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfinio, phosphono, sulfamoyl, mono-C₁₋₆ alkylsulfamoyl, di-C₁₋₆ alkylsulfamoyl, C₁₋₆ alkylthio, C₆₋₁₀ arylthio, C₁₋₆ alkylsulfinyl, C₆₋₁₀ arylsulfinyl, C₁₋₆ alkylsulfonyl and C₆₋₁₀ arylsulfonyl;

R⁴ is (i) a hydrogen atom or (ii) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino;

ring A is a 5- to 7-membered heterocyclic group optionally containing, besides carbon atoms and an oxygen atom, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 4 substituents selected from the

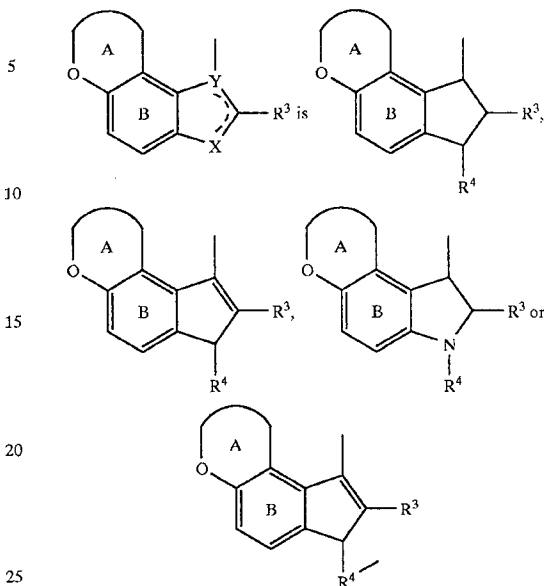
group consisting of (i) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino, (ii) a halogen, (iii) C₁₋₆ alkoxy, (iv) C₆₋₁₀ aryloxy, (v) formyl, (vi) C₁₋₆ alkyl-carbonyl, (vii) C₆₋₁₀ aryl-carbonyl, (viii) formyloxy, (ix) C₁₋₆ alkyl-carbonyloxy, (x) C₆₋₁₀ aryl-carbonyloxy, (xi) carboxyl, (xii) C₁₋₆ alkoxy-carbonyl, (xiii) C₇₋₁₁ aralkyloxy-carbonyl, (xiv) carbamoyl, (xv) an optionally halogenated C₁₋₄ alkyl, (xvi) oxo, (xvii) amidino, (xviii) imino, (xix) amino, (xx) mono-C₁₋₄ alkylamino, (xxi) di-C₁₋₄ alkylamino, (xxii) 3- to 6-membered cyclic amino, (xxiii) C₁₋₃ alkylenedioxy, (xxiv) hydroxy, (xxv) nitro, (xxvi) cyano, (xxvii) mercapto, (xxviii) sulfo, (xxix) sulfinio, (xxx) phosphono, (xxxi) sulfamoyl, (xxxii) mono-C₁₋₆ alkylsulfamoyl, (xxxiii) di-C₁₋₆ alkylsulfamoyl, (xxxiv) C₁₋₆ alkylthio, (xxxv) C₆₋₁₀ arylthio, (xxxvi) C₁₋₆ alkylsulfinyl, (xxxvii) C₆₋₁₀ arylsulfinyl, (xxxviii) C₁₋₆ alkylsulfonyl and (xxxix) C₆₋₁₀ arylsulfonyl; and ring B is a benzene ring which may be substituted by 1 or 2 substituents selected from the group consisting of

(i) a halogen,

(ii) a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl or C₆₋₁₄ aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino,

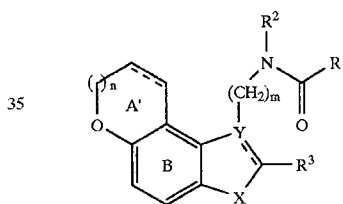
(iii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and C₆₋₁₄ aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino, (iv) a C₁₋₆ alkanoylamino group, (v) a C₁₋₆ alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, carboxyl, C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl, C₆₋₁₀ aryl-carbamoyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy and an optionally halogenated C₁₋₆ alkyl-carbonylamino or (vi) a C₁₋₃ alkylenedioxy group.

3. A compound as claimed in claim 1, wherein



wherein R⁴ is an optionally substituted hydrocarbon group.

4. A compound as claimed in claim 1 which is a compound of the formula:



wherein ring A' is an optionally substituted, oxygen-containing heterocyclic ring;

n is an integer of 0 to 2;

— and — are independently a single bond or a double bond.

5. A compound as claimed in claim 1, wherein R¹ is

- (i) an optionally substituted C₁₋₆ alkyl group,
- (ii) an optionally substituted C₃₋₆ cycloalkyl group,
- (iii) an optionally substituted C₂₋₆ alkenyl group,
- (iv) an optionally substituted C₆₋₁₄ aryl group,
- (v) an optionally substituted mono- or di-C₁₋₆ alkylamino group,
- (vi) an optionally substituted C₆₋₁₄ arylamino group or
- (vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group.

6. A compound as claimed in claim 1, wherein R¹ is an optionally halogenated C₁₋₆ alkyl group.

7. A compound as claimed in claim 1, wherein R² is a hydrogen atom or an optionally substituted C₁₋₆ alkyl group.

8. A compound as claimed in claim 1, wherein R² is a hydrogen atom.

9. A compound as claimed in claim 1, wherein R³ is a hydrogen atom or an optionally substituted hydrocarbon group.

10. A compound as claimed in claim 1, wherein R³ is a hydrogen atom.

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11. A compound as claimed in claim 1, wherein R^4 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

12. A compound as claimed in claim 1, wherein X is CHR^4 .

13. A compound as claimed in claim 1, wherein X is CHR^4 and is a single bond.

14. A compound as claimed in claim 13, wherein X is CH_2 .

15. A compound as claimed in claim 1, wherein X is NR^4 .

16. A compound as claimed in claim 1, wherein Y is C or CH.

17. A compound as claimed in claim 1, wherein Y is CH.

18. A compound as claimed in claim 1, wherein m is 2.

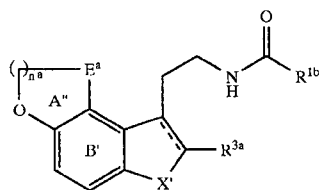
19. A compound as claimed in claim 1, wherein ring A is a tetrahydrofuran ring.

20. A compound as claimed in claim 1, wherein ring A is unsubstituted.

21. A compound as claimed in claim 1, wherein ring B is unsubstituted.

22. A compound as claimed in claim 4, wherein n is 0 or 1.

23. A compound as claimed in claim 1 which is a compound of the formula:



wherein R^{1b} is C_{1-6} alkyl,

X' is CH_2 , NH or NCHO,

..... is a single bond or double bond,

R^{3a} is a hydrogen atom or phenyl,

E^a is CH_2CH_2 , $CH=CH$, CH_2O , $CH=N$, CONH or CH_2NH ,

n^a is 0 or 1,

ring A' is a 5- or 6-membered oxygen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and

ring B' is a benzene ring which may be substituted by a halogen.

24. A compound claimed in claim 23, wherein is single bond and X' is NH.

25. A compound claimed in claim 1, which is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

26. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide.

27. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide.

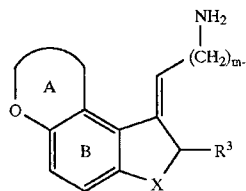
28. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

29. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

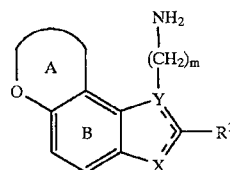
30. A process for producing a compound as claimed in claim 1, which comprises:

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reacting a compound of the formula (i):



or a salt thereof, or (ii):



or a salt thereof, with a compound of the formula:

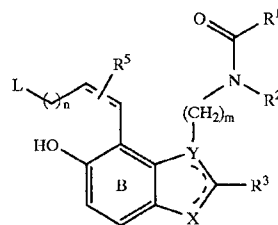


or a salt or a reactive derivative thereof; and

if necessary, subjecting the resultant compound to reduction and/or alkylation.

31. A process for producing a compound as claimed in claim 4, which comprises:

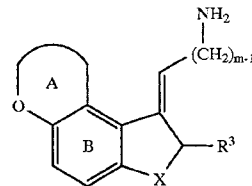
subjecting to cyclization a compound of the formula:



wherein R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxy group, a nitro group, a cyano group or an optionally substituted amino group; L represents a leaving group, or a salt thereof; and

if necessary, subjecting the resultant compound to reduction.

32. A compound of the formula:



wherein R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

x represents CHR^4 , NR^4 , O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;

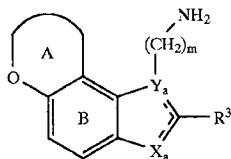
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ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;
 ring B represents an optionally substituted benzene ring;
 and

m represents an integer of 1 to 4, or a salt thereof.
 33. A compound of the formula:



wherein X^a represents CHR^{4a} , NR^{4a} , O or S in which R^{4a} represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y^a represents C, CH or N, provided that when X^a is NH or NCH_3 , Y^a is CH or N;

— represents a single bond or a double bond;

R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring;
 and

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m represents an integer of 1 to 4, or a salt thereof.

34. A pharmaceutical composition which comprises a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

35. A composition as claimed in claim 34 wherein said compound or said pharmaceutically acceptable salt has a binding affinity for melatonin receptor.

36. Method for treating or preventing diseases related to the action of melatonin in mammals which comprises administering to a subject in need thereof a therapeutically effective amount of a composition as claimed in claim 35.

37. A method as claimed in claim 36 which regulates circadian rhythm.

38. A method as claimed in claim 36 which regulates sleep-awake rhythm.

39. A method as claimed in claim 36 which regulates time zone change syndrome.

40. A method as claimed in claim 36 which treats or prevents sleep disorders.

41. A process of manufacturing a pharmaceutical composition comprising the steps of selecting a compound or pharmaceutically acceptable salt of claim 1 and admixing said compound or salt with a pharmaceutically acceptable carrier.

* * * * *

Original Contributions

Efficacy and Tolerability of Donepezil in Vascular Dementia Positive Results of a 24-Week, Multicenter, International, Randomized, Placebo-Controlled Clinical Trial

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Stephen Salloway, MD; Jane Hecker, MD; Alistair Burns, MD; Carlos Perdomo, MS;
Dinesh Kumar, MS; Raymond Pratt, MD; and the Donepezil 307 Vascular Dementia Study Group

Background and Purpose—Clinical observations suggest that patients with vascular dementia (VaD) may benefit from treatment with cholinesterase inhibitors. This study evaluated the efficacy and safety of donepezil for relieving symptoms of dementia in VaD.

Methods—Patients (n=603; mean age, 73.9 years; 55.2% men) with probable (70.5%) or possible (29.5%) VaD, according to criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIREN), were randomized to 24 weeks of treatment with donepezil 5 mg/d (n=198), donepezil 10 mg/d (5 mg/d for first 28 days; n=206), or placebo (n=199). Analyses were based on the intent-to-treat population.

Results—At week 24, both donepezil groups showed significant improvement in cognition versus placebo on the Alzheimer's Disease Assessment Scale—cognitive subscale (mean change from baseline score effect size: donepezil 5 mg/d, -1.90 ; $P=0.001$; donepezil 10 mg/d, -2.33 ; $P<0.001$). Significant improvements in patients' global function were seen versus placebo at week 24 (observed cases), on the Clinician's Interview-Based Impression of Change—Plus version only for patients on donepezil 5 mg/d ($P=0.014$), and on the Sum of the Boxes of the Clinical Dementia Rating only for patients on 10 mg/d ($P=0.007$). Donepezil-treated patients showed significant benefits in activities of daily living over placebo on the Alzheimer's Disease Functional Assessment and Change Scale (mean change from baseline score effect size at week 24: donepezil 5 mg/d, -1.31 , $P=0.02$; donepezil 10 mg/d, -1.31 , $P=0.02$). Donepezil was well tolerated. Withdrawal rates due to adverse events were relatively low (placebo, 11.1%; donepezil 5 mg/d, 11.1%; donepezil 10 mg/d, 21.8%; $P=0.005$ versus placebo).

Conclusions—These data demonstrate that donepezil is an effective and well-tolerated treatment for VaD and show it may have an important place in the management of this condition. (*Stroke*. 2003;34:2323-2332.)

Key Words: dementia ■ donepezil ■ randomized controlled trials

During the last 2 decades, studies have confirmed that cognitive impairment arising from cerebrovascular disease (CVD) and resulting in vascular dementia (VaD) is the most common form of dementia after Alzheimer disease (AD) in many parts of the world¹ and may indeed be more common than AD in some populations.²

VaD can result from multiple types of CVD, including recurrent strokes and white matter lesions.³ At present, the management of VaD focuses on secondary prevention strategies to limit the occurrence of further strokes. However, the management of the symptoms of dementia in VaD patients is

See Editorial Comment, page 2331

often overlooked because no treatment is currently approved for this indication.

Clinical evidence suggests that, in VaD patients, vascular lesions may produce cholinergic dysfunction similar to that seen in AD patients.^{4,5} Since reduced cholinergic neurotransmission provides the rationale for the use of cholinomimetics in AD,⁶ cholinergic agents that have proven benefits in this condition may also be useful in the management of VaD.

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A list of the members of the 307 Vascular Dementia Study Group appears in Acknowledgments.

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Donepezil, a potent acetylcholinesterase inhibitor, provides significant benefits in cognition, global function, and activities of daily living (ADL) in patients with mild to moderate AD.^{7,8} In AD patients, donepezil can maintain cognitive status at near baseline values for up to 52 weeks,⁹ as well as preserving functional abilities,¹⁰ delaying nursing home placement,¹¹ and ameliorating behavioral symptoms.¹² Recently, Erkinjuntti et al¹³ demonstrated therapeutic effects of a cholinesterase inhibitor in a heterogeneous group, which included patients with AD plus cerebrovascular lesions (AD plus CVD) and patients with probable VaD; however, coexisting AD may have accounted for the observed treatment effects. Therefore, there is as yet no conclusive evidence of beneficial effects of cholinergic agents in VaD.

We report here the results of a 6-month, randomized, placebo-controlled study of donepezil in VaD patients. The study was designed to determine the efficacy and tolerability of donepezil (5 and 10 mg/d) versus placebo in patients with VaD, excluding patients with AD plus CVD or with prestroke dementia.¹⁴ This study is therefore 1 of the first 2 large-scale, international, randomized, double-blind, placebo-controlled trials of a cholinomimetic in patients with probable or possible VaD, diagnosed according to the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIREN).¹⁵

Subjects and Methods

Men and women (aged ≥ 40 years) with a diagnosis of possible or probable VaD of >3 months' duration, together with clinical and radiological evidence of CVD, were enrolled. A board-certified radiologist applied the NINDS-AIREN criteria to the CT and MR images, and the investigator classified patients as having probable or possible VaD according to all available clinical and imaging information. Patients with hypertension, type 1 or 2 diabetes mellitus, or heart disease were eligible provided the diseases were stable or controlled by medication for at least 3 months. Patients with medication-controlled depression could be enrolled, and patients with a history of recent stroke were also eligible providing that they had not been hospitalized for stroke in the previous 3 months.

