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帕罗西汀治疗阿尔兹海默症合并抑郁对血清 NE 以及 5-HT 表达的影响 *

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摘要 目的：探讨帕罗西汀治疗阿尔兹海默症合并抑郁对血清去甲肾上腺素 (Noradrenaline，NE) 以及 5- 羟色胺 (5-hydroxytryptamine，5-HT)表达的影响。**方法：**2017 年 9 月到 2019 年 8 月选择在本院诊治的 98 例阿兹尔海默症合并抑郁患者，根据治疗方法的不同分为帕罗西汀组 50 例与多奈哌齐组 48 例。多奈哌齐组给予多奈哌齐治疗，帕罗西汀组在多奈哌齐组治疗的基础上给予帕罗西汀治疗，两组治疗观察 3 个月，记录血清 NE、5-HT 表达变化情况。**结果：**帕罗西汀组的总有效率是 96.0 % (48/50)，显著高于多奈哌齐组的 79.2 % (38/48) (P<0.05)。两组治疗前的 MMSE 评分对差异比无统计学意义(P<0.05)，两组治疗后的 MMSE 评分显著高于治疗前(P<0.05)，且帕罗西汀组也显著高于多奈哌齐组(P<0.05)。帕罗西汀组治疗期间的便秘、嗜睡、头晕、心动过速、肝功能异常等不良反应发生率为 40.0 % (20/50)，多奈哌齐组为 31.3 % (15/48)，两组对比差异无统计学意义(P>0.05)。两组治疗前血清 NE、5-HT 含量对比差异无统计学意义(P>0.05)；两组治疗后的血清 NE、5-HT 含量显著高于治疗前(P<0.05)，且帕罗西汀组也显著高于多奈哌齐组(P<0.05)。**结论：**帕罗西汀治疗阿尔兹海默症合并抑郁能促进血清 NE、5-HT 的释放，改善患者的认知功能，提高治疗效果确切，且不会增加不良反应。

关键词：帕罗西汀；阿尔兹海默症；抑郁；去甲肾上腺素；5- 羟色胺

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Effects of Paroxetine on Alzheimer's Disease Combined with Depression on Serum NE and 5-HT Expression*

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ABSTRACT Objective: To investigate the effect of paroxetine in the treatment of Alzheimer's disease combined with depression on serum noradrenaline (NE) and 5-hydroxytryptamine (5-HT) expression. **Methods:** From September 2017 to August 2019, 98 cases of patients with Alzheimer's disease and depression who were selected for treatment in our hospital were selected and divided into 50 cases of paroxetine group and 48 cases of donepezil group accorded to different treatment methods. The donepezil group were treated with donepezil, and the paroxetine group were given paroxetine on the basis of the donepezil group. The two groups were observed for 3 months, and the changes in serum NE and 5-HT expression were recorded. **Results:** The total effective rates of the paroxetine group were 96.0 % (48/50), which were significantly higher than 79.2 % (38/48) of the donepezil group (P<0.05). There was no significant difference in the MMSE score pretherapy between the two groups (P<0.05). The MMSE scores of the two groups post-treatment was significantly higher than pretherapy (P<0.05), and the paroxetine group was also significantly higher than that of the donepezil group (P<0.05). The incidences of adverse reactions such as constipation, drowsiness, dizziness, tachycardia, and abnormal liver function during the treatment of paroxetine in the paroxetine group were 40.0 % (20/50), so that were 31.3 % (15/48) in the donepezil group, compared were no statistically significant difference (P>0.05). There was no statistically significant difference in serum NE and 5-HT levels between the two groups pretherapy (P>0.05). The levels of serum NE and 5-HT in the two groups post-treatment were significantly higher than pretherapy (P<0.05), and the paroxetine group were significantly higher than that in the donepezil group (P<0.05). **Conclusion:** Paroxetine in the treatment of Alzheimer's disease combined with depression can promote the release of serum NE and 5-HT, improve the cognitive function of patients, and improve the treatment effect without increasing the incidence of adverse reactions.

Key words: Paroxetine; Alzheimer's disease; Depression; Norepinephrine; 5-hydroxytryptamine

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前言

阿尔兹海默症(Alzheimer's disease,AD)是一种神经退行性疾病,又称痴呆症[1,2]。抑郁是以行为障碍、认知障碍、情感障碍为主要临床表现的常见精神疾病，具有病程长和进展慢等特点[3]。随着人口老龄化程度的加剧,阿尔兹海默症合并抑郁患者逐渐增加,对患者身心健康产生了严重的影响,也已经成为了一种公共卫生问题[4]。当前治疗该病的药物比较多见,包括帕罗西汀、氨磺必利、多奈哌齐等[5,6]。多奈哌齐是非典型抗精神病药物,然而长时间使用容易使患者产生较强的依赖心理,停药后容易复发,也比较难改善患者的阴性症状[7,8]。帕罗西汀为一种五羟色胺再摄取抑制剂,口服后吸收迅速,半衰期比较短,因此具有极强的稳定性,与人体蛋白的结合率比较高。其能促进多巴胺的释放,解除突触前抑制,从而发挥抗抑郁作用[9,10]。5-羟色胺(5-hydroxytryptamine,5-HT)和去甲肾上腺素(Noradrenaline,NE)在机体情绪、情感和睡眠中发挥重要作用[11,12]。两者表达下降可导致机体产生抑郁，从而在临床上出现认知障碍、甚至导致自残自杀等行为[13,14]。本文具体探讨了帕罗西汀治疗阿尔兹海默症合并抑郁对血清 NE 以及 5-HT 表达的影响,以明确帕罗西汀的作用效果与机制。现总结报告如下。

