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·临床研究·

文拉法辛联合认知行为疗法治疗帕金森病抑郁、认知功能障碍的临床疗效评价*

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摘要 目的：探讨文拉法辛联合认知行为疗法治疗帕金森病(PD)抑郁、认知功能障碍的临床疗效和安全性。**方法：**选择我院收治的60例PD合并抑郁、认知功能障碍患者并将其随机分为三组，分别为对照组(单用文拉法辛治疗)，联合奥氮平组(文拉法辛联合奥氮平)，联合认知行为疗法组（文拉法辛联合认知行为疗法），每组20例，于治疗前及治疗后4、8周末采用汉密尔顿抑郁量表(HAMD)进行抑郁程度评定，简易精神状态评价量表(MMSE)和事件相关电位(event-related potentials，ERPs)P300进行认知功能评定。**结果：**治疗4、8周时，三组的HAMD评分均较治疗前有不同程度下降，P300潜伏期较治疗前有不同程度缩短，P300波幅、MMSE评分有不同程度升高(P＜0.05)，联合奥氮平组和联合认知行为疗法组HAMD评分较对照组明显下降，P300潜伏期较对照组明显缩短，P300波幅、MMSE评分明显升高(P＜0.05)，联合认知行为疗法组HAMD评分较联合奥氮平组明显下降，P300潜伏期明显缩短，P300波幅、MMSE评分明显升高(P＜0.05)。三组均无特殊不良反应。**结论：**文拉法辛联合认知行为疗法治疗PD抑郁、认知功能障碍疗效确切，能显著改善患者抑郁症状，提高患者的认知功能，疗效较单用文拉法辛或文拉法辛联合奥氮平治疗更好，且安全性高。

关键词：文拉法辛；奥氮平；认知行为疗法；帕金森病；抑郁；认知功能障碍

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Evaluation of the Clinical Effect of Venlafaxine Combined with Cognitive Behavioral Therapy on the Parkinson's Disease with Depression and Cognitive Dysfunction*

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ABSTRACT Objective: To investigate the clinical efficacy and safety of venlafaxine combined with cognitive behavior therapy in the treatment of Parkinson's disease (PD) combined with depression and cognitive dysfunction. **Methods:** Sixty Parkinson's patients with depression and cognitive dysfunction in our hospital were randomly divided into three groups: the control group (treated with venlafaxine alone), venlafaxine combined with olanzapine, venlafaxine combined with cognitive behavior therapy group, 20 cases in each group. The degree of depression was assessed by Hamilton Depression Scale(HAMD) before and at 4 and 8 weeks after the treatment, The degree of cognitive dysfunction was assessed by Mini-Mental State Examination (MMSE)and event-related potentials P300 before and at 4 and 8 weeks after the treatment. **Results:** At 4 and 8 weeks after treatment, the HAMD scores of three groups were decreased to different degrees than those before treatment, P300 latency was shorter than those before treatment, P300 amplitude and MMSE scores were increased to different degrees (P<0.05). The HAMD scores of combined olanzapine group and combined cognitive behavior therapy group were significantly lower than that of the control group. The latency of P300 were significantly shorter than that of the control group, and the P300 amplitude and MMSE score were significantly increased (P<0.05). The HAMD score of combined cognitive behavior group was significantly lower than that of the olanzapine group, the P300 latency was shortened, the P300 amplitude and MMSE score were significantly increased (P<0.05). There was no special adverse reactions in the three groups. **Conclusion**: Venlafaxine combined with cognitive behavior therapy was effective in the treatment of PD relted depression and cognitive dysfunction, it could significantly improve the symptoms of depression, cognitive function and was superior to venlafaxine or venlafaxine combined with olanzapine treatment with high safety.