Exclusion criteria included clinical or radiological evidence of neurodegenerative disorders other than VaD (eg, Parkinson disease), dementia due to AD (according to NINDS-Alzheimer's Disease and Related Disorders Association [ADRD] criteria) or other conditions not associated with CVD, prior diagnosis of AD and subsequent cognitive impairment due to stroke or other CVD (prestroke dementia), a Mini-Mental State Examination (MMSE)¹⁶ score >26 or <10 , and the occurrence of new strokes within the 28 days before baseline. Patients with major depression or other psychiatric disorders (according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) were excluded. Patients who had experienced a myocardial infarction within 3 months of enrollment were excluded (although these patients could be reconsidered for inclusion once 3 months had elapsed), as were those with clinically relevant hepatic, pulmonary, gastrointestinal, or life-threatening disease. Additional reasons for exclusion included pregnancy, a history of alcohol or drug abuse, or a known hypersensitivity to donepezil. Patients were not permitted to receive anticholinergic drugs or cholinergic agents other than donepezil during the study period. Sympathomimetic amines and antihistamines were not permitted within 48 hours of a clinic visit, and anxiolytics, tranquilizers, hypnotics, and antipsychotics were not permitted within 72 hours of any clinic visit.

All subjects had to be outpatients under the care of a consistent caregiver and with sufficient speech, comprehension, and motor

function to enable completion of all procedures. Before study enrollment, the caregiver and patient (or legal representative) gave written, informed consent to participate in the study, which was conducted according to the Declaration of Helsinki and its subsequent amendments and in compliance with the regulations of the US Food and Drug Administration. The protocol was reviewed and approved by the designated human subjects' review board at each participating site.

Study Design

This was a multinational, multicenter, 24-week, double-blind, randomized, placebo-controlled, parallel-group study that ran from June 1997 until September 2001. Patients were assigned to 1 of 3 treatment groups by a computer-generated randomization protocol. Patients received single daily doses of donepezil 5 mg, donepezil 10 mg, or matching placebo to ensure blinding. Patients in the donepezil 10 mg/d treatment arm received donepezil 5 mg/d for the first 4 weeks and 10 mg/d thereafter.

Psychometric evaluations, physical and neurological examinations, laboratory determinations, and measurements of vital signs were performed at screening, baseline, and (together with checks for medication compliance and adverse events) at weeks 6, 12, 18, and 24. Patients also underwent a CT or MRI scan at screening if this had not been performed within the previous 6 months.

Efficacy Assessments

The primary efficacy outcome measures were the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)¹⁷ and the Clinician's Interview-Based Impression of Change-Plus version (CIBIC-plus).¹⁸ The Clinician's Interview-Based Impression of Severity (CIBIS) at baseline was used as a reference for subsequent CIBIC-plus ratings. The clinician rating the CIBIC-plus was blind to the patient's psychometric test scores and adverse events.

Secondary efficacy end points were based on the MMSE,¹⁶ the Sum of the Boxes of the Clinical Dementia Rating (CDR-SB),¹⁹ and the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).¹⁰ The ADFACS provides a measure of instrumental and basic ADL. Patients with permanent motor or sensory deficits, in whom a change in ADL may not be observable, were categorized on the ADFACS as "not assessable" in affected domains and assessed only on unaffected domains.

Safety Assessments

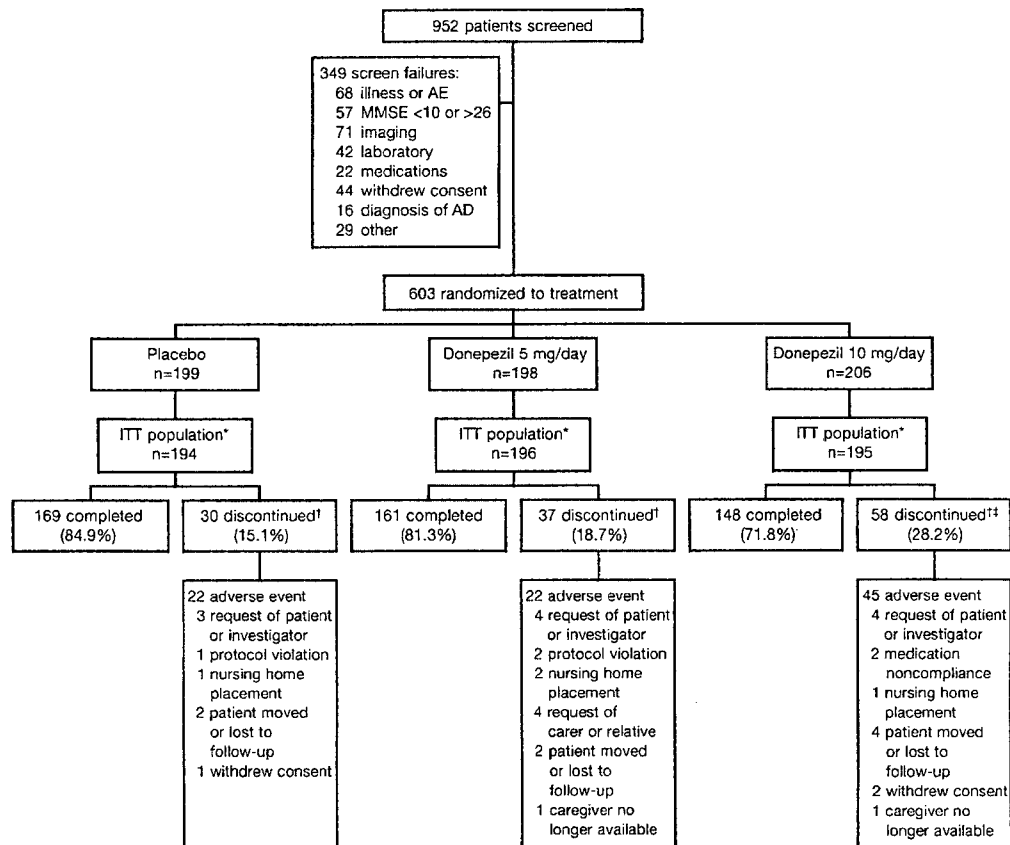
Safety and tolerability of study medication were assessed by comparing rates of discontinuation and treatment-emergent adverse events between treatment groups, as well as changes from baseline in laboratory test values and vital signs, ECG abnormalities, and changes on physical examination.

Statistical Analysis

The determination of sample size was based on a review of the results of phase 3 trials of donepezil in AD patients.^{7,8} The sample size was adjusted from 450 to 600 after a blinded determination of CIBIC-plus variance indicated that a larger sample was required. On this basis, a total population of 600 patients (200 per treatment arm) was required to have an 80% chance of detecting a 0.3-point improvement in CIBIC-plus between active treatment and placebo at the 0.05 significance level, allowing for a dropout rate of 20%. Patients who discontinued treatment were not replaced.

Analysis of efficacy was based on the intent-to-treat (ITT) population, which included all patients who received at least 1 dose of study medication, had baseline data, and had at least 1 postbaseline efficacy assessment. Within the ITT population, analyses were based on either observed cases at week 24 or end point, defined as last observation carried forward (LOCF), to week 24. Subgroup analyses were performed on patients with possible VaD and on patients with probable VaD. All patients who received at least 1 dose of study medication were included in the safety analysis.

Baseline demographic characteristics were analyzed with the Fisher exact test or χ^2 test (for categorical measures) or ANOVA (for



*18 patients were excluded from the ITT population (5 from the placebo group, 2 from the donepezil 5 mg/day group and 11 from the donepezil 10 mg/day group) because they did not have a baseline, or at least one post-baseline assessment, or at least one efficacy assessment.

†11 patients died during the study (4 in the placebo group, 1 in the donepezil 5 mg/day group, and 6 in the donepezil 10 mg/day group). An additional 4 patients died within 4 weeks of discontinuing from the study.

‡One patient had two reasons for discontinuation.

Figure 1. Patient disposition. AE indicates adverse event.

continuous measures). Differences between the treatment groups for linear efficacy measures were assessed by ANCOVA models that included baseline score as covariate, treatment (dose), and center. Categorical efficacy assessments were analyzed with a Cochran-Mantel-Haenszel test. The least squares mean changes from baseline scores to weeks 6, 12, 18, and 24 and end point are presented for variables analyzed with the ANCOVA models.

All statistical tests were 2-tailed and were performed at the 0.05 significance level.

Results

Patients

A total of 603 patients were enrolled and randomized to treatment, and 478 (79.3%) completed the study (Figure 1). Premature withdrawal was due primarily to adverse events in both placebo- and donepezil-treated patients.

The placebo and donepezil treatment groups were well matched with respect to baseline demographics, medical history, presence of cardiovascular risk factors, and baseline assessment scores (Table 1). The majority (70.5%) of patients met NINDS-AIREN criteria for probable VaD, and practically all patients (98.7%) had abnormal CT or MRI scans (Table 1). More than 75% of patients had an abrupt onset of cognitive impairment, and 58% showed a stepwise deterioration in cognition after onset of impairment.

Mean overall compliance with study medication was 95.6% in the donepezil 5 mg/d group, 95.0% in the donepezil 10 mg/d group, and 95.7% in the placebo group.

Virtually all enrolled patients (99.2%) were taking concomitant medications. Antithrombotics for stroke prevention were among the most commonly received (83.7% of all patients: placebo, 81.9%; donepezil 5 mg/d, 84.3%; donepezil 10 mg/d, 85.0%), as well as antihypertensive agents acting on the renin-angiotensin system (32.5% of patients) and diuretics (30.8% of patients). Mood-enhancing medications (including antidepressants) were taken by 37.6% of patients, and mood-stabilizing (psycholeptic) medications were taken by 22.6% of patients.

Primary Efficacy Analyses

Patients treated with donepezil 5 mg/d and 10 mg/d demonstrated significant improvements versus placebo at all time points on the ADAS-cog (Figure 2 and Table 2).

Subanalyses of the ADAS-cog results revealed significant differences in favor of donepezil over placebo in probable VaD patients (least squares mean change from baseline score effect size at end point: donepezil 5 mg/d, -1.67 , $P=0.02$; donepezil 10 mg/d, -2.60 , $P<0.001$). A trend toward treat-

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TABLE 1. Patient Demographics and Baseline Characteristics

	Donepezil			
	Placebo n=199	5 mg/day n=198	10 mg/day n=206	Total n=603
Male/Female	115/84	111/87	107/99	333/270
Age, mean±SE (range)	74.2±0.6 (45–91)	73.7±0.6 (47–91)	73.9±0.6 (46–89)	73.9±0.3 (45–91)
Clinical diagnosis,* n (%)				
Probable VaD	145 (72.9)	135 (68.2)	145 (70.4)	425 (70.5)
Possible VaD	54 (27.1)	63 (31.8)	61 (29.6)	178 (29.5)
Cardiovascular disease	180 (90.5)	176 (88.9)	182 (88.3)	538 (89.2)
Hypertension	132 (66.3)	143 (72.2)	140 (68.0)	415 (68.8)
Smoking	117 (58.8)	127 (64.1)	130 (63.1)	374 (62.0)
Diabetes	37 (18.6)	32 (16.2)	42 (20.4)	111 (18.4)
Hypercholesterolemia	86 (43.2)	82 (41.4)	83 (40.3)	251 (41.6)
Angina/coronary artery disease	54 (27.1)	55 (27.8)	57 (27.7)	166 (27.5)
Abnormal CT or MRI	195 (98.0)	195 (98.5)	205 (99.5)	595 (98.7)
≥1 stroke or TIA pre-dementia	144 (72.4)	144 (72.7)	147 (71.4)	435 (72.1)
Cortical stroke only	36 (18.1)	44 (22.2)	49 (23.8)	129 (21.4)
Subcortical stroke only	72 (36.2)	65 (32.8)	75 (36.4)	212 (35.2)
White matter lesions only†	35 (17.6)	35 (17.7)	39 (18.9)	109 (18.1)
Multiple lesion locations	45 (22.6)	38 (19.2)	35 (17.0)	118 (19.6)
Minimal lesions	11 (5.5)	16 (8.1)	8 (3.9)	35 (5.8)
Focal signs	152 (76.4)	154 (77.8)	156 (75.7)	462 (76.6)
Focal symptoms	122 (61.3)	117 (59.1)	129 (62.6)	368 (61.0)
Hachinski Ischemia Scale score, mean±SE (range)‡	10.0±0.2 (0–16)	9.8±0.2 (0–17)	10.0±0.2 (3–17)	10.0±0.1 (0–17)
Baseline score, LS mean±SE				
ADAS-cog	20.1±0.7	21.2±0.8	20.9±0.7	...
MMSE	21.7±0.3	21.9±0.3	21.8±0.3	...
CDR-SB	6.1±0.2	6.4±0.2	6.1±0.2	...
ADFACTS	15.9±0.7	17.3±0.8	15.3±0.7	...
CIBIS rating at baseline, n (%)				
Borderline mentally ill	8 (4.0)	10 (5.1)	15 (7.3)	33 (5.5)
Mildly ill	91 (45.7)	87 (43.9)	96 (46.6)	274 (45.4)
Moderately ill	86 (43.2)	71 (35.9)	72 (35.0)	229 (38.0)
Markedly ill	14 (7.0)	26 (13.1)	20 (9.7)	60 (10.0)
Severely ill	0	4 (2.0)	3 (1.5)	7 (1.2)

*By NINDS-AIREN.

†Periventricular and nonperiventricular.

‡Measured at screening.

ment benefit was also observed in the possible VaD group, although conclusions in this subgroup are not robust because of the small sample size (least squares mean change from baseline score effect size at end point: donepezil 5 mg/d, -1.73 , $P=0.07$; donepezil 10 mg/d, -0.94 , $P=0.32$).

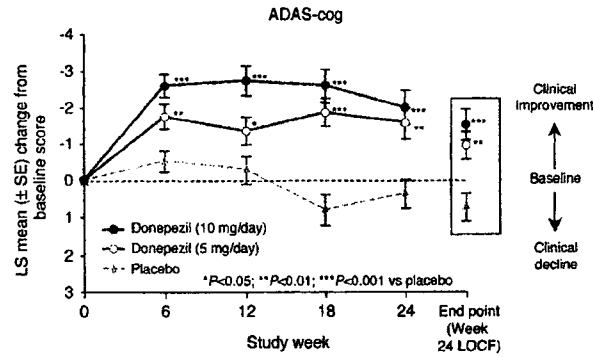
Improvement in global function, as assessed by the CIBIC-plus, was observed in a greater proportion of donepezil- than placebo-treated patients in the 5 mg/d group but not in the 10 mg/d group, at week 24 (observed cases) and at end point (Table 2).

Secondary Efficacy Analyses

Significant improvements on the MMSE versus placebo were observed in the donepezil 10 mg/d group at all postbaseline

evaluations and in the donepezil 5 mg/d group at week 18 (observed cases) and at end point (Table 2). Placebo-treated patients demonstrated postbaseline improvements on the MMSE throughout the study.

Results on the CDR-SB demonstrated that overall dementia levels were improved in the donepezil 10 mg/d treatment group compared with placebo at all evaluations, reaching statistical significance at weeks 6 ($P=0.047$), 18 ($P=0.006$), 24 ($P=0.007$), and end point ($P=0.022$) (Table 2). Significant benefits versus placebo were not observed on the CDR-SB in the donepezil 5 mg/d group. After an initial improvement, placebo-treated patients declined below baseline on the CDR-SB at weeks 18 and 24 and at end point.

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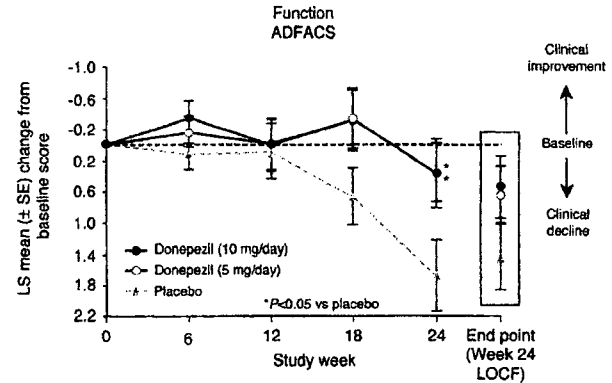
Don 10 mg	n=186	182	162	146	143	186
Don 5 mg	n=186	179	171	154	153	185
Placebo	n=188	187	174	168	160	188

Figure 2. ADAS-cog least squares (LS) mean change from baseline score in donepezil- and placebo-treated patients. Don indicates donepezil.