1 资料与方法

1.1 研究对象

2017 年 9 月到 2019 年 8 月选择在本院诊治的 98 例阿兹海默症合并抑郁患者,纳入标准:符合阿尔兹海默症合并抑郁;法定监护人或患者本人完成书面知情同意书的签署工作;年龄 55-75 岁;医院伦理委员会批准了此次研究;既往无精神疾病病史,无嗜酒及精神类药物依赖史;治疗前 1 周未使用任何抗精神病药物。排除标准:自杀倾向明显或出现严重的冲动行为者;既往对此次研究所用药物过敏者;目前患有心血管疾病、脑器质性疾病等患者;有严重视力障碍或色盲者;精神病家族史(2 系 3 代内直系亲属明确诊断者)；严重睡眠障碍需要服药的患者;嗜酒、吸毒的患者。根据治疗方法的不同分为两组,两组的一般资料对比无差异(P>0.05)。

表 1 一般资料对比

Table 1 Comparison of general information

Groups	n	Gender (Male/Female)	marital status (Married / not married)	Years of education (years)	BMI (kg/m^2)	Age (year)	Course of disease (year)
Paroxetine group	50	26/24	45/5	10.76±2.14	22.10±2.14	56.13±2.49	5.35±1.42
Donepezil group	48	24/24	43/5	10.66±1.05	22.41±1.82	56.24±3.18	5.24±1.09

1.2 治疗方法

多奈哌齐组:给予多奈哌齐治疗,口服多奈哌齐(国药准字 H20050978,卫材(中国)药业有限公司)5 mg/d,然后逐渐调整剂量到 10-20 mg/d。

帕罗西汀组:在多奈哌齐组治疗的基础上给予帕罗西汀治疗,口服盐酸帕罗西汀(国药准字 H20040533,浙江华海药业)20 mg,1 次 /d。两组均治疗 3 个月。

1.3 观察指标

(1) 疗效标准：根据汉密尔顿抑郁量表进行判定,(治愈 + 显著进步)/ 本组例数×100.0 %= 总有效率。(2) 在治疗前后采用简明精神状态检查量表 (Mini-Mental State Examination,MMSE)评定患者的认知功能,临界分为 24 分,分界值以下为认知功能缺损,以上为正常。(3) 记录在治疗期间两组的心动过速和便秘等不良反应情况。(4) 在治疗前后抽取患者的空腹外周肘部静脉血 3-5 mL，以 3 000 r/min 分离 10 min，保存上清液,应用酶联免疫法测定血清 NE、5-HT 含量。

1.4 统计方法

选择 SPSS 19.00 对本研究所有数据进行分析,计数数据采用百分数或者例数表示,计量资料选择均数±标准差($\bar{x}\pm s$)描述,对比采用独立样 t 检验、x^2 分析,检验水准为 α=0.05。

2 结果

2.1 两组总有效率对比

帕罗西汀组的总有效率是 96.0 % (48/50),显著高于多奈哌齐组的 79.2 % (38/48) (P<0.05)。见表 2。

表 2 两组总有效率对比(例,%)

Table 2 Comparison of total effective rates between the two groups (n,%)

Groups	n	Recure	Significant progress	Progress	Invalid	Total effective rate
Paroxetine group	50	40	8	1	1	48 (96.0)*
Donepezil group	48	28	10	7	3	38 (79.2)

Note: Compared to the donepezil group , *P<0.05.

2.2 两组治疗前后 MMSE 评分变化对比

两组治疗前的 MMSE 评分对差异比无统计学意义(P<0.05),治疗后两组的 MMSE 评分均显著高于治疗前(P<0.05),且帕罗西汀组也显著高于多奈哌齐组(P<0.05)。见表 3。

2.3 两组治疗期间的不良反应情况对比

帕罗西汀组治疗期间的便秘、嗜睡、头晕、心动过速、肝功能异常等不良反应发生率为 40.0 % (20/50),奈哌齐组为 31.3 % (15/48),两组对比差异无统计学意义(P>0.05)。见表 4。

表 3 两组治疗前后 MMSE 评分变化对比(分，$\bar{x}\pm s$)

Table 3 Comparison of changes in MMSE scores between the two groups pretherapy and post-treatment (scores，$\bar{x}\pm s$)

Groups	n	Pretherapy	Post-treatment
Paroxetine group	50	15.77±2.83	27.28±2.47*#
Donepezil group	48	16.02±1.88	23.28±3.85*

Note: Compared to the same group pretherapy, *P<0.05, compared with the donepezil group post-treatment, #P<0.05.