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前言

帕金森病(Parkinson's disease,PD)是以中脑黑质多巴胺能神经元的变性缺失和路易小体形成为病理特征的神经变性疾病,主要以静止性震颤、运动迟缓、肌强直和姿势步态障碍为临床特点。PD 患者除了运动障碍外,还多存在非运动症状,包括抑郁、认知功能障碍、焦虑、失眠、自主神经紊乱、精神异常等[1]。抑郁、认知功能障碍是 PD 患者常见的非躯体症状,30%-40% 的 PD 患者患有严重的抑郁、认知功能障碍,影响其疗效及生活质量[2,3]。许多 PD 患者早期即出现抑郁、认知功能障碍,并受 PD 影响,故 PD 抑郁、认知功能障碍症状和治疗不等同于单纯抑郁、认知功能障碍。目前,PD 抑郁、认知功能障碍治疗的效果不佳。究其原因,除患者依从性差外,抗抑郁、改善认知功能障碍药物与抗帕金森药物之间可能存在相互作用,传统抗抑郁、改善认知功能障碍药物会加重帕金森症状,使治疗变得更加复杂。目前,临床上常使用三环类抗抑郁药(TCAs)、选择性 5- 羟色胺(5-hydroxytryptamine,5-HT)再摄取抑制剂(SSRIs)、5-HT/去甲肾上腺素(Norepinephrine,NE)再摄取抑制剂(SNRIs)等治疗抑郁、认知功能障碍。其中,5-HT/NE 类药物阻断 5-HT 与 NE 神经递质的再摄取,同时对组胺受体、胆碱能受体以及α1 受体具有较低的亲和力,从而避免了类似 TCAs 的不良反应,代表药物为文拉法辛[4]。大量文献报道单纯使用文拉法辛可改善帕金森病患者抑郁症状[5,6]。随着抑郁的缓解,PD 的认知功能也有明显的改善 [7]。有研究指出文拉法辛联合奥氮平治疗 PD 抑郁、认知功能障碍症状比单一用药起效更快[8]。而与单一应用文拉法辛治疗相比,联合认知行为疗法治疗 PD 抑郁、认知功能障碍症状可增强患者的兴趣和满足感,改善患者的人际关系及适应性,可一定程度上治疗患者精神障碍,延缓病情进展[9,10]。而文拉法辛联合认知行为疗法与文拉法辛联合奥氮平治疗 PD 合并抑郁、认知功能障碍症状患者疗效差异尚不明确。本研究旨在对这两种治疗方法的疗效和安全性进行比较。

1 资料与方法

1.1 研究对象

随机选取本院神经内科 2015 年 10 月～2016 年 11 月期间住院及门诊患者 60 例。其中,男 34 例,女 26 例,年龄 54～76 岁,平均(65± 3)岁,发病时间 1～10 年,平均(3.6± 2.1)年。纳入标准:(1) 符合帕金森病的诊断标准;(2) 汉密尔顿抑郁量表(HAMD)评分＞14 分;(3)简易精神状态检查表(MMSE)评分<27 分;(4)未进行抗抑郁及抗认知功能障碍治疗;(5)意识清楚;(6)随访资料完整;(7)知情同意。排除标准:(1)帕金森综合征或者帕金森叠加综合征患者;(2)既往有抑郁病史的患者;(3)既往有认知功能障碍的患者;(4)脑卒中病史的患者,其他因多种原因导致的脑白质发生病变的患者;(5)合并心、肝、肾等严重疾病的患者;(6)不能配合。

1.2 方法

1.2.1 **治疗方法** 入组患者在 PD 正规治疗的基础上,随机双盲分成三组。三组患者年龄、性别、受教育程度的比较差异无统计学意义(P>0.05)。对照组:20 例,男 11 例,女 9 例,给予盐酸文拉法辛胶囊(怡诺思,辉瑞制药有限公司生产)75 mg,Bid。联合奥氮平组:20 例,男 12 例,女 8 例,口服盐酸文拉法辛胶囊、奥氮平片(再普乐,英国礼来公司生产)2.5 mg,Qd。联合认知行为疗法组:20 例,男 11 例,女 9 例,口服盐酸文拉法辛胶囊同时给予认知行为疗法,干预者首先对患者进行心理评估,尽可能地与患者和其家属深入沟通,充分了解患者的家庭背景、生活环境以及心理背景,找准其心理症结;其次,干预者要主动表示对患者的关心,特别是通过掌握患者的负性情绪和行为,多给予患者相应的正能量,鼓励其与医务人员、家属和病友真诚地交流,从各个方面获取鼓励与支持,减少各种负性情绪;然后,干预者通过告知患者相关疾病知识,纠正患者对疾病的误解和猜疑,让其了解积极配合的重要性,鼓励患者改变消极认识,树立积极向上的生活态度;最后,干预者通过教患者听轻音乐,调节呼吸,哭泣发泄,肌松训练等方式帮助患者舒缓负性情绪,放松身心。固定干预者,每日进行 1 次,每次 30 min。

1.2.2 **评价方法** 三组患者在研究期间所服抗 PD 药物及剂量不做调整。于治疗前和治疗后第 4、8 周分别进行 MMSE 评分、HAMD 评分及事件相关电位 P(ERP)300 测试。P300 测试:采用英国牛津 Oxford Medelec Synergy 诱发电位系统完成听觉 P300 检测,电极位置参照国际脑电图学会 10/20 标准,参考电极置于右耳 M2 点,记录电极置于中央中线 Cz 点,前额 FPz 点接地,电极阻抗 <5 K,分析时间为 1000 ms。患者接受双耳的短音刺激,刺激频率为 1 次 /s,刺激持续时间 10 ms,灵敏度为 5 V,带通低频滤波 0.1 Hz,高频滤波 50 Hz,叠加 200 次。其中,标准刺激为频率 1000 Hz,强度为 85 dB,占 80%;偏差刺激为频率 2000 Hz,强度为 95 dB,占 20%,随机出现,穿插在标准刺激中。患者带上耳机,当听到偏差刺激时按鼠标,听到标准刺激不做反应,每例重复 2 次,取平均值。固定操作人员于治疗前及治疗后 4 周及 8 周各检测 2 次,分析指标:记录并分析 3 组受试者治疗前后 MMSE 评分、HAMD 评分、P300 潜伏期及波幅。