Analysis of the ADFACS total scores demonstrated significant functional benefits of donepezil treatment; ADFACS scores in donepezil-treated patients were maintained close to baseline, whereas placebo-treated patients declined (Figure 3 and Table 2). Separate analysis of the ADFACS instrumental ADL (IADL) items also demonstrated significant treatment differences (Table 2).

Safety Analyses

As expected in this patient population, there was a high incidence of adverse events in all treatment groups. The proportion of donepezil-treated patients experiencing



Don 10 mg	n=189	185	164	148	143	189
Don 5 mg	n=181	173	164	152	151	181
Placebo	n=180	179	166	161	155	180

Figure 3. ADFACS least squares (LS) mean change from baseline score in donepezil- and placebo-treated patients. Don indicates donepezil.

treatment-emergent adverse events was similar to placebo (88.4%) in the 5 mg/d group (88.9%, $P=1.0$) and higher than placebo in the 10 mg/d group (94.7%, $P=0.03$). Generally, adverse events were mild to moderate in intensity, were transient, and resolved without the need to discontinue study medication. The adverse events most commonly reported were those affecting the digestive system, the musculoskeletal system, and the nervous system (Table 3), and the nonserious adverse events most commonly leading to discontinuation were nausea, diarrhea, agitation, and dizziness. A similar number of patients in each group discontinued treat-

TABLE 2. Efficacy Measure Outcomes in Placebo- and Donepezil-Treated Patients at Week 24 LOCF (Primary End Point) and Week 24 Observed Cases

	Week 24 LOCF			Week 24 Observed Cases		
	Placebo n=199	Donepezil		Placebo n=199	Donepezil	
		5 mg/day n=198	10 mg/day n=206		5 mg/day n=198	10 mg/day n=206
CIBIC-plus category, n (%)						
Marked improvement	2 (1.0)	4 (2.0)	3 (1.5)	2 (1.2)	4 (2.5)	3 (2.0)
Moderate improvement	19 (9.8)	13 (6.6)	15 (7.7)	17 (10.5)	11 (6.9)	14 (9.5)
Minimal improvement	37 (19.1)	53 (27.0)	37 (19.0)	33 (20.4)	46 (28.8)	28 (19.1)
No change	76 (39.2)	82 (41.8)	85 (43.6)	60 (37.0)	65 (40.6)	62 (42.2)
Minimal worsening	43 (22.2)	32 (16.3)	47 (24.1)	35 (21.6)	27 (16.9)	35 (23.8)
Moderate worsening	14 (7.2)	9 (4.6)	8 (4.1)	13 (8.0)	6 (3.8)	5 (3.4)
Marked worsening	3 (1.6)	3 (1.5)	0	2 (1.2)	1 (0.6)	0
Change from baseline score, LS mean $\pm$ SE						
ADAS-cog	0.72 $\pm$ 0.40	-0.96 $\pm$ 0.39†	-1.52 $\pm$ 0.40‡	0.34 $\pm$ 0.40	-1.56 $\pm$ 0.43†	-1.99 $\pm$ 0.45‡
MMSE	0.39 $\pm$ 0.23	1.04 $\pm$ 0.21*	1.49 $\pm$ 0.20‡	0.57 $\pm$ 0.24	1.10 $\pm$ 0.24	1.53 $\pm$ 0.22†
CDR-SB	0.11 $\pm$ 0.12	-0.01 $\pm$ 0.12	-0.25 $\pm$ 0.11*	0.12 $\pm$ 0.13	-0.07 $\pm$ 0.13	-0.36 $\pm$ 0.12†
ADFACS	1.44 $\pm$ 0.42	0.64 $\pm$ 0.36	0.53 $\pm$ 0.38	1.68 $\pm$ 0.46	0.37 $\pm$ 0.38*	0.37 $\pm$ 0.44*
IADL	0.87 $\pm$ 0.32	-0.02 $\pm$ 0.25*	0.13 $\pm$ 0.27	0.99 $\pm$ 0.37	-0.11 $\pm$ 0.28*	0.03 $\pm$ 0.31*

CIBIC-plus (comparison across all categories): $P<0.05$ for overall donepezil treatment (5 and 10 mg/day) vs placebo, and donepezil 5 mg/day vs placebo, at week 24 observed cases.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ vs placebo.

TABLE 3. Adverse Events and Cardiovascular and Cerebrovascular Adverse Events

	Donepezil		
	Placebo n=199	5 mg/day n=198	10 mg/day n=206
≥1 AE, n (%)	176 (88.4)	176 (88.9)	195 (94.7)*
Nausea	14 (7.0)	17 (8.6)	33 (16.0)†
Diarrhea	20 (10.1)	35 (17.7)*	30 (14.6)
Cramps and leg cramps	3 (1.5)	15 (7.6)†	28 (13.6)†
Anorexia	3 (1.5)	11 (5.6)*	17 (8.3)†
Vomiting	6 (3.0)	13 (6.6)	17 (8.3)*
Headache	9 (4.5)	20 (10.1)*	15 (7.3)
Abnormal dreams	4 (2.0)	7 (3.5)	13 (6.3)*
Rhinitis	6 (3.0)	7 (3.5)	14 (6.8)
≥1 cardiovascular AE	36 (18.1)	41 (20.7)	42 (20.4)
Hypertension†	8 (4.0)	10 (5.1)	11 (5.3)
Syncope	3 (1.5)	4 (2.0)	8 (3.9)
Bradycardia	3 (1.5)	7 (3.5)	3 (1.5)
Hypotension	3 (1.5)	1 (0.5)	3 (1.5)
Stroke	6 (3.0)	8 (4.0)	12 (5.8)
TIA	11 (5.5)	9 (4.5)	3 (1.5)*

Adverse events (AEs) are presented if they occurred in >5% of donepezil-treated patients and at least twice the incidence in the placebo group. Cardiovascular and cerebrovascular AEs are presented if they occurred in >2% of patients, with the exception of hypotension, which is additionally included as it is of particular relevance in this patient population.

* $P<0.05$, † $P<0.01$ vs placebo.

‡New onset or worsening.

ment because of stroke (placebo, 4 patients; donepezil 5 mg/d, 4 patients; donepezil 10 mg/d, 6 patients).

Stroke was reported by 6 patients (3.0%) in the placebo group, 8 (4.0%) patients in the donepezil 5 mg/d group, and 12 patients (5.8%) in the 10 mg/d group. Stroke was considered to be unrelated to study medication in all but 2 cases (1 in the donepezil 5 mg/d group and 1 in the 10 mg/d group). Most strokes (placebo, 3 patients; donepezil 5 mg/d, 5 patients; donepezil 10 mg/d, 10 patients) were classified as serious adverse events. Stroke was the most common serious adverse event in the donepezil treatment groups and the second most common serious adverse event (after transient ischemic attack) in the placebo group.

Serious adverse events other than death were reported in 107 patients: 30 (15.1%) in the placebo group, 32 (16.2%) in the donepezil 5 mg/d group, and 45 (21.8%) in the donepezil 10 mg/d group. No apparent treatment effect was associated with the type or incidence of drug-related serious adverse events.

Fifteen patients died during the study or within 4 weeks of discontinuing treatment, of whom 7 (3.5%) were in the placebo group, 2 (1.0%) in the donepezil 5 mg/d group, and 6 (2.9%) in the donepezil 10 mg/d group. Stroke was the cause of death in 3 patients (1 in each treatment group). All deaths were considered by the investigator to be unrelated to

study medication, apart from 1 death (lung carcinoma) in the placebo group.

No clinically meaningful changes from baseline were observed in vital signs, physical examination findings, or ECG status. There were also no clinically meaningful changes from baseline in clinical chemistry, hematology, or urinalysis tests in any of the treatment groups.

Discussion

Donepezil is a beneficial treatment for patients with VaD, defined by NINDS-AIREN criteria, on the basis of this large-scale, international, randomized, double-blind, placebo-controlled clinical trial of donepezil in patients with VaD.

Observations on the ADAS-cog and the MMSE demonstrate that treatment with donepezil 5 or 10 mg/d was significantly more effective than placebo in improving cognition in patients with VaD. Results on the CIBIC-plus, a measure of overall clinical response to treatment, were less conclusive: a significant treatment effect was observed in the donepezil 5 mg/d group but not in the 10 mg/d group. However, treatment with donepezil 10 mg/d was significantly more effective than placebo on other efficacy measures such as the CDR-SB and, importantly, the ADFACS, an assessment of instrumental and basic ADL and a surrogate measure of executive function.²⁰

To determine the efficacy and safety of cholinesterase inhibitors in patients with VaD, it is essential to consider the outcome of treatment in AD and VaD patients separately.²¹ Adherence to the NINDS-AIREN criteria was central to selecting VaD patients and excluding those with AD, and VaD patients enrolled in this and other studies^{13,22–24} differ from patients with AD^{7,8,22} or mixed dementia¹³ with respect to demographics, comorbid conditions, and nature of disease progression. Almost all patients in this study population had a history of clinically evident cerebrovascular or cardiovascular disease, and many had concomitant hypertension, diabetes mellitus, or hypercholesterolemia. Consistent with a diagnosis of VaD, the majority of patients had focal neurological signs, an abrupt onset of dementia, and a history of stepwise cognitive deterioration.²² Placebo-treated VaD patients showed little change from baseline over 24 weeks on both the ADAS-cog and MMSE. CIBIC-plus scores in placebo-treated patients at week 24 were centered on the “no change” category.

Because enrolled patients were required to be stable with respect to comorbid conditions and those with recent or frequent transient ischemic attacks or strokes, major depression, or uncontrolled hypertension or diabetes were excluded, our study population was not typical of all VaD patients. Thus, while longitudinal studies have shown that VaD patients may show rates of cognitive decline similar to those in AD patients over ≥1 year,^{25,26} the populations enrolled in this and other studies^{22–24} represent VaD patients who remain stable for 6 months.

Since the placebo arm did not show decline during this study, it would appear that any progression of underlying vascular disease had little impact on performance. Because vascular disease progression and its (lack of) effect on performance should have been similar among the 3 treatment

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groups, benefits in global function were difficult to assess since the active treatment groups were required to show improvement to demonstrate a positive treatment response. Furthermore, any worsening of comorbid conditions, such as recurrent CVD, or adverse events may have masked beneficial treatment effects in VaD patients, particularly in the 10 mg/d group.

Assessment of drug efficacy in VaD patients is still largely dependent on psychometric tools used in, and in some cases specifically designed for, AD trials. However, in contrast to AD patients, those with VaD tend to show early and prominent executive dysfunction,²⁷ for which specific screening tools/efficacy assessments were not widely used when this trial was initiated. If measures that more directly addressed executive dysfunction had been used, it is possible that larger treatment effects would have been identified. In the absence of such tools, a detailed evaluation of ADL, and IADL in particular, may constitute a surrogate measure of executive dysfunction in patients with VaD because executive function is one of the factors thought to influence the ability to perform IADL.²⁰

Cognitive improvements in donepezil-treated patients, as assessed by the ADAS-cog and MMSE, were accompanied by a beneficial effect in IADL/ADL, as measured by the ADFACS. Since stabilization or improvement in IADL is likely to have a significant impact on patient independence and caregiver burden, the changes observed on these psychometric scales could reasonably be expected to translate into real-world clinical benefits. This is consistent with an AD trial in which donepezil increased the "median time to a clinically evident decline in function" by 5 months, compared with placebo, during a 1-year period.¹⁰ Given the functional stabilization observed in the present study, it seems likely that donepezil may exert a similar effect in VaD patients.

Although benefits of a cholinesterase inhibitor in a heterogeneous group predominantly composed of patients with AD plus CVD have been reported by Erkinjuntti et al,¹³ results from large-scale, placebo-controlled trials of cholinesterase inhibitors in patients with VaD, excluding AD patients, have yet to be published. The overall study results presented here suggest that treatment with donepezil is effective in improving cognition and preventing functional deterioration in patients with mild to moderate possible or probable VaD. Furthermore, although the level of statistical significance on the CIBIC-plus is reduced in this study when controlling for multiple comparisons, beneficial effects were seen in other global measures (such as the CDR-SB) that may be less affected by worsening comorbid conditions or adverse events. Significant results in a second, randomized, double-blind trial of identical design to this study (n=616) have also been reported.²⁸ Combined analyses performed on the overall cohort from these 2 trials extend the findings of this study and reveal significant cognitive benefits in donepezil- versus placebo-treated patients in the subgroups of possible VaD and probable VaD.²⁹

Donepezil was well tolerated by VaD patients in this study, despite the prevalence of comorbid cardiovascular disease and high rates of administered concomitant medications. The adverse events that occurred with greater frequency in

donepezil-treated patients were similar to those seen in earlier AD trials⁷⁻¹⁰ as well as the VaD trial with an identical design to this study²⁸ and were consistent with the cholinomimetic action of donepezil. In most cases, adverse events were transient, were mild to moderate in intensity, and rarely resulted in the need to withdraw study medication. The overall rates of treatment-emergent adverse events in both placebo- and donepezil-treated VaD patients were similar to those in the comparable VaD study.²⁸ The higher incidence of adverse events in VaD versus AD trials^{8,9} is likely the result of the significant comorbid medical conditions in the VaD population. Indeed, many adverse events and almost all serious adverse events reported were associated with underlying medical conditions and were considered to be unrelated to study medication.

These data suggest that donepezil offers a safe and effective means of treating VaD. Given the observation that dementia is a significant independent risk factor for reduced survival after ischemic stroke, possibly because of a greater burden of underlying CVD in stroke patients who develop dementia,³⁰ these findings have important implications for the management of patients with VaD. The dose of 5 mg/d is clinically effective, although 10 mg/d may be better in some patients provided that it is well tolerated. Thus, to achieve maximal efficacy the dose may be increased slowly, with careful monitoring for adverse effects.

In summary, this large-scale, randomized, double-blind, placebo-controlled trial demonstrated that, compared with placebo, treatment with donepezil 5 or 10 mg/d produced significant cognitive and functional benefits in patients with probable and possible VaD. Donepezil was also well tolerated in this population. Despite the limitations of using AD psychometric tools, this study nonetheless provides a good indication of the potential benefits to be gained from the use of donepezil in VaD patients. As this and another large-scale trial with an identical design have shown,²⁸ donepezil is an effective symptomatic treatment for VaD.

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Review

Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists

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Abstract

Circadian rhythm sleep disorders (CRSDs), whether chronic or transient, affect a broad range of individuals, including many elderly, those with severe visual impairments, shift workers, and jet travelers moving rapidly across many time zones. In addition, various forms of insomnia affect another large sector of the population. A feature common among CRSDs and some forms of insomnia is sensitivity to the hormone melatonin, which is secreted by the pineal gland. Accumulating evidence suggests that melatonin may regulate the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although the light–dark cycle is the primary signal that entrains the circadian clock to environmental cycles, exogenous melatonin has been shown to entrain the clock in individuals with no light perception and free-running circadian rhythms. Furthermore, studies have reported beneficial effects of melatonin for treatment of certain insomnias. Together, these studies suggest that melatonin may be useful for treating some insomnias and CRSDs. In these contexts, use of melatonin as a supplement has been popular in the United States. Unfortunately, the therapeutic potential of melatonin has been difficult to realize in clinical trials, possibly owing to non-specific actions of the agent and its unfavorable pharmacokinetic properties when administered orally. In an attempt to take advantage of the therapeutic opportunities available through the brain's melatonin system, researchers have developed several melatonin agonists with improved properties in comparison to melatonin. Some of these agents are now in clinical trials for treatment of insomnia or CRSDs.