表 4 两组治疗期间的不良反应情况对比(例，%)

Table 4 Comparison of adverse reactions during treatment between the two groups(n,%)

Groups	n	Drowsiness	Astriction	Dizzy	Sychnosphygmia	Abnormal liver function	Total
Paroxetine group	50	5	6	4	3	2	20(40.0)
Donepezil group	48	4	4	5	1	1	15(31.3)

2.4 两组治疗前后血清 NE、5-HT 含量对比

两组治疗前血清 NE、5-HT 含量对比差异无统计学意义(P>0.05)；治疗后两组的血清 NE、5-HT 含量均显著高于治疗前(P<0.05)，且帕罗西汀组高于奈哌齐组(P<0.05)。见表 5。

表 5 两组治疗前后血清 NE、5-HT 含量对比(ng/L，$\bar{x}\pm s$)

Table 5 Comparison of serum NE and 5-HT content between the two groups pretherapy and post-treatment (ng/L, $\bar{x}\pm s$)

Groups	n	NE		5-HT	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Paroxetine group	50	41.45±2.10	87.98±2.85*#	228.76±24.91	399.87±34.81*#
Donepezil group	48	41.09±1.88	69.87±3.11*	229.97±30.14	314.83±25.01*

Note: Compared to the same group pretherapy, *P<0.05, compared with the donepezil group post-treatment, #P<0.05.

3 讨论

阿尔兹海默症为一种以进行性认知功能障碍和记忆损害为特征的神经系统退行性疾病，在临床上主要表现为认知和记忆能力降低[14,15]。抑郁为阿尔兹海默症最常见的并发症之一，在临床上主要表现为睡眠障碍、丧失兴趣、情绪和性格的变化等，严重影响了患者的身心健康，也加重了阿尔兹海默症者的致残率和病死率[16,17]。

本研究显示帕罗西汀组的总有效率是 96.0 %，显著高于多奈哌齐组的 79.2 %；两组治疗后的 MMSE 评分显著高于治疗前，帕罗西汀组也显著高于多奈哌齐组，表明帕罗西汀的应用能改善患者的认知功能，提高治疗效果。阿兹海默症合并抑郁的治疗目标为完全缓解患者的症状和社会功能，多奈哌齐为喹诺酮类衍生物，神经生化研究表明精神抑郁可能与多巴胺功能亢进有关，抗精神病药物通过阻滞多巴胺受体而发挥抗精神病作用。因其可下调多巴胺功能亢进，在不同的通路上通过调节受体发挥不同作用，但是药效持续效应较差[18]。帕罗西汀为现阶段抗抑郁症的主要药物，能改善患者认知障碍，促进神经功能、认知功能的恢复[19]。当前也有研究显示帕罗西汀能通过特异性阻断边缘系统和突触前多巴胺受体来发挥其抗精神病作用，能消除突触前抑制，使前额皮质的多巴胺性能传递增加，还能有效提高患者全身机能，持续发挥疗效作用[20,21]。

本研究显示两组治疗后的血清 NE、5-HT 含量显著高于治疗前，观察组也显著高于对照组。临床研究表明阿兹海默症是一种由血液凝固失常、遗传、脂质代谢异常、环境等因素有关的疾病，其病理学特征主要为脑实质内细胞外间隙及脑血管壁内的淀粉样蛋白的沉积，改变了神经元内的钙稳态，引起氧化应激反应，轴突运输遭到破坏[22]。NE、5-HT 可作用于多巴胺能及肾上腺素能神经末梢，保持神经的兴奋性，能控制下丘脑激素的分泌及释放，调节垂体前叶促激素释放。NE、5-HT 表达下降时可降低对应神经元兴奋性，影响机体精神及情绪调节，加剧脑部神经元损伤，加重病情[23,24]。帕罗西汀作为一种 5-HT 再摄取抑制剂，能减轻应激源刺激强度，能改善脑部血流，减少神经细胞毒性，促进神经元功能恢复，从而促进 NE、5-HT 等神经递质分泌[25-27]。

本研究显示帕罗西汀组治疗期间的便秘、嗜睡等不良反应发生率为 40.0 %，多奈哌齐组为 31.3 %，表明帕罗西汀的应用并不会增加不良反应的发生。虽然 SSRIs 是目前临床上治疗精神障碍的主要药物，但是仍存在一定的不良反应。同时目前有关抗精神病药物的联合用药问题尚未取得一致见解，单一用药的疗效欠佳，但是具有很好的安全性，联合用药可能会增加患者的不良反应[28-30]。本研究也有一定的不足，没有设定安慰剂组，没有采用双盲研究，样本量不够大，研究时间不够长，将在后续研究中进行总结分析。

总之，帕罗西汀治疗阿尔兹海默症合并抑郁能促进血清 NE、5-HT 的释放，改善患者的认知功能，提高治疗效果。

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