1.2.3 **安全性评估** 在治疗前及治疗后 4、8 周分别进行血常规、肝肾功能和心电图检测。

1.3 统计学分析

用 SPSS17.0 软件进行统计分析,计量资料以($\bar{x}$± s)表示,采用 t 检验,以 P＜0.05 为差异有统计学意义。

2 结果

2.1 三组临床疗效的比较

治疗 4、8 周时,三组的 HAMD 评分均较治疗前有不同程度下降,P300 潜伏期较治疗前有不同程度缩短,P300 波幅、MMSE 评分有不同程度升高(P＜0.05),联合奥氮平组和联合认知行为疗法组 HAMD 评分较对照组明显下降,P300 潜伏期较对照组明显缩短,P300 波幅、MMSE 评分明显升高 (P＜0.05),

联合认知行为疗法组 HAMD 评分较联合奥氮平组明显下降，P300 潜伏期较对照组明显缩短，P300 波幅、MMSE 评分明显升高(P<0.05)，见图 1、图 2 及表 1。

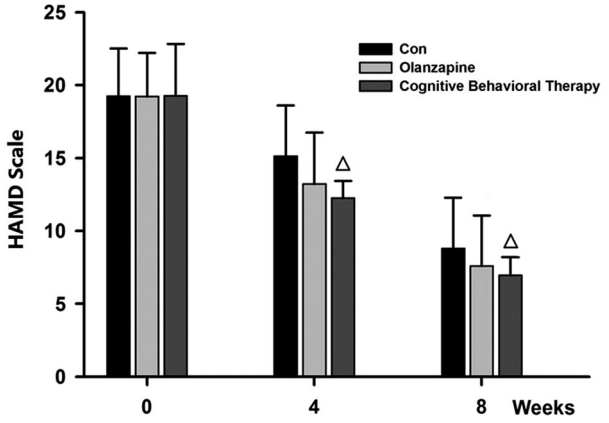

图 1 三组患者治疗前、治疗 4 周与治疗 8 周后的 HAMD 量表得分对比

Fig.1 Comparison of the HAMD scores between the three groups before treatment and at 4, 8 weeks after treatment

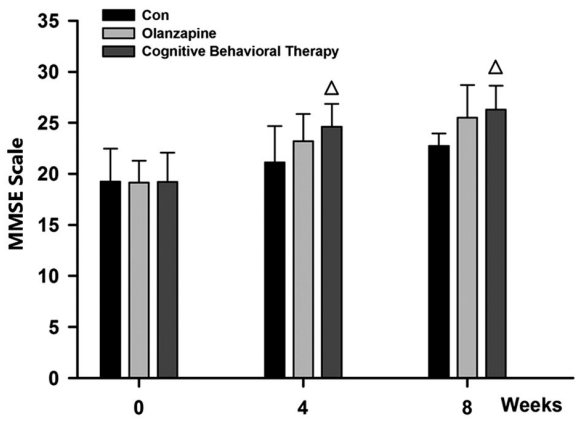

图 2 三组患者治疗前、治疗 4 周与治疗 8 周后的 MMSE 量表得分对比

Fig.2 Comparison of the MMSE scores between the three groups before treatment and at 4, 8 weeks after treatment

表 1 三组患者治疗前、治疗 4 周与治疗 8 周后 P300 潜伏期、波幅的比较($\bar{x}\pm s$)

Table 1 Comparison of the P300 latent period, amplitude between the three groups before treatment and at 4, 8 weeks after treatment($\bar{x}\pm s$)

	Before treatment			At 4 weeks after treatment			At 8 weeks after treatment		
	Con	Olanzapine	Cognitive Behavioral Therapy	Con	Olanzapine	Cognitive Behavioral Therapy	Con	Olanzapine	Cognitive Behavioral Therapy
P300latent period(ms)	325.65± 26.34	325.87± 26.56	325.76± 26.12	322.53± 24.78	320.54± 23.14	318.23± 21.5	319.46± 22.45	315.78± 24.12	311.67± 23.54
P300 amplitude (μV)	2.22± 0.98	2.23± 1.03	2.22± 0.87	2.26± 1.07	2.30± 1.43	2.33± 1.12	2.30± 1.34	2.38± 0.96	2.43± 1.23