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Keywords: Melatonin; Circadian rhythm; Sleep; Suprachiasmatic nucleus; Pineal gland; Insomnia**1. Introduction**

Melatonin, first identified in 1958 [1], is secreted by the pineal gland during the night in a wide range of species. This cycle of melatonin secretion is a robust hormonal signal that can act as a ‘time-giver’ (zeitgeber) to indicate time of environmental darkness [2]. In photoperiodic species such as hamsters and sheep, in which reproductive cycles are dependent on the seasons, seasonal changes in night length are encoded as changes in melatonin secretion. This hormonal signal synchronizes the onset of the reproductive cycle during the appropriate season [3,4].

In non-photoperiodic species such as humans, the circadian rhythm of melatonin secretion is thought to contribute to other functions of the circadian clock, such as consolidation of sleep [5] and regulation of the circadian rhythm of core body temperature [6].

The master clock controlling circadian rhythms is located in the suprachiasmatic nucleus of the hypothalamus [7]. Lesions of the SCN appear to abolish all circadian rhythms in rodents [8,9]. In primates, SCN lesions disrupt many circadian rhythms, but leave some intact, suggesting that other neuronal centers contribute to circadian rhythmicity in primates [10–13]. However, the rhythms that persist after SCN ablation are often less stable or robust, suggesting that the SCN is important for maintaining these rhythms as well. The SCN clock is also regulated by factors outside the SCN, including signals from the retina encoding

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environmental light levels [14] and melatonin secreted from the pineal gland [2,15–21]. Early studies in birds implicated melatonin in the control of circadian rhythms, since removal of endogenous melatonin by pinealectomy could abolish free-running circadian rhythms of sparrows housed in constant darkness [15]. Furthermore, continuous treatment with exogenous melatonin could alter free-running circadian rhythms [16] and pineal transplants could restore rhythmicity in pinealectomized birds [17]. The pineal gland does not play such a central role in the regulation of circadian rhythm in mammals, since pinealectomy does not disrupt mammalian rhythms to any large extent. However, studies in rats demonstrate that exogenous melatonin can also entrain free-running rhythms of mammals [17]. Further support for melatonin as an important regulator of the circadian clock comes from findings that neurons of the SCN express high levels of melatonin receptors, and from observations that treatment of SCN neurons with melatonin can acutely alter neuronal activity [20] and phase-shift the neuronal firing rate *in vitro* [18,21].

In addition to its effects on the circadian clock, melatonin may have sleep-promoting properties. In some studies of human subjects, melatonin has been found to induce sedation, lower core body temperature, and induce other changes associated with sleep [5,6,22–24]. However, in nocturnal animals, melatonin is also secreted during the dark phase of the circadian cycle—the time when these animals are increasing their activity [25]. Thus, melatonin is not a universal sleep-inducing hormone but, rather, acts as a hormonal signal indicating time of darkness [26–28].

In humans, administration of exogenous melatonin in the early evening advances the phase of circadian rhythms; administration in the early morning delays the phase [27]. However, the phase-delaying effects of melatonin are less robust and are not consistently observed [29]. Because of its phase-shifting properties, melatonin has been studied as a potential treatment for circadian rhythm sleep disorders (CRSDs) (e.g. delayed-phase sleep syndrome, advanced-phase sleep syndrome, and free-running rhythms in blind people) [28,30]. In addition, the sedative and mild hypnotic properties of melatonin, and its availability as a ‘natural supplement’, have led to widespread use of the agent for insomnia, especially in the United States. However, both uses are supported by only limited clinical trial data. Furthermore, melatonin has some properties that would be expected to limit its usefulness as an oral agent—properties such as a short half-life, high first-pass metabolism, and binding to multiple melatonin receptors [31–36].

Several analogs of melatonin have been developed in an effort to find better treatments for CRSDs or insomnia. Some of these agents are selective for specific melatonin receptors and have other advantageous properties. Clinical trials of specific agents are underway, although limited data are available to date. After reviewing the neurobiology of the melatonin system and the possible use of melatonin for treating sleep and circadian disorders, we will discuss some

of the results with the most promising melatonin agonists in clinical trials.

2. Neurobiology of the melatonin system

2.1. Melatonin receptors

The older literature on melatonin describes two major classes of receptors: ML_1 (high affinity) and ML_2 (low affinity) receptors. The ML_1 receptor is a member of the large family of receptors with 7 membrane-spanning domains—a family that includes the serotonin and β -adrenergic receptors. In contrast, the ML_2 receptor is a distinct molecular species.

ML_1 receptors are of clear importance to the nervous system. Molecular cloning revealed that there are at least 3 subtypes of ML_1 receptors: Mel_{1a} , Mel_{1b} , and Mel_{1c} [32]. To date, Mel_{1c} receptors have not been found in mammals. Of particular interest to our discussion are the Mel_{1a} and Mel_{1b} receptors, which are now referred to as the MT_1 and MT_2 receptors, respectively. These receptors are classic G-protein-linked receptors that inhibit adenylate cyclase. Additionally, MT_1 receptors activate protein kinase C- β , whereas MT_2 receptors inhibit the soluble guanylate cyclase pathway [37] while stimulating protein kinase C [21,38]. MT_1 receptors have the most widespread distribution in the rodent brain, account for the majority of melatonin-binding sites in most target tissues, and are widely believed to account for many melatonin actions in the brain [20]. Both MT_1 and MT_2 subtypes of the ML_1 receptor appear to have roles in regulating the SCN circadian clock (see later) [38].

The ML_2 (also named MT_3) receptor was poorly characterized and enigmatic until a recent study identified it as a form of quinone reductase [39]. This enzyme is widely distributed in different tissues and across different species [40]. The importance of melatonin-binding to this enzyme is unclear. Specific melatonin agonists are becoming available, which lack binding to the MT_3 /quinone reductase receptor [36,41,42]; these agents will help to isolate the specific effects mediated by the high-affinity melatonin receptors, and may become important options for pharmacologic treatment of insomnia or CRSDs without the potential for side effects from interactions with the MT_3 /quinone reductase binding site (see Section 4).

2.2. Control of melatonin release

As with most other circadian rhythms, the circadian pattern of melatonin release is controlled by the SCN. The primary source of melatonin is the pineal gland, which secretes the hormone into the cerebrospinal fluid and circulation. Some melatonin is also generated in the retina, but this source is thought not to contribute to circulating levels [43]. The SCN controls pineal melatonin release through a multi-synaptic pathway, the final link of which is

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a noradrenergic synapse from the superior cervical ganglion to the pineal gland [44]. The projections from the superior cervical ganglion release norepinephrine onto pinealocytes during the night. Norepinephrine, acting mostly through β_1 adrenergic receptors, increases intracellular cAMP levels in the pinealocytes leading to an increase in synthesis of melatonin [45,46]. Indeed, it has been shown that the final enzyme in the synthetic pathway for melatonin (*N*-acetyltransferase) is expressed in pinealocytes in a circadian fashion; that rhythm is abolished by lesions of the SCN [47].

Several neurotransmitters—and drugs that interact with neurotransmitter systems—modify melatonin synthesis in the pineal gland; such agents include α_2 -adrenoceptor agonists [48], β -adrenoceptor antagonists [49], and benzodiazepines acting through GABA receptors [50]. Nocturnal exposure to bright light immediately and acutely suppresses melatonin secretion via degradation of pineal *N*-acetyltransferase [52,53]. The signal by which light mediates this regulation is transmitted from the retina through the SCN to the pineal.

In the absence of environmental signals such as light input from the retina, the SCN maintains a circadian rhythm with a period either slightly shorter or longer than 24 h (i.e. about a day or 'circa diem'). Under such conditions, the organism is said to be free-running, and the rest-activity/sleep–wake cycles will gradually become out of phase with the 24-h day/night cycle. When the organism is exposed to normal daylight cycles, the circadian rhythm is entrained to the 24-h cycle of the sun. Such entrainment is mediated, in large part, by light signals received by the retina and relayed to the SCN through the retino-hypothalamic tract [7]. This pathway is activated by melanopsin-containing photoreceptors in the ganglion cell layer of the retina [53,54]. Unlike the visual pathways of the eye and brain, which are concerned with image formation and processing, the retino-hypothalamic pathway is dedicated to transmitting information about the presence and intensity of light.

Nocturnal exposure to light has been shown to affect the expression of specific genes in the SCN known as clock genes, such as period (*per*) [55,56]. The level of *per* expression within cells of the SCN determines the phase of the circadian clock. Thus, exposure to bright light in the evening causes a phase delay in the circadian clock, whereas similar exposure in the late night causes a phase advance [56]. Because the SCN clock controls pineal melatonin release, such phase shifts will be manifest as changes in the timing of melatonin secretion. Indeed, the level of circulating melatonin is one of the most reliable measures of the phase of the circadian clock in humans [2,30].

2.3. Effects of melatonin on the circadian clock

As mentioned earlier, melatonin receptors are expressed in specific nuclei in the brain, including the SCN. Interestingly, while the SCN clearly controls the timing of the melatonin rhythm, melatonin exerts reciprocal effects on

the SCN. For example, in rats maintained in constant darkness, exogenous melatonin entrained the activity cycle [17]. The direct effects of melatonin on the SCN have been examined using an isolated brain slice preparation, in which the circadian clock continues to cycle for several days [18]. In this preparation, application of melatonin at times corresponding to dusk or dawn caused phase shifts in the circadian rhythm of electrical activity recorded from SCN neurons. Melatonin applied at other times had little or no effect on the SCN clock [21].

Later studies extended this work and described two distinct effects of melatonin on SCN neurons: acute inhibition of electrical activity and phase-shifting of the clock [20]. Transgenic mice with disrupted MT_1 receptors were used to study the role of MT_1 versus MT_2 receptors in these effects. In SCN neurons from mice lacking MT_1 receptors, melatonin failed to acutely inhibit electrical activity as it does in normal mice, but the phase-shifting effects of melatonin were largely intact. Other experiments, using pharmacological or transgenic approaches, further support the importance of MT_2 receptors in the phase-shifting effects of melatonin on the SCN clock [37,38, 57,58]. For example, transgenic mice with a disruption in the MT_2 gene exhibited no evidence that the circadian clock was sensitive to melatonin, although melatonin still elicited acute inhibition of SCN neurons [57].

The receptor specificity for phase-shifting and acute inhibitory effects of melatonin may vary across species. For example, a species of hamster that naturally lacks MT_2 receptors still exhibits circadian rhythms, and the rhythm phase-advances in response to exogenous melatonin [59]. In general, however, the results from various animal studies suggest that the MT_1 and MT_2 receptors have distinct functional roles in the SCN, albeit with some overlapping function. These distinct roles provide great potential for receptor-specific pharmacological agents to affect specific aspects of the sleep–wake cycle and/or circadian rhythmicity.

The distinct functional roles of MT_1 and MT_2 receptors may provide the opportunity to develop specific agents that promote sleep without phase-shifting the circadian clock, or the converse. Ligands that are highly selective for one subtype (MT_1 or MT_2) of receptor have become available in recent years, but are still the subject of structure–activity studies [41,58,60–63]. Progress in the development of such compounds will lead to a much greater understanding of the distinctive roles of the melatonin receptor subtypes. Furthermore, such compounds hold promise as potentially useful for treating sleep disorders or CRSDs. At this time, these agents require further study in experimental systems before their efficacy in humans can be assessed.

2.4. Circadian cycle of melatonin sensitivity

Melatonin receptors in the SCN are not expressed at constant levels. Several studies in different mammalian

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species have reported that receptor protein and mRNA levels in the SCN vary on a circadian basis, and that expression levels are influenced by light and melatonin [64–68]. In general, levels of MT₁ receptors are low during the subjective day and highest during the subjective night, when melatonin secretion is also peaking. The implications of these findings for pharmacological use of melatonin are not clear. For example, exogenous melatonin is known to promote sedation in humans when administered during the day [69,70], at a time when SCN melatonin receptor levels are expected to be low. If the sedative properties of exogenous melatonin are mediated by the SCN, these findings suggest that exogenous melatonin is able to activate the small number of receptors present in the SCN during the day. Alternatively, the sedative effects of melatonin may be mediated by other brain centers regulating sleep, or perhaps even sites in the peripheral circulation involved in regulation of core body temperature [5,24,71,72].

3. Melatonin for insomnia and circadian rhythm sleep disorders

3.1. Sleep in healthy subjects

In humans, as in other animals, circulating levels of melatonin are highest during the night [73]. Furthermore, electrophysiological studies have found that the timing of highest urinary excretion of 6-sulfatoxymelatonin (a reliable indicator of melatonin levels in the general circulation) is correlated with the greatest increase in nocturnal sleepiness [72]. Such studies have engendered great interest in the potential for use of exogenous melatonin as a sleep-promoting agent.

Melatonin is not required for sleep in humans. For example, patients who have had their pineal gland removed for medical reasons often experience little disturbance in their sleep–wake cycle [2]. Nevertheless, several studies have examined the ability of exogenous melatonin to promote sleep in humans, often with conflicting results [28,74–80]. Here we focus on the mechanisms that may underlie the differential effects of melatonin on the sleep–wake cycle.

In healthy human subjects, administration of 0.3 or 1 mg of melatonin in the early evening was associated with reduced sleep latency and improved sleep efficiency [23,81]. Another study, which used EEG to monitor sleep parameters, found no effect of 5 mg melatonin on normal sleep [82]. Overall, melatonin has had variable efficacy when studied as a hypnotic agent [75]. There are several possible explanations for this variability.

One possible explanation is that the sedative or hypnotic effects of melatonin are dependent on the time of day, or the phase of the circadian rhythm. For example, the hypnotic effects of melatonin in humans vary depending on the time of administration [70], consistent with the circadian

phase-resetting properties of melatonin, which also depend on time of administration [17,18,21,27]. A recent, well-controlled study in healthy human volunteers compared the effects of melatonin on nocturnal sleep (melatonin administered at 23:30 h) with its effects on evening sleep (melatonin administered at 18:00 h) [22]. The two times of administration were examined in separate, double-blind, placebo-controlled studies that also involved administration of temazepam as a positive control using a crossover design. Patients were monitored by EEG, measurement of core body temperature, and testing of cognitive performance after awakening. Melatonin administered at night (23:30) had no significant effect on nighttime sleep in healthy individuals. In contrast, melatonin administered in the early evening (18:00) had hypnotic activity similar to temazepam.

Other studies have concluded that ‘physiologic’ doses of melatonin have little or no effect on nighttime sleep in healthy individuals, but that high ‘pharmacologic’ doses can have hypnotic activity [24]. It is widely believed that the lack of effect of exogenous melatonin on nighttime sleep is a result of high levels of endogenous melatonin–melatonin receptors in the SCN may already be exposed to saturating concentrations of the endogenous hormone. This hypothesis has not been thoroughly tested. Furthermore, so-called ‘physiologic’ concentrations are often based on levels found in the general circulation. However, studies in sheep have suggested that melatonin levels in the cerebrospinal fluid (CSF) from the third ventricle may be as much as 20-fold higher than levels in the general circulation [83]. Thus, when administering melatonin by the oral route, high doses may be needed to influence the levels of melatonin perfusing the relevant brain structures, such as the SCN. Alternatively, a lower dose of a melatonin receptor agonist with improved solubility, bioavailability, or transport properties may be able to act on brain melatonin receptors to influence sleep propensity at nighttime, even in healthy individuals with normal levels of endogenous melatonin.

Another difficulty associated with pharmacologic use of exogenous melatonin is that serum levels vary widely among individuals [31]. Such variability can have a detrimental effect on clinical trials, introducing variability that obscures potential efficacy. Improved agents with better absorption and lower first-pass metabolism are likely to improve the consistency of clinical trials and may prove more efficacious than melatonin itself.

An ideal hypnotic agent will increase total sleep time and sleep efficiency, in addition to reducing sleep latency. While some studies have reported that exogenous melatonin improves sleep efficiency, this effect is not consistently observed [75]. The lack of effect on sleep efficiency or total sleep time may not be surprising given the short half-life of melatonin in the circulation (less than 1 h) [31]. An agent with a longer half-life may have a better opportunity to activate brain melatonin receptors and influence sleep properties long enough to improve sleep efficiency and total sleep time. Indeed, accumulating evidence supports

the concept that melatonin participates in the consolidation of sleep into prolonged nighttime episodes [5]. And, it has been suggested that a continuous delivery system for melatonin may be beneficial for some patients with impaired sleep efficiency or sleep consolidation [5]. A longer-acting melatonin receptor agonist may be a viable alternative.

It has also been suggested that methodological differences in monitoring the sleep–wake cycle may underlie some of the conflicting data regarding the effects of melatonin on sleep. While the gold standard for monitoring sleep is the use of EEG/EMG recordings to monitor brain state and sleep stages, the use of actigraphy for monitoring movement to define sleep–wake activity is often used as an easy and reliable substitute. It has been hypothesized that melatonin may act as a muscle relaxant, reducing body movements, thereby leading to more sleep as defined by actigraphy measurements [84]. Indeed, this proposed effect of melatonin may underlie its soporific effects.

3.2. *Sleep in subjects with insomnia*

Several studies have examined the use of melatonin for elderly or medically ill patients with insomnia [85–89]. Melatonin levels decline as an individual ages [90–93], and it has been suggested that sleep disruption in the elderly is related to declining melatonin levels. Others have argued, however, that much of the decline in melatonin secretion occurs during adolescence [94] and that there is little additional decline during adulthood in healthy individuals [95]. However, some brain degenerative diseases, particularly Alzheimer's disease, are associated with markedly low levels of melatonin [96–98]. Many of these patients experience insomnia or other disturbances associated with the sleep–wake cycle, such as 'sundowning' syndrome [74,99,100]. Several small studies have shown beneficial effects associated with use of melatonin in such patients [101–104].

Insomnia is a common complaint in elderly populations; the most common therapies prescribed for these patients are benzodiazepines or benzodiazepine agonists. Long-term use of benzodiazepines is not recommended because of concerns about the potential for dependence or abuse. Unfortunately, many elderly patients experience difficulty discontinuing benzodiazepine hypnotics. Melatonin has been studied as an agent to help reduce or eliminate the use of benzodiazepines among these patients [105]. This study found that elderly patients with insomnia who received controlled-release melatonin were significantly more likely to successfully discontinue benzodiazepines in comparison to those receiving placebo.

3.3. *Circadian rhythm sleep disorders*

Melatonin has also been proposed and studied as a treatment for CRSDs, or for treatment of conditions

associated with misalignment of activity rhythms with the light–dark cycle, such as shift work and jet lag. The rationale for these studies comes from observations that exogenous melatonin can entrain or phase-shift circadian rhythms under appropriate circumstances [29,30,106–110]. However, because circadian rhythms can also be entrained by light and other environmental signals, the effects of melatonin can be obscured. The phase-shifting effects of melatonin can be observed only at certain phases of the circadian cycle, nearly 12 h out of phase from the phase-shifting effects of light [111]. Light also affects endogenous melatonin secretion [51], as does posture [106]. All these influences on the circadian cycle, and on melatonin secretion, have made it difficult to fully understand melatonin's ability to phase-shift human circadian rhythms.

Perhaps the clearest examples of the effects of melatonin on circadian rhythmicity have come from studies of exogenous melatonin administered to blind individuals, especially those with no perception of light. Such individuals often experience free-running rhythms of endogenous melatonin secretion, and concomitant sleep disturbances because their activity rhythms are at times out of phase with social cues for sleeping and wakefulness [112–115]. In many instances, exogenous melatonin is able to stably entrain the sleep–wake cycle of these individuals to a 24-h cycle [113,116–118].

Several studies have also examined the use of melatonin for shift workers or for jet lag [119–121]. In two placebo-controlled studies simulating shift work, subjects receiving melatonin exhibited significantly better adaptation to a phase shift in the light–dark cycle as compared to those receiving placebo [122,123]. Such adaptation included modest improvements in ability to sleep during the day [123] and shifts in circadian rhythms of endogenous melatonin and core body temperature [122]. A systematic review of melatonin for jet lag has concluded that melatonin may be useful for minimizing effects of the phase shift imposed by flights across many time zones [124].

As with treatment of insomnia, a melatonin receptor agonist with enhanced pharmacological properties may be more effective than exogenous melatonin for phase-shifting human circadian rhythms, and may lead to more reliable results from clinical trials. As discussed earlier, a melatonin receptor agonist with a longer half-life may be more suitable for promoting sleep. However, for inducing phase shifts or for maintaining circadian phase, the situation is more complex. Indeed, there is evidence that a short-acting agonist may be more effective for inducing phase shifts. For example, multiple doses of melatonin are often less effective for inducing phase shifts in comparison to a single dose administered early in the subjective night [29,125,126]. These results are likely a consequence of the phase-response curve for the phase-shifting effects of melatonin. Long-acting melatonin, or a long-acting agonist, may be active during both phase-advance and phase-delay portions of the phase-response curve, thereby canceling or weakening any

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phase-shifting effects. These issues will need to be resolved before melatonin agonists become useful and reliable for inducing circadian phase shifts.

4. Melatonin receptor agonists

In mechanistic and preclinical studies, melatonin has shown much potential for treatment of sleep disturbances and CRSDs. Unfortunately, that potential has been difficult to realize in clinical studies, owing to some of the physical, biological, and pharmacokinetic properties of melatonin we have discussed, as well as the relative lack of large-scale clinical trials partially owing to the fact that melatonin cannot be patented. In an effort to take advantage of the biological actions of melatonin for treatment of sleep disturbances in humans, several groups have developed melatonin analogs that act as agonists or antagonists at melatonin receptors. In general, the melatonin receptor agonists have so far shown the greatest potential for clinical usefulness. Here we discuss three of the more prominent examples of melatonin receptor agonists that are furthest along in clinical development.

4.1. Agomelatine (S20098); developed by Servier

Agomelatine is a naphthalenic analog of melatonin that is a high-affinity agonist at MT₁ and MT₂ receptors [42]. In terms of published studies in animal models, it is the most thoroughly characterized melatonin receptor agonist to date. However, agomelatine is an antagonist at 5-HT_{2C} and 5-HT_{2B} receptors [127]. This action has been shown to be associated with changes in dopaminergic and adrenergic pathways in the frontal cortex of rats [127]. Owing to its unique pharmacologic profile, agomelatine is being developed for treatment of anxiety disorders and depression [128,129]. In addition, experiments performed with this agent have provided valuable information about the actions of melatonin receptor agonists.

Agomelatine has effects on electrical activity of SCN neurons that are similar to those of melatonin [130]. In addition, in a manner that mimics the effects of melatonin, agomelatine is able to facilitate re-entrainment of circadian rhythms in response to a phase shift in the light–dark cycle [131–133]. Importantly for its implications to human studies, this effect of agomelatine has been observed in diurnal species [132]. In addition, like melatonin, agomelatine is able to entrain the free-running circadian rhythms of rats maintained in constant darkness; this effect is abolished by lesions of the SCN but not by pinealectomy [134]. Overall, experiments with agomelatine establish that a selective melatonin receptor agonist can mimic the regulatory effects of melatonin on circadian rhythms.

In most cases, the effects of agomelatine on sleep and circadian rhythms have been attributed to its agonist activity at melatonin receptors. Nevertheless, agomelatine has other

effects in the CNS attributable to antagonism at 5-HT receptors. The agent is currently in phase I clinical trials for treatment of anxiety disorders and depression.

4.2. Ramelteon (TAK-375); developed by Takeda

Ramelteon is an indenofuran derivative that has high selectivity and high affinity for MT₁ and MT₂ receptors [135,136]. It has a longer half-life than melatonin in humans [137], and thus may have superior properties as a sleep-promoting agent. Unlike agomelatine, ramelteon exhibited no binding to any of a large number of receptors or potential binding sites in receptor-binding studies [138]. Although a metabolite of ramelteon did exhibit some binding to 5-HT_{2B} receptors, this interaction occurred with such low affinity that it is unlikely to influence pharmacologic use of this agent.

Ramelteon has been studied in animal models of insomnia as well as CRSDs. The agent promotes sleep in freely moving monkeys [135] and cats [36]. In addition, like agomelatine and melatonin, it is able to enhance the rate of re-entrainment in response to a shift in the light/dark cycle in rats [139]. The effects of ramelteon are associated with very little impairment of cognitive or motor performance, and there is no evidence that the drug has rewarding properties that could lead to dependence [139].

In early-stage clinical studies, ramelteon has shown promise in patients exposed to the first-night effect model of transient insomnia and in patients with chronic insomnia [140,141]. It is currently in phase III studies for insomnia and circadian rhythm sleep disorders.

4.3. LY 156735; developed by Eli Lilly

LY 156735 is a β -substituted analog of melatonin that was developed to have a higher potency than the parent compound [142]. In addition, LY 156735 is reported to have a better pharmacokinetic profile in comparison to melatonin. For example, when administered orally LY 156735 is reported to have a bioavailability that is nearly an order of magnitude higher than melatonin, and an area under the curve that was about 6-fold higher than melatonin [143].

In early-stage clinical studies, LY 156735 reduced sleep onset time in patients with moderate sleep-onset insomnia [144]. Interestingly, the agent had little effect on sleep latency in healthy volunteers when administered at bedtime [145]. In contrast to melatonin, it did not lower core body temperature when administered during daytime [145]. LY 156735 was administered to healthy volunteers in a study of its ability to improve adaptation to a phase-advance in the light–dark cycle [143]. Subjects were housed in a temporal isolation unit and exposed to a phase-advance of 9 h. One of two doses of LY 156735 (5 or 0.5 mg) or placebo was administered at times just preceding lights-out of the post-phase-advance schedule. Subjects adapted to the phase shift significantly faster when receiving the high dose of

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the study drug as compared to the low dose or placebo [143]. LY 156735 is still in early stages of clinical development.

5. Conclusion

The melatonin system has a well-established role in regulating the circadian clock and the rhythms the clock controls. In pre-clinical studies, melatonin has shown great promise for treatment of insomnia or CRSDs. However, the physicochemical and pharmacokinetic properties of melatonin have slowed realization of that potential. The development of selective melatonin agonists with improved properties has enhanced the prospects of manipulating the melatonin system to treat patients with a range of sleep disorders.

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Tacrine Therapy is Associated with Reduced Mortality in Nursing Home Residents with Dementia

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OBJECTIVES: To investigate the extent to which treatment with tacrine is associated with a reduction in mortality in nursing home residents with dementia.

DESIGN: We performed a retrospective cohort study using the Systematic Assessment and Geriatric drug use via Epidemiology database, which contains data collected with the Minimum Data Set on a cross-section of over 400,000 nursing home residents in five U.S. states.

SETTING: Retrospective data analysis of residents in nursing homes.

PARTICIPANTS: We identified 1,449 users of tacrine and 6,119 nonusers matched on facility, date of tacrine use, level of cognitive function, and dementia diagnosis.

MEASUREMENTS: Comparisons of the two groups were made for sociodemographic variables, dementia severity, number of medications, and major comorbid illness (heart disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease, malnutrition), and survival over the 3-year study period.

RESULTS: Based on Cox proportional hazards models, tacrine users showed a significantly lower mortality rate than nonusers. The hazard rate ratio was 0.76 (95% CI = 0.70–0.83). After adjusting for the confounding variables of sociodemographic factors, level of function in activities of daily living, cognitive function, number of drugs, and comorbid illnesses, this survival advantage was still significant at 0.85 (95% CI = 0.77–0.93).

CONCLUSION: Treatment of nursing home residents with tacrine is associated with lower mortality. This observation has implications for the socioeconomic impact of cholinesterase inhibitor therapy in those with advanced dementia and for quality of life issues in the nursing home that deserve future investigation. *J Am Geriatr Soc* 50:35–40, 2002.

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Key words: cognitive disorders; dementia; epidemiology

Four cholinesterase inhibitors that appear to be modestly effective for the reduction of cognitive impairments arising from mild to moderate Alzheimer's disease (AD) are now available for prescription use. The first cholinesterase inhibitor approved for usage in 1993 was tacrine, followed by donepezil in 1997, rivastigmine in 2000, and galantamine in 2001. Although approval of cholinesterase inhibitors has hinged on the demonstration of 3- to 6-month efficacy on psychometric measures of cognition and clinical global measures of function, it is only recently that information has begun to accumulate suggesting that such medications may help to preserve daily living function^{1–7} and reduce behavioral problems,^{3,7–11} providing sustained benefit over periods of 2 years or longer.¹²

In a retrospective analysis of subjects who participated in one of the pivotal trials of tacrine and who were followed for at least 2 years in open-label treatment, high doses (>80 mg/day) were associated with a reduced likelihood of nursing home placement, compared with those on lower doses.¹³ This observation was postulated to be secondary to the drug's beneficial effects¹⁴ rather than to other confounding variables. Furthermore, there was a trend toward lower mortality among those who received more than 120 mg/day. The number of nursing home placements in this study was small, though, and it is possible that tacrine users were healthier than nonusers.¹⁵ Another study demonstrated a delay in nursing home placement for AD subjects in clinical trials regardless of the pharmacological agent.¹⁶

These preliminary data have led to speculations that treatment of outpatients with AD with cholinesterase inhibitors may translate to economic savings through delayed institutionalization. Subsequent cost-effectiveness analyses have postulated a delay in nursing home placement as a key feature of cost saving with cholinesterase inhibitor therapy, without considering whether there may be prolonged longevity in institutionalized treated patients. For example Henke et al.¹⁷ reported a cost savings of \$36,500 over 5 years for patients who continued high-dose tacrine

up to, but not after nursing home placement. They assumed that there was no extension of life with tacrine use and that usage terminated once patients entered a nursing home. Similar assumptions have been made by studies of cost-effectiveness for donepezil treatment,^{18,19} but Wimo et al.²⁰ demonstrated that postponement of nursing home placement with tacrine would result in a net cost savings of 4.6% that would be essentially negated if treatment increased survival by 1 year (thereby resulting in a net cost savings of 0.1%).

Although usage of tacrine in the nursing home has been reported to be as low as 0.5%,²¹ it is likely that newer agents with fewer side effects will be more widely prescribed in the community and continued to be used after nursing home placement. In other patients, tacrine may be started in the nursing home in the hopes of alleviating behavioral problems or improving activities of daily living (ADLs).²² Therefore, further data are needed to assess the effect of cholinesterase inhibitors on long-term outcomes in the nursing home.