2.2 三组患者不良反应发生情况的比较

三组用药前后血、尿常规、肝功能、肾功能、心电图均无明显异常，对照组发生口干 1 例，联合奥氮平组发生嗜睡 2 例，头晕 1 例，口干 1 例，联合认知行为疗法组发生胃肠道反应 1 例，口干 1 例，三组均无特殊不良反应，坚持服用后患者能耐受。

3 讨论

抑郁是 PD 的常见症状，可早于 PD 运动症状出现，贯穿 PD 病程。PD 抑郁的发病基础与中枢神经系统的器质性病变相关，但其发生机制尚不明确。目前研究提出的理论包括 5-HT 及 NE 的减少、额叶皮质烟碱受体减少[11]，多巴胺、去甲肾上腺素系统受损、损害累及额叶等[12]。PD 患者常合并认知功能障碍，发病率高达 20%[13]。关于 PD 认知功能障碍的发病机制及其相关病变部位目前还不明确[14,15]，有研究推测可能起源于大脑皮质，特别是双侧额叶的损害[16]，这与 PD 抑郁发病部位相似，额叶的损害将进一步导致执行功能的下降，执行功能下降正是 PD 认知功能障碍的核心表现[17]。PD 抑郁和认知功能障碍有相似的发病机制，有研究显示抑郁会加重 PD 患者的认知功能障碍[18]，而改善 PD 患者抑郁有助于提高认知功能[7,19-20]。

文拉法辛具有作用于 5-HT 和 NE 能神经的双重作用，尤其在较高剂量时可抑制 NE 再摄取[21]，相关文献研究也证实文拉法辛对 PD 抑郁、认知功能障碍的起效迅速、疗效好，且药物依从性较好[5,6,22,23]。本研究中，实验组均采用文拉法辛作为基础治疗。奥氮平作为一种非典型抗精神病药物近年来被逐渐应用于抑郁症的辅助治疗或作为增效剂使用[24-26]。有研究显示在治疗 PD 抑郁、认知功能障碍方面，奥氮平有确切的辅助和增效剂作用，与文拉法辛联合治疗 PD 抑郁、认知功能障碍症状比单用文拉法辛效果好[8]。聂利珞等研究发现文拉法辛联合认知行为疗法对 PD 抑郁、认知功能障碍有效[27]，有研究认为认知行为疗法的有效性可以与药物治疗或者心理动力学的疗效相比[28]，认知行为疗法有助于提高使用抗抑郁药治疗的患者的疗效[29]。

本研究结果显示：文拉法辛联合认知行为疗法的治疗效果优于文拉法辛联合奥氮平组和单用文拉法辛组，与关报道相同[28]。究其原因，我们认为主要有以下三个方面。首先，认知行为疗法能有效改善 PD 患者抑郁和认知功能障碍。PD 抑郁、认知功能障碍是发生在社会心理因素下的异质状态(heterogeneous condition)，其药物治疗的疗效很可能受到如社会环境、生活应激、人格因素和治疗依从性等各个方面因素的影响[30]。而 PD 患者多为老年人，本身常合并慢性基础性疾病，再加上抑郁和认知功能障碍，得病后更容易产生心理问题进而影响到 PD 药物治疗的疗效，加重抑郁和认知功能障碍症状。而认知功能疗法在对患者进行心理评估的基础上，改善患者的不良心境[31]。其次，认知行为疗法能增强患者治疗的依从性，Kendler 等[32]认为心理社会应激的持续存在是导致抑郁、认知功能障碍疗效不佳

的重要原因。PD 抑郁、认知功能障碍患者往往治疗时间长、就医次数多、药物使用数量大、种类繁杂，自理能力变差等因素造成其产生心理问题，进而对药物治疗的依从性下降。而认知功能疗法通过对患者的治疗，能使患者关注到自身积极力量，调动其主动性，配合进行治疗。奥氮平作为文拉法辛的辅助和增效剂作用，促进其药效进一步发挥，并不能弥补药物治疗的不足，不能有效增加患者治疗的依从性，甚至还可能因药物不良反应而降低治疗依从性。最后，认知行为疗法能修复部分中枢神经功能。脑组织可塑性理论认为脑组织可以通过学习、训练的方法修复部分因损伤而丧失的神经功能[33]。而认知行为疗法能通过积极的干预方法，激发出患者潜能，改善部分受损区域功能，从而改善患者的抑郁和认知功能障碍[26]。

综上所述，文拉法辛联合认知行为疗法治疗 PD 抑郁、认知功能障碍疗效确切，能显著改善患者抑郁症状，提高患者的认知功能，疗效较单用文拉法辛或文拉法辛联合奥氮平治疗更好，且安全性高。本研究存在一定局限性，如样本量偏小，未做卫生经济评价等，这些均有待进一步研究。

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