To investigate whether treatment with tacrine is associated with a reduction in mortality in nursing home residents with dementia, we performed a retrospective cohort study of a large number of tacrine-treated patients using the Systematic Assessment and Geriatric drug use via Epidemiology (SAGE) database, a multisource cross-linked long-term-care database that contains data collected with the Minimum Data Set (MDS) on a cross-section of over 400,000 nursing home residents in five U.S. states.^{23,24}

We conducted a retrospective matched cohort design using the SAGE database. The SAGE database combines data collected during the Health Care Financing Administration's (HCFA) Multi-State, Case-Mix and Quality Demonstration Project. Data were collected on the federally mandated Resident Assessment Instrument (RAI), which includes the 300-item MDS.²⁵

METHODS

All Medicare/Medicaid-certified nursing homes ($n = 1,492$) in five U.S. states (Kansas, Maine, Mississippi, New York, South Dakota) collected MDS data on over 400,000 residents living in long-term care from 1992 through 1996. Detailed information regarding the specific time characteristics of the database is found elsewhere.^{23,26,27} We provide a brief summary of the SAGE database below.

SAGE Database

Information such as sociodemographic data, numerous clinical items including all active clinical diagnoses, and variables describing the degree of physical dependence and cognitive functioning is included in the MDS.^{23,25} An extensive list of symptoms, signs, syndromes, treatments, and indicators describing each resident's behavior and mood is also included in the MDS.^{23,25} Trained clinical professionals (e.g., nurses, social workers, therapists) are called on to assess resident performance over all shifts during the prior 7-day period. Each item has its own explicit definition. Cues are provided for how to ask questions, what to observe, and who to contact for information. Each assessor is directed to interact directly with the resident, review the record, and gather information on resi-

dent performance from direct care and licensed professional staff.²⁸

Summary scales to describe performance on ADLs, cognition, mood status, behavioral problems, social engagement, communication, mobility, and urinary continence are embedded in the MDS.^{28,29} The ADL score, a five-item, six-level score, measures performance in physical function. This scale is based on resident's dependency in dressing, eating, toileting, bathing, locomotion, transferring, and incontinence.²⁹ We classified residents as mildly impaired (ADL score 0–1), moderately impaired (ADL score 2–3), or severely impaired (ADL score 4–5).

To measure level of cognitive impairment, we used a seven-level scale whose reliability and validity have been demonstrated in comparison with other research instruments, including the Mini-Mental State Examination and clinical criteria.^{28,30,31} Seven separate direct measures of cognitive performance were included in the MDS: short- and long-term memory, orientation items (recall of season, location of room, identity of staff, and that the resident is in a nursing home), and a single item assessing the ability of the resident to make decisions about activities that are a daily part of life. The MDS also includes a number of indirect measures of cognition: an item indicating comatose status, two measures of communication skills, and eight measures of ADLs. Based on these items, we categorized residents as having minimal impairment (cognitive performance scale (CPS) score 0–1), moderate cognitive impairment (CPS score 2–3), or severe cognitive impairment (CPS score 4–6).

Nursing home staff also recorded as many as 18 different drugs received by each resident in the 7 days preceding the assessment. Information on the resident's drug therapy included brand/generic name, dosage, route and frequency of administration, and whether the order was standing or prn.²³ We translated the drugs initially coded using National Drug Codes into therapeutic classes and subclasses using the Master Drug Database (MediSpan™ Inc., Indianapolis).^{23,26} We considered antipsychotics, hypnotics (antihistamines, benzodiazepines, barbiturates), and anxiolytics (benzodiazepines, nonbenzodiazepines) as other pharmacological treatments of dementia behavior problems. For tacrine users, we estimated the maximum daily dose achieved by taking the largest value when multiplying the dosage of tacrine by the times per day received for each available MDS assessment. Drug use on the MDS is captured in an intermittent fashion. As such, we were only able to estimate duration of use by evaluating the presence of tacrine use on each available MDS assessment and determining the differences in dates from the start of tacrine use and the date of the last MDS assessment with tacrine noted.

Study Population

From an initial population of over 400,000 residents in nursing homes between 1992 and 1996 in Maine, Mississippi, South Dakota, and New York who were aged 65 and older, we identified 1,449 people who had received tacrine. We did not include residents from Kansas because, at the time of the study, our match rates to HCFA's eligibility files for these residents were low. In the current study, 944 of the tacrine users initiated therapy before entering the nursing home.

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We identified up to five residents who lived in the same facility as tacrine users but were not receiving tacrine (and did not have any documentation of tacrine use in our database), matched on index date $\pm$ 3 months, cognitive impairment defined by CPS, and dementia diagnosis. When more than five matched nonusers were available, we randomly selected five. The methodology for the selection of these nursing home residents has been previously described in a cross-sectional analysis of tacrine users from the SAGE database.²¹ In the present study, we further restricted the matching to include a facility identifier. We did not include the 66 residents with whom we could not match any eligible nonusers.

We defined AD based on section K of the MDS, which is the listing of active clinical diagnoses, at their initial MDS assessment. The AD diagnosis is based on the physician's judgment using information obtained from the medical record, including physical examination of the patient, medication and other treatment orders, and hospital discharge documentation.^{29,31} In general, although the MDS diagnoses have excellent reliability and have been used in previous studies employing SAGE data,^{26,32,33} the specific diagnosis of AD is likely underdocumented in this data set. In addition to cases classified as "dementia not of the Alzheimer type" many are classified as "dementia with etiology unspecified." Because of the potential for diagnostic misclassification, we matched each tacrine user to nonusers on the basis of CPS and the MDS dementia diagnosis to enhance comparability between the tacrine user and nonuser groups.

Although tacrine is approved specifically for probable AD, we included such patients with other or nonspecified dementia diagnoses, because the majority of patients with possible AD are found at post mortem to have had AD.³⁴

Furthermore, evidence is accumulating that dementia with Parkinson's disease and dementia with Lewy bodies also have a cholinergic deficit that may be amenable to tacrine treatment. People with vascular dementia are often found to also have AD and therefore respond to treatment.

Analysis

We compared distributions of sociodemographic factors (those not used in the matching process), functional characteristics, and medication use in tacrine users and nonusers. Survival intervals were calculated from the date of the index MDS assessment to the date of death. The index MDS assessment was defined as the first assessment indicating tacrine use. We determined information on death by linking residents with the Medicare enrollment files via the Health Claim Number present in the MDS form. We examined all events occurring within 3 years of follow-up or until March 1997 (the last date for which we had information regarding deaths). For those residents still alive at final follow-up, survival intervals were censored at that time.

To evaluate survival differences by tacrine use, we created a Cox proportional hazards model and derived adjusted survival curves for users and nonusers from the model. We also used a Cox proportional hazards model to estimate the hazard rate ratios, adjusting for potential confounders. We considered age, gender, race, dementia severity (ADL and CPS), number of medications, and major comorbid illnesses (heart disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease, malnutrition) as potential confounders. These factors include those that have been previously shown to affect mortality in nursing home residents with AD.³⁵⁻³⁹

Nutritional status was determined by calculating body mass index based on the resident's body weight and height

Table 1. Sociodemographic Characteristics of Tacrine Users and Matched Controls

Characteristic	Tacrine Users (N = 1,449)	Tacrine Nonusers (N = 6,119)
Age, mean $\pm$ standard deviation (SD)	82 $\pm$ 7.2	84 $\pm$ 7.6
65-74, %	14	11
75-84, %	48	37
$\geq$ 85, %	38	52
Female, %	69	75
Ethnicity, %		
Non-Hispanic white, %	90	89
African American, %	8	9
Other, %	2	2
Number of anti-dementia medications, mean $\pm$ SD	7.3 $\pm$ 4.4	6.9 $\pm$ 4.5
Antipsychotic, %	25	19
Anxiolytic, %	18	13
Antidepressant, %	15	11
Comorbid disease		
Coronary artery disease, %	21	23
Arrhythmia, %	9	12
Heart failure, %	16	22
Malnutrition, %*	31	38
Cancer, %	5	7
Diabetes mellitus, %	16	17
Chronic obstructive pulmonary disease, %	11	12

*Body mass index < 21 kg/m². Missing data for height and/or weight on 390 tacrine users and 3,414 nonusers.

Table 2. Dementia Features and Tacrine Treatment

Characteristic	Tacrine Users	Tacrine Nonusers
	%	
Dementia diagnosis*		
Alzheimer's disease	35	32
Non-Alzheimer's disease dementia	34	38
Dementia with unspecified diagnosis	30	30
Dementia severity (CPS)*		
Mild	21	20
Moderate	44	44
Severe	35	36
ADL impairment		
Mild	17	14
Moderate	47	38
Severe	36	48
Maximum tacrine dose†		
≤40	68.2	—
60–80	22.3	—
>80	9.5	—
Duration of tacrine use		
<6 months	75.4	—
≥6 months <12 months	12.5	—
≥12 months <18 months	5.4	—
≥18 months <24 months	4.2	—
>24 months	2.5	—

*Marching variables.

†For the 1,341 tacrine users with valid information regarding the tacrine drug regimen.

ADL = activities of daily living; CPS = cognitive performance scale.

when collected as part of the assessment. This measure has shown extremely good validity when compared with anthropometric variables.⁴⁰ We considered residents with a body mass index (BMI) of less than 21 kg/m² to be malnourished. The extent of missing data was nontrivial for BMI. As a result, we created a dummy variable for the missing BMI category for inclusion in the multivariable models. To evaluate (and exclude) departures from the proportionality assumption for each model, we estimated the log-log survival function. From the final models, we derived rate ratios and corresponding 95% confidence intervals. All analyses were performed using SAS version 8.1 (SAS Inc., Cary, NC).

RESULTS

Demographic and clinical features of the two treatment groups are presented in Table 1. Tacrine users were more likely to be male and to receive antipsychotics or anxiolytics and less likely to have heart failure or to be malnourished as indicated by BMI. Comorbid illness was otherwise comparable between users and nonusers of tacrine.

Dementia characteristics of the two treatment groups are presented in Table 2. ADL impairment was less severe in tacrine users at baseline, despite comparable severity of cognitive impairment. Severe ADL impairment was seen in 12% fewer tacrine users.

Based upon dose classifications established in two prior pivotal drug trials of tacrine,^{1,41} we defined "subther-

apeutic" doses of tacrine as ≤40 mg/day and "high" doses of tacrine as >80 mg/day. Sixty-eight percent of users were identified as receiving subtherapeutic doses. Ten percent of users were receiving high doses of tacrine. Twenty-five percent of users received the drug for at least 6 months.

At the end of 36 months, the predicted survival rate of high-dose tacrine users was 53.1%, which is equivalent to the survival rate at 30 months among nonusers. The 3-year predicted survival rate for nonusers was 47.3%. Over the 3 years of study, tacrine users showed a lower mortality rate than nonusers (hazard rate ratio (HRR) = 0.76; 95% CI = 0.70–0.83). The tacrine effect remained after adjustment for sociodemographic factors, level of function in ADLs, cognitive function, number of drugs, and comorbid illnesses (HRR = 0.85; 95% CI = 0.77–0.93) (see Table 3 and Figure 1). The HRR for users with a maximum tacrine dose of ≤40 mg was 0.81 (95% CI = 0.73–0.90). The HRR for users with a maximum tacrine dose between 60 and 80 mg was 0.90 (95% CI = 0.75–1.08). Users of high-dose tacrine (>80 mg/day) experienced the greatest survival advantage (HRR = 0.74; 95% CI = 0.56–1.0).

DISCUSSION

We found that tacrine use was associated with prolonged survival in nursing home residents. This translates into an approximate 6-month increase in length of life associated with the use of tacrine over 3 years. The strongest association was observed in those taking the highest dose of tacrine. High-dose tacrine usage was associated with a 24% reduction in mortality rate compared with not taking tacrine after adjusting for independent risk factors for mortality, including measures of dementia severity.

Our results strengthen and extend the previous observation of Knopman et al.,¹³ who observed a trend toward lower mortality in outpatients receiving >120 mg tacrine daily. As pointed out in their study, and applicable to our study as well, tacrine tolerance may simply have served as a marker for healthier subjects with better prognosis for longevity.

Because our study was not blinded or controlled by random treatment assignment, a causal relationship between tacrine's pharmacological effects and mortality cannot be established, even though we attempted to control for multiple confounding factors that are known to affect mortality. Tacrine users were more likely to be male and more likely to be receiving major and minor tranquilizers. Because male gender^{35,36,39} and tranquilizer use³⁸ have been shown to be markers of higher mortality, these factors biased against tacrine having a negative relationship with mortality. Nevertheless, the survival data appear to be robust in the presence of such counteractive factors. Tacrine users also tended to have a somewhat lower prevalence of major comorbid illnesses, such as heart failure, that adversely affect survival.^{36,39}

It should be noted that tacrine users had a higher level of function in ADLs at baseline, despite comparable levels of cognitive impairment compared with controls. This may be related to the therapeutic effect of cholinesterase inhibition on ADLs as demonstrated in previous studies of outpatients.^{1–7} If such relative preservation of ADLs continued during treatment in the nursing home, this might

Table 3. Relationship Between Tacrine Use and Survival (Cox Models)

Tacrine use	Hazard Rate Ratio	95% Confidence Interval
Versus no use	0.76	0.70–0.83
Versus no use, adjusted for sociodemographic factors	0.78	0.71–0.85
Versus no use, adjusted for sociodemographic factors, dementia severity (ADL, CPS)	0.81	0.74–0.89
Versus no use, adjusted for sociodemographic, ADL, CPS, other psychotropic drugs	0.81	0.75–0.89
Versus no use, adjusted for sociodemographic, ADL, CPS, psychotropic drugs, comorbid conditions	0.85	0.77–0.93

ADL = activities of daily living; CPS = cognitive performance scale.

explain tacrine's association with lower mortality, because greater impairment in ADLs has been associated with shorter survival in AD.³⁵ Nevertheless, when we adjusted for these factors and for sociodemographic variables, cognition, and presence of comorbid conditions, tacrine's relationship was slightly attenuated but still significant.

Prolongation of survival for tacrine users in the nursing home has socioeconomic implications. The savings expected from such treatment through delay in nursing home placement may be counterbalanced by an increased cost of more prolonged care for tacrine users in the nursing home. This issue will likely become of greater importance as cholinesterase inhibitors with fewer side effects come into more widespread usage in the community.

These data are subject to limitations bound by the data collection. Our ability to estimate the duration of drug use is admittedly limited using MDS data. Nurses collected snapshots of drug use at approximate 3-month intervals. Also, the estimation of duration is a function of availability of MDS drug data collection (ending in 1996 in states other than New York and 1995 in some facilities in New York). As a result, the estimated duration of tacrine usage in this sample may have been shorter than the true duration of use.

This same source of error affected our ability to estimate the maximum dose achieved. We found that doses used in the nursing home were generally less than those re-

ported to be efficacious in clinical trials. In well-controlled clinical trials, 80 mg/day is the lowest dose shown to be efficacious.⁴¹ As such, many of the users classified as reaching a maximum dose of 40 mg/day may in fact have been titrated to higher doses unobserved by the limitations of the MDS assessments. Monthly dosage changes, including temporary dose reductions and rechallenges after normalization of liver transaminase elevations, may not have been accurately captured. This source of error is the most likely explanation of the nonlinear effects observed in the dose-response analysis.

Finally, these data raise important ethical issues about the use of cholinesterase inhibitors in nursing home residents, particularly those with advanced dementia. We did not examine outcomes other than mortality. In medical practice, treatment decisions for such patients should consider the quality of life engendered by life-extending treatments.⁴² Because of the limitations of the data set, we could not determine cause of death as a potential quality-of-life outcome associated with tacrine therapy. Also, it is unknown whether tacrine users may have had less impaired behavior or ADLs during the period of this study than nonusers.

The more frequent use of tranquilizers among tacrine users is surprising in light of recent reports of reduced psychiatric symptoms with cholinesterase inhibitor therapy.^{3,7-11} This association suggests a possible negative impact on treatment cost and quality of life, but it is possible that tacrine was added to tranquilizer therapy in some cases for the express purpose of reducing already existent prominent behavior problems. Such unresolved issues should serve to stimulate future outcomes research on cholinesterase inhibitor therapy in the nursing home setting.

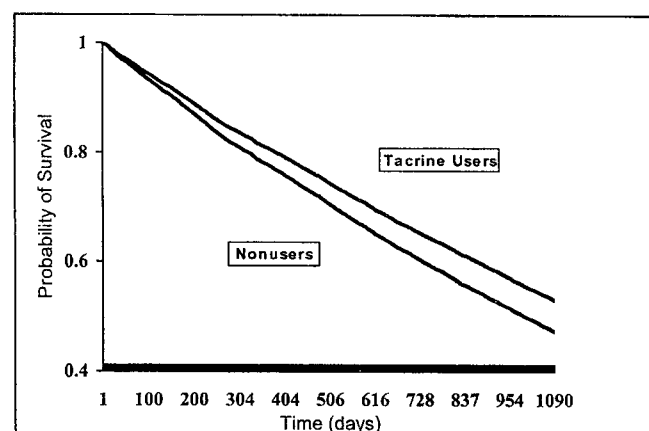
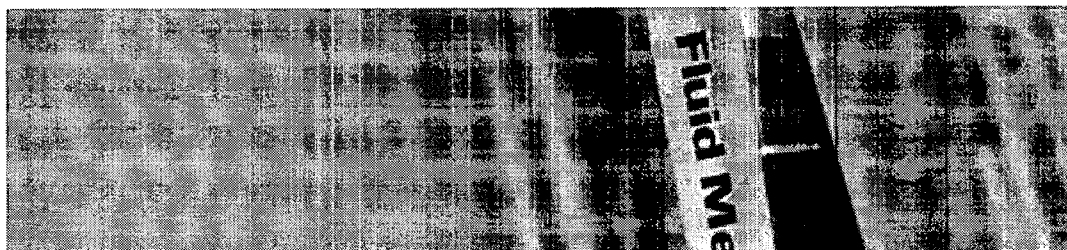


Figure 1. Probability of survival for tacrine users and nonusers, adjusted for demographic and clinical variables.

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An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia

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Résumé / Abstract

Background: Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia worldwide. Galantamine, an acetylcholinesterase inhibitor and allosteric nicotinic modulator, has shown broad clinical benefits in patients with mild to moderate dementia due to AD, probable VaD, or AD with cerebrovascular disease (CVD)-so-called mixed dementia. Objective: The purpose of this study was to evaluate the efficacy and safety profiles of galantamine 24 mg/d in patients with VaD or AD with CVD over the longer term (>6 months). Methods: This was an open-label extension of a 6-month double-blind study of galantamine. Patients who had been randomized to receive galantamine 24 mg/d or placebo in the double-blind phase were eligible to continue open-label treatment with galantamine 24 mg/d for 6 months. The primary efficacy end point was change in cognition, based on scores on the 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11). Secondary measures included changes in functional ability (as measured on the Disability Assessment for Dementia [DAD]) and behavior (as measured on the Neuropsychiatric Inventory [NPI]). Safety and tolerability were also monitored. Results: Four hundred fifty-nine patients (240 men, 219 women; mean [SE] age, 75.2 [0.33] years) entered the open-label phase. Of these patients, 195 (42.5%) had a diagnosis of probable VaD, and 238 (51.9%) had a diagnosis of AD with CVD; the remainder had an inconclusive diagnosis. At month 12 of the study, improvements from baseline (the start of the double-blind phase) in ADAS-cog/11 scores were observed in both the group that received placebo during the double-blind phase (placebo/galangamine group: -0.3 point; 95% CI, -1.64 to 1.06) and the group that received galantamine during the double-blind phase (galantamine/ galantamine group: -0.9 point; 95% CI, -1.73 to 0.03). Improvement in functional ability was demonstrated by statistically significant mean (SE) changes from baseline in DAD score in both the placebo/galangamine group (-7.4 [1.68]; $P \leq 0.001$) and the galantamine/galangamine group (-3.6 [1.33]; $P \leq 0.01$). There was no significant change in mean (SE) NPI scores in either group (0.2 [0.98] and 0.1 [0.70], respectively). Galantamine treatment was well tolerated. Conclusions: In these patients with VaD and AD with CVD, galantamine treatment produced similar sustained benefits in terms of maintenance of or improvement in cognition (ADAS-cog/11), functional ability (DAD), and behavior (NPI) after 12 months.

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Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists.

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Circadian rhythm sleep disorders (CRSDs), whether chronic or transient, affect a broad range of individuals, including many elderly, those with severe visual impairments, shift workers, and jet travelers moving rapidly across many time zones. In addition, various forms of insomnia affect another large sector of the population. A feature common among CRSDs and some forms of insomnia is sensitivity to the hormone melatonin, which is secreted by the pineal gland. Accumulating evidence suggests that melatonin may regulate the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although the light-dark cycle is the primary signal that entrains the circadian clock to environmental cycles, exogenous melatonin has been shown to entrain the clock in individuals with no light perception and free-running circadian rhythms. Furthermore, studies have reported beneficial effects of melatonin for treatment of certain insomnias. Together, these studies suggest that melatonin may be useful for treating some insomnias and CRSDs. In these contexts, use of melatonin as a supplement has been popular in the United States. Unfortunately, the therapeutic potential of melatonin has been difficult to realize in clinical trials, possibly owing to non-specific actions of the agent and its unfavorable pharmacokinetic properties when administered orally. In an attempt to take advantage of the therapeutic opportunities available through the brain's melatonin system, researchers have developed several melatonin agonists with improved properties in comparison to melatonin. Some of these agents are now in clinical trials for treatment of insomnia or CRSDs.

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Memantine for dementia.

Areosa SA, Sherriff F.

BACKGROUND: Alzheimer's disease, vascular and mixed dementia are the three commonest forms of dementia affecting older people. There is evidence that the excitatory activity of L-glutamate plays a role in the pathogenesis of Alzheimer's disease and in the damage from an ischaemic stroke. A low affinity antagonist to N-Methyl-D-aspartate (NMDA) type receptors, such as memantine, may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. **OBJECTIVES:** To determine the clinical efficacy and safety of memantine for people with Alzheimer's disease, or vascular or mixed dementia. **SEARCH STRATEGY:** Trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 15 April 2003 using the terms: memantin*, D-145, DMAA, DRG-0267. All major health care databases and trial databases within the scope of the group are searched regularly to keep this Register up to date. **SELECTION CRITERIA:** Double-blind, parallel group, placebo-controlled, randomized and unconfounded trials in which memantine was administered to people with dementia. **DATA COLLECTION AND ANALYSIS:** Data were extracted, pooled where possible, and weighted mean differences, standardized mean differences or odds ratios were estimated. Intention-to-treat (ITT) and observed cases (OC) analyses are reported, where data were available. **MAIN RESULTS:** Effect of memantine in patients with moderate to severe Alzheimer's disease: analysis of the change from baseline at 28 weeks gave statistically significant results in favour of memantine for 20 mg/day on cognition (MD: 6.1. 95% CI 2.99 to 9.21, P=0.0001) activities of daily living (MD 2.10, 95% CI 0.46 to 3.74, p=0.01) and in the global clinical impression of change measured by the CIBIC-Plus at 28 weeks (MD -0.30, 95% CI -0.58 to -0.02, p=0.04), in all cases the analysis was the ITT-LOCF population (Reisberg 2000). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of memantine for the number who suffer agitation. Effect of memantine in patients with mild to moderate vascular dementia: analysis of the change from baseline at 28 weeks gave statistically significant results in favour of memantine (20 mg/day) for cognition (MD -2.19, 95% CI -3.16 to -1.21, P<0.0001) but there was no benefit for the clinical impression of change, or for global measures of dementia (MMM300, and MMM500). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of memantine for the number who suffer agitation. Effect of memantine in patients with Alzheimer's disease and vascular dementia at 12 weeks: there was no statistically significant difference between memantine (10 mg/day) and placebo in activities of daily living. There was a benefit in favour of memantine (10 mg/day) compared with placebo at 12 weeks, for the numbers improved in terms of clinical impression of change (60/82 compared with 38/84 - OR 3.30, 95% CI 1.72 to 6.33, P=0.0003) (Winblad 1999). Effect of memantine in patients with vascular dementia, Alzheimer's disease and dementia of non-specified type at 6 weeks: there were beneficial effects on cognition (Ditzler 1991), activities of daily living (Ditzler 1991, Pantev 1993), behaviour (Pantev 1993) and global scales (Gortelmeyer 1992; Pantev 1993; Ditzler 1991) and in global impression of change (Gortelmeyer 1992; Ditzler 1991). There were no significant differences between memantine and placebo for the number of drop-outs and total number of adverse effects, but a significant difference in favour of placebo for the number who suffer restlessness. **REVIEWER'S CONCLUSIONS:** There is a beneficial effect

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of memantine (20 mg/day) for patients with moderate to severe Alzheimer disease on cognition and functional decline but not in the clinical impression of change. Patients with moderate to severe Alzheimer disease on cognition and functional decline but not in the clinical impression of change. Patients with mild to moderate vascular dementia receiving memantine 20 mg/day had less cognitive deterioration at 28 weeks but again this effect was not clinically discernible. There is a possible beneficial effect on cognition, function and global scales for memantine at 6 weeks in mixed populations. The drug is well tolerated and the incidence of adverse effects is low. More studies are needed.

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Rivastigmine in subcortical vascular dementia: an open 22-month study.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A.

Dipartimento di Fisiologia e Patologia, Università degli Studi di Trieste, Trieste, Italy.
moretti@univ.trieste.it

Further to recent data indicating that patients with vascular dementia (VaD) show a cholinergic deficit, we aimed to determine whether rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), has any effects on the symptoms of VaD. Patients aged 65-80, with a diagnosis of dementia and probable VaD, received rivastigmine 3-6 mg/day (n=8) or cardioaspirin (n=8) in an open study for 22 months. At 22 months, patients treated with rivastigmine showed significant improvements in executive function and behavioural symptoms (both $p < 0.05$ vs. both baseline and control group), which were reflected in reduced caregiver stress ($p < 0.05$ vs. baseline and controls). Baseline scores of global response, cognition, word fluency and activities of daily living were maintained in patients receiving rivastigmine, and there was no increase in benzodiazepine or neuroleptic intake. In contrast, the control group showed no improvements in any domain, and significant deterioration in global response and executive function (both $p < 0.05$ vs. baseline and rivastigmine group). Side effects in both groups were tolerable and there were no study withdrawals. Long-term rivastigmine treatment appeared to be safe and effective in this patient population. In particular, improvements in domains particularly relevant to this condition were observed. These benefits may reflect the drug's dual inhibitory effects on the cholinergic system, and its particular activity in frontal areas of the brain. A large, double-blind study of rivastigmine in patients with VaD would be worthwhile.

PMID: 12417373 [PubMed - indexed for MEDLINE]

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Rivastigmine in vascular dementia.
[Expert Opin Pharmacother. 2004]

Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open, 16-month, comparative study.
[Int J Clin Pract. 2004]

Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients.
[Am J Alzheimers Dis Other Dement. 2003]

Analysis of outcome in retrieved dropout patients in a rivastigmine vs placebo, 26-week, Alzheimer disease trial.
[Arch Neurol. 2003]

Rivastigmine in frontotemporal dementia: an open-label study.
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1: J Med Chem. 2002 Sep 12;45(19):4222-39.



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Synthesis of a novel series of tricyclic indan derivatives as melatonin receptor agonists.**Uchikawa O, Fukatsu K, Tokunoh R, Kawada M, Matsumoto K, Imai Y, Hinuma S, Kato K, Nishikawa H, Hirai K, Miyamoto M, Ohkawa S.**

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan. uchikawa_osamu@takeda.co.jp

To develop a new therapeutic agent for sleep disorders, we synthesized a novel series of tricyclic indan derivatives and evaluated them for their binding affinity to melatonin receptors. In our previous paper, we proposed a conformation of the methoxy group favorable for the binding of the MT(1) receptor. To fix the methoxy group in an active conformation, we decided to synthesize conformationally restricted tricyclic indan analogues with the oxygen atom in the 6-position incorporated into a furan, 1,3-dioxane, oxazole, pyran, morpholine, or 1,4-dioxane ring system. Among these compounds, indeno[5,4-b]furan analogues were found to be the most potent and selective MT(1) receptor ligands and to have superior metabolic stability. The optimization of substituents led to (S)-(-)-22b, which showed very strong affinity for human MT(1) ($K(i) = 0.014$ nM), but no significant affinity for hamster MT(3) ($K(i) = 2600$ nM) or other neurotransmitter receptors. The pharmacological effects of (S)-(-)-22b were studied in experimental animals, and it was found that a dose of 0.1 mg/kg, po promoted a sleep in freely moving cats, as demonstrated by a decrease in wakefulness and increases in slow wave sleep and rapid eye movement sleep, which lasted for 6 h after administration. Melatonin (1 mg/kg, po) also had a sleep-promoting effect, though it lasted only 2 h. A new chiral method for the synthesis of (S)-(-)-22b starting from 60, which was prepared from 59 employing asymmetric hydrogenation with the (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-Ru complex, was developed. (S)-(-)-22b (TAK-375) is currently under clinical trial for the treatment of insomnia and circadian rhythm disorders.

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Synthesis of a novel series of benzocycloalkene derivatives as melatonin receptor agonists. [J Med Chem. 2002]

Mapping the melatonin receptor. 6. Melatonin agonists and antagonists derived from 6H-isoindolo[2,1-a]indoles, 5,6-dihydroindolo[2,1-a]isoquinolines, and 6,7-dihydro-5H-benzocyclopino[2,1-a]indoles. [J Med Chem. 2000]

Synthesis and structure-affinity-activity relationships of novel benzofuran derivatives as MT(2) melatonin receptor selective ligands. [J Med Chem. 2002]

Pharmacological characterization of human recombinant melatonin mt(1) and mt(2) receptors. [J Med Chem. 2000]

Synthesis of phenalene and acenaphthene derivatives as new conformationally restricted ligands for melatonin receptors. [J Med Chem. 2000]

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Therapeutic perspectives for melatonin agonists and antagonists.**Delagrangé P, Atkinson J, Boutin JA, Casteilla L, Lesieur D, Misslin R, Pellissier S, Pénicaut L, Renard P.**

Institut de Recherches Internationales SERVIER, 6 Place des Pléiades, 92415 Courbevoie Cedex, France. philippe.delagrangé@fr.netgrs.com

Melatonin is a neurohormone synthesized in the pineal gland during the dark period in all species, including humans. The diversity and differences in melatonin receptor distribution in the brain and extracerebral organs suggest multiple functional roles for melatonin. Administration of melatonin agonists reduces neophobia and treatment with a melatonin antagonist during the dark period reverses the anxiolytic-like effect of endogenous melatonin. Chronic treatment with agonists prevents various perturbations induced by chronic mild stress. Melatonin in vivo directly constricts cerebral arterioles in rats and decreases the lower limit of cerebral blood flow autoregulation, suggesting that melatonin may diminish the risk of hypoperfusion-induced cerebral ischemia. At the extracerebral level, melatonin regulates intestinal motility in rats. The intestinal postprandial motor response is shorter in the dark phase than in the light phase and this reduction is reversed in animals pretreated with a melatonin antagonist. Moreover, melatonin reduces the duration of cholecystokinin excitomotor effect. Endogenous melatonin may modulate intestinal motility to coordinate intestinal functions such as digestion and transit and control the metabolism of the animal. An adipocyte melatonin binding site may also participate in this control. Melatonin is involved in a wide range of physiological functions. The question remains as to whether evolution, adaptation and diurnal life have modified the physiological role of melatonin in humans. Moreover, the functional role of each of the receptor subtypes has to be characterized to design selective ligands to treat specific diseases.

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Nychthemeral variations of cholecystokinin action on intestinal motility in rats: effects of melatonin and S 20928, a melatonin receptor antagonist. [Peptides. 2000]

Effect of melatonin on motility pattern of small intestine in rats and its inhibition by melatonin receptor antagonist S 22153. [J Pineal Res. 2000]

Human pineal physiology and functional significance of melatonin. [Front Neuroendocrinol. 2004]

Melatonin: an endogenous negative modulator of 12-lipoxygenation in the rat pineal gland. [Biochem J. 1999]

Melatonin reduces anxiety induced by lipopolysaccharide in the rat. [Neurosci Lett. 2001]

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Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia.**Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S.**

Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan. asayama@nms.ac.jp

Previously, we reported that morning bright light therapy improved sleep time and cognitive function in Alzheimer type of dementia. We conducted a double blind study to examine the effects of melatonin on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type of dementia. The subjects were 9 persons given a placebo (PLA), and 11 given melatonin (3 mg)(MLT). The mean age was 79.2+/-6.4 (17 females and 3 males). The drugs were given at 20:30 each day for 4 weeks. We checked sleep time and activity by Actigraph through one week before and the 4th week after drug administration. Cognitive and non-cognitive functions were evaluated with the clinical dementia rating scale (CDR), and Mini Mental State Examination (MMSE), and the Alzheimer's Disease Assessment Scale (ADAS). We successfully recorded Actigraph data from 18 patients (PLA8, MLT10). The mean sleep time change ratio and SD of the administration of PLA in the night was 0.2+/-13.7%, and MLT was 33.2+/-37.6%. The mean activity counts and SD of the administration of PLA in the night was 29.8+/-77.0%; in MLT it was 44.9+/-21.9%. Melatonin significantly prolonged the sleep time ($p=0.017$) and decreased activity ($p=0.014$) in the night (21:00-6:00) in the MLT group, although no significant difference in sleep time or activity in the daytime (6:00-21:00) was recognized between the two groups. In comparison with ADAS cognition score changes, the mean change and SD in the PLA was 0.3+/-3.7; in MLT it was -4.3+/-3.6 points. In comparison with ADAS non-cognition score, the mean change and SD in the PLA group was 0.8+/-1.0, in the MLT group it was -4.1+/-2.2 points. There were also significant differences between the PLA and the MLT groups in the comparison with the score improvement of ADAS cognition ($p=0.017$) and non-cognition ($p=0.002$), otherwise there was no significant difference in improvement of MMSE between both groups. Melatonin administration had effect to improve sleep time and night activity, but no significant effect to improve daytime naps and activity. Although melatonin administration might have less strong effect on circadian rhythm than morning bright light therapy we previously reported, cognitive and non-cognitive functions were improved. Melatonin seemed to be useful for care of the Alzheimer type of dementia patients.

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[Effects of bright light on cognitive disturbances in Alzheimer-type dementia] *Nippon Ika Daigaku Zasshi*. 1999Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. *Alz Dis Ther*. 2003Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*. 2008Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database Syst Rev*. 2003Effects of melatonin in two individuals with Alzheimer's disease. *Percept Mot Skills*. 1998

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Search PubMed  for [Advanced Search \(beta\)](#)[Limits](#) [Preview/Index](#) [History](#) [Clipboard](#) [Details](#)Display [AbstractPlus](#)  Show 20  Sort By  Send to [All: 1](#) [Review: 0](#)☐ 1: [Percept Mot Skills. 1998 Aug;87\(1\):331-9.](#)[Links](#)**Effects of melatonin in two individuals with Alzheimer's disease.****Jean-Louis G, Zizi F, von Gizycki H, Taub H.**Department of Psychiatry, University of California, San Diego, La Jolla, CA 92037, USA.
gjeanlouis@ucsd.edu

Dementia has been associated with circadian rhythm disturbances expressed in several dimensions including body temperature, hormonal concentrations, sleep and wakefulness patterns, and rest-activity cycles. These disturbances may be the result of a dampening in the amplitude of the circadian rhythm. One of the symptoms associated with the aging process has been a decline in the amplitude of the melatonin rhythm. Here, the results of melatonin administration to two patients with Alzheimer's disease are presented. Melatonin administration enhanced and stabilized the circadian rest-activity rhythm in one of the patients along with some reduction of daytime sleepiness and an improvement in mood. The other patient, who was characterized by less cognitive impairment, showed no significant changes associated with melatonin ingestion. Interestingly, the acrophase of rest-activity was delayed for about one hour in both patients. These results suggest that melatonin may have beneficial effects in some patients with Alzheimer's disease.

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Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. [J Nippon Med Sch. 2003]

Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment. [J Pineal Res. 1998]

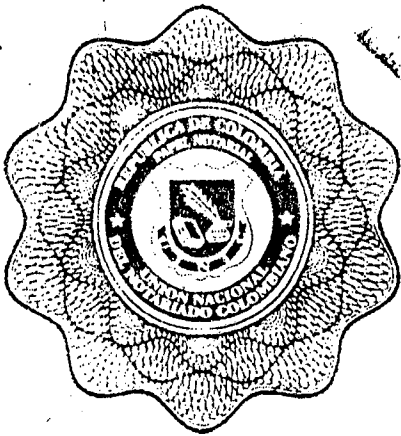
Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. [J Am Geriatr Soc. 2008]

The use of melatonin in Alzheimer's disease. [Neuro Endocrinol Lett. 2002]

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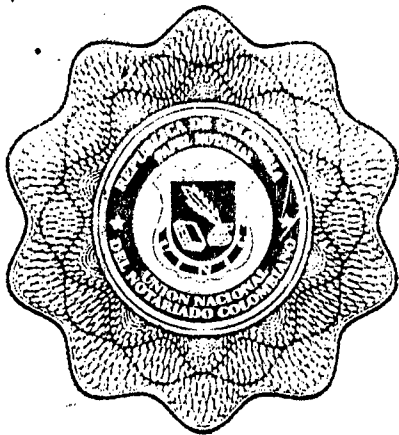
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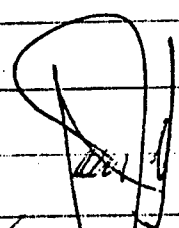
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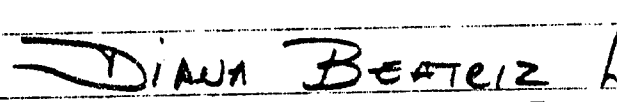
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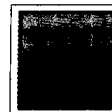
PAGINA No. 2

28406						
E.P.	101	31/01/1966	NOTARIA	CUARTA	DE	CALI 01/02/1966
31039						
E.P.	552	21/03/1968	NOTARIA	CUARTA	DE	CALI 01/04/1968
35711						
E.P.	4964	12/12/1972	NOTARIA	CUARTA	DE	CALI 16/01/1973
2975	IX					
E.P.	1956	30/05/1973	NOTARIA	CUARTA	DE	CALI 13/06/1973
4337	IX					
E.P.	4964	12/12/1972	NOTARIA	CUARTA	DE	CALI 28/11/1973
5994	IX					
E.P.	5579	12/11/1973	NOTARIA	CUARTA	DE	CALI 28/11/1973
5995	IX					
E.P.	4406	30/09/1974	NOTARIA	CUARTA	DE	CALI 28/11/1974
10887	IX					
E.P.	192	03/02/1978	NOTARIA	CUARTA	DE	CALI 14/02/1978
25355	IX					
E.P.	3479	07/09/1979	NOTARIA	CUARTA	DE	CALI 19/09/1979
34204	IX					
E.P.	4274	12/12/1984	NOTARIA	NOVENA	DE	CALI 19/12/1984
73088	IX					
E.P.	1155	21/05/1985	NOTARIA	SEPTIMA	DE	CALI 03/06/1985
76917	IX					
E.P.	1553	20/06/1986	NOTARIA	SEPTIMA	DE	CALI 08/07/1986
85997	IX					
E.P.	1458	09/06/1987	NOTARIA	SEPTIMA	DE	CALI 24/12/1987
3508	IX					
E.P.	7222	14/12/1988	NOTARIA	TERCERA	DE	CALI 19/12/1988
13847	IX					
E.P.	4530	04/09/1989	NOTARIA	TERCERA	DE	CALI 07/09/1989
21508	IX					
E.P.	3865	02/08/1990	NOTARIA	TERCERA	DE	CALI 13/08/1990
31708	IX					
E.P.	8305	13/12/1995	NOTARIA	TERCERA	DE	CALI 23/01/1996
557	IX					
E.P.	4559	16/11/1999	NOTARIA	TERCERA	DE	CALI 26/11/1999
7911	IX					
E.P.	6.004	02/12/2004	NOTARIA	TERCERA	DE	CALI 14/12/2004
13371	IX					
E.P.	6241	27/12/2006	NOTARIA	TERCERA	DE	CALI 19/01/2007
625	IX					
E.P.	389	07/02/2008	NOTARIA	TERCERA	DE	CALI 19/02/2008
1880	IX					

CERTIFICA

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 3

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 4

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

PRIMER SUPLENTE DEL GERENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

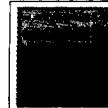
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 5

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY

C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE(ON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 6

SEGUNDO RENGLON
ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RO) NOMBRA(S):

REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA
NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE MAYO DE 2008
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 23 DE MAYO DE 2008 No. 5771 DEL LIBRO IX

FUE(RO) NOMBRA(S):

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 7

REVISOR FISCAL PRINCIPAL

ALFREDO LOPEZ CAMPO

C.C.8241912

REVISOR FISCAL SUPLENTE

ANDERSON DAVID RODRIGUEZ REYES

C.C.16916373

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000

NUMERO DE ACCIONES: 750,000,000

VALOR NOMINAL: \$10

CAPITAL SUSCRITO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CAPITAL PAGADO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A

UBICADO EN: --K 1 46A 70 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL A?O 2008

CERTIFICA:

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 8

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

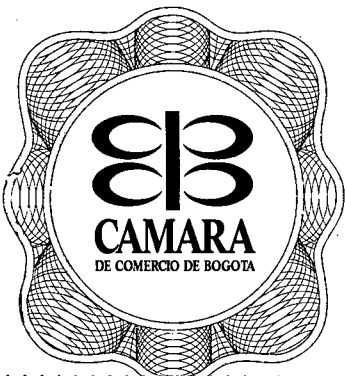
CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 28 DE
MARZO DE 2008 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080730

Hora Certificado 10:11:53

Operacion : 02NBM0730001

PAGINA No. 9

PRESENTE CERTIFICADO.

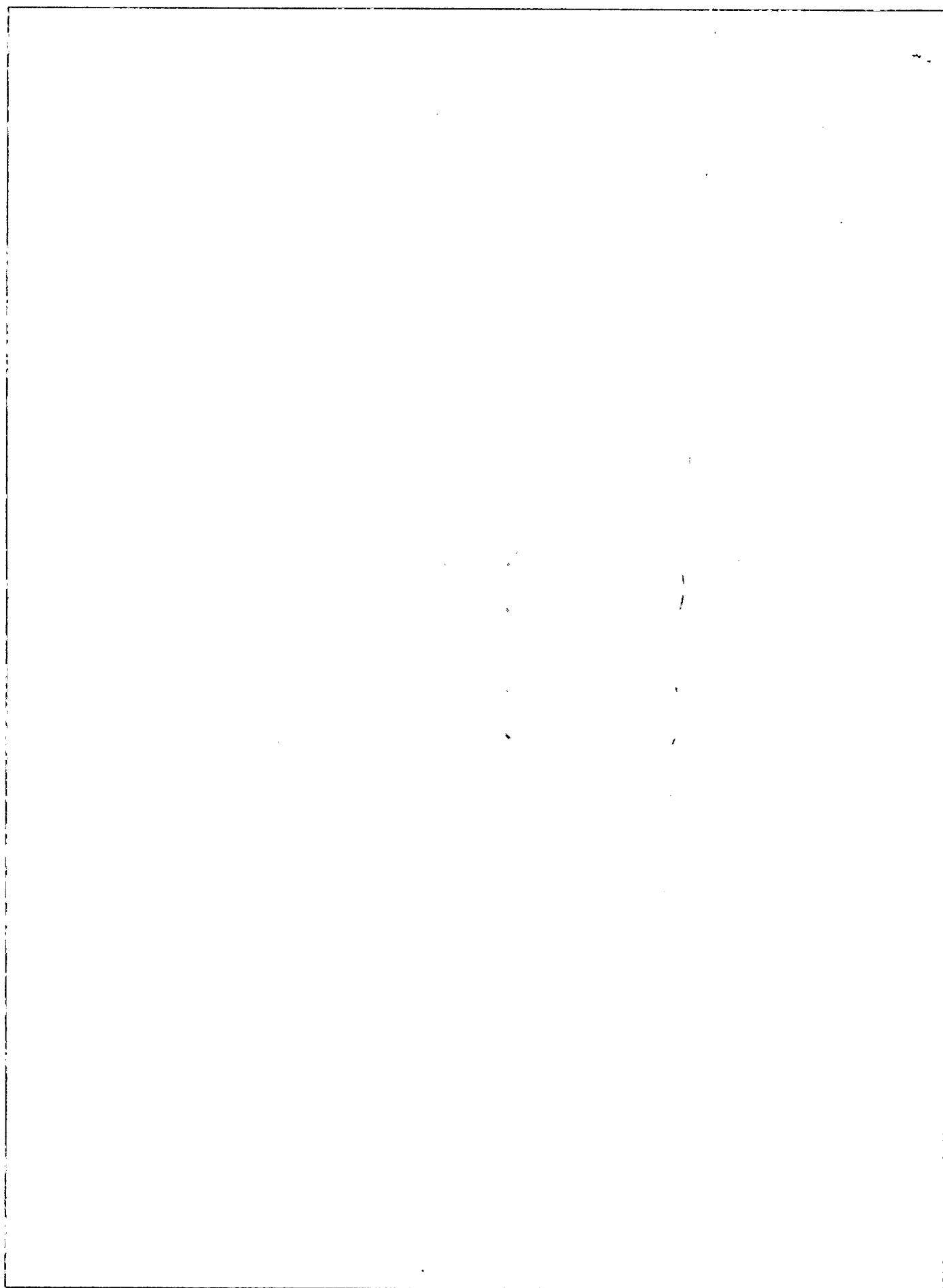
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 30 DIAS DEL MES DE JULIO

DEL AÑO 2008 HORA: 10:10:10


SERGIO FERRANDO CAMPO GARCIA



775⁵⁸

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-104245-00004-0000

Fecha: 2008-07-30 15:33:32 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 58

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 60,877
FECHA : JULIO 30 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	4643866	29/07/2008	1,596,000.00

***** CONCEPTO *****

ANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LENAS COMERCIALES	266,000.00
	TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 11572

ASUNTO:	Radicación PCT N°	07-104245
	Trámite	011
	Evento	379
	Actuación	440
	Folios	010

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

12 SET. 2008

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 11573

ASUNTO:	Radicación PCT N°	07-104245
	Trámite	011
	Evento	379
	Actuación	440
	Folios	051

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano - Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

12 SET 2000

El anterior oficio fue notificado por fijación en lista de fecha,_____.

202021