

· 帕金森病专题 ·

帕金森病抑郁的治疗新进展

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【摘要】 抑郁是帕金森病(PD)常见的非运动症状,其严重影响患者的生活质量,增加照料者的负担。然而,PD抑郁往往不易识别,治疗率较低。PD抑郁的治疗虽不乏可选择的药物和方法,但尚缺乏高质量的循证医学证据。现从药物、重复经颅磁刺激、脑深部刺激、电休克、认知行为疗法等方面阐述PD抑郁的治疗进展。

【关键词】 帕金森病; 抑郁; 治疗; 综述

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【Abstract】 Depression is a frequent non-motor symptom of Parkinson disease (PD). It may have serious impacts on the quality of life of PD patients and their caregivers. Depressive symptoms in PD often remain unrecognized, as a result, it remains untreated. Although there are many selectable drugs and methods for the treatment of PD depression, there is no evidence of high quality evidence-based medicine. This review illustrates progress of PD depression treatment from respects of drugs, rTMS, deep brain stimulation, electroshock, cognitive behavioral therapy and so on.

【Key words】 Parkinson disease; Depression; Treatment; Review

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帕金森病(Parkinson disease, PD)是常见的中枢神经系统变性疾病,抑郁是其常见非运动症状之一,文献报道PD患者抑郁的发病率为2.7%~90%^[1],而治疗率仅20%~30%^[2]。研究证实PD抑郁不仅可以加快患者运动症状的进展,而且严重影响其日常生活能力,增加照料者的负担^[3]。因此,了解PD抑郁治疗的现状、分析未来可行的方法凸显重要。本文检索国内外近年关于PD抑郁治疗的随机对照研究(randomized controlled trial, RCT)、综述及Meta分析文献,结合国内外PD抑郁相关治疗指南,分别从药物、重复经颅磁刺激、脑深部刺激、电休克、认知行为疗法等方面,全面综述PD抑郁的治疗进展。

一、药物治疗

1. PD治疗药物: 部分PD抑郁和运动症状波动相关,表现为“关期”抑郁,持续的多巴胺能刺激药物改善运动症状波动的同时,改善抑郁症状。近期

一项小样本前瞻性临床研究,将口服左旋多巴/卡比多巴转变成肠内输注治疗3个月,患者的运动症状波动及抑郁症状均明显改善^[4]。另一项为期6个月的多中心前瞻性观察研究显示阿扑吗啡能改善晚期PD患者的情绪障碍,且疗效优于左旋多巴肠内输注治疗^[5]。临床研究显示多巴受体激动剂普拉克索能有效改善PD患者的抑郁症状^[6]。最近研究发现,普拉克索能降低脂多糖诱导的大鼠海马区炎症介质的水平,提示其抗抑郁效应还可能依赖于其抗炎机制^[7]。罗匹尼罗是选择性强效非麦角类多巴胺受体激动剂,研究发现罗匹尼罗显著改善伴运动症状波动的PD患者的抑郁症状^[8]。此外,国内一项RCT研究显示罗匹尼罗辅助治疗能改善晚期PD患者的抑郁量表评分^[9]。而多巴受体激动剂罗替戈汀对PD抑郁疗效的研究结果却有所不同。RECOVER研究发现罗替戈汀组较安慰剂组显著改善

PD患者贝克抑郁量表评分^[10]。而近期一项RCT研究显示,与安慰剂对照相比,罗替戈汀并没有显著改善PD患者的抑郁症状^[11]。新一代单胺氧化酶抑制剂雷沙吉兰以治疗PD的推荐剂量1 mg/d,对PD中重度抑郁症状无改善,而较大剂量雷沙吉兰(2 mg/d)则可能具有改善患者运动和抑郁症状的双重功效^[12-13]。

2. 抗抑郁药物:近年关于抗抑郁药治疗PD抑郁的RCT研究较少,主要为Meta分析和综述,其中两项关于三环类抗抑郁药(tricyclic antidepressants, TCAs)和选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)治疗PD抑郁的Meta分析显示两者均有良好的疗效和安全性^[14-15],但TCAs可能导致或加重某些非运动症状,如口干、便秘、精神错乱和记忆力下降等,因此更多PD抑郁患者首选SSRIs治疗^[16]。PD患者抑郁症状的不同临床表型,对于抗抑郁药物的反应同样存在差异,一项纳入115例患者的RCT研究结果显示,帕罗西汀或文拉法辛治疗过程中,患者的情感症状较早改善,然后是躯体性症状,而认知功能的改善则需要更长时间^[17]。

二、重复经颅磁刺激

重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)是一种无创的利用脉冲磁场对大脑皮质特定部位给予重复刺激的治疗手段。rTMS作为一种非侵入性方法,无需手术和麻醉,且其耐受性较好。但目前关于rTMS治疗PD抑郁的研究数据并非一致。Xie等^[18]纳入8项rTMS治疗PD抑郁RCT进行Meta分析提示,与假刺激组相比,rTMS可显著改善汉密尔顿抑郁量表评分($P < 0.01$)。亚组分析显示,高频rTMS和SSRIs抗抑郁疗效相当,且能改善运动症状。随后一项随机、双盲、安慰剂对照研究结果显示,双侧初级运动皮层高频rTMS治疗PD轻度或中度抑郁有效,但对重度抑郁患者的疗效仍需进一步研究^[19]。一项小样本随机单盲模拟对照研究支持,左侧前额叶背外侧区皮层高频rTMS是治疗PD患者抑郁症状的有效方法^[20]。但是,近期另一项纳入61例PD抑郁患者的多中心、随机、双盲、模拟对照临床研究结果与之不同,结果提示左侧前额叶背外侧区皮层高频rTMS对情绪症状无改善^[21]。最近一篇纳入9项RCT的Meta分析提示高频rTMS治疗PD抑郁症状的疗效并不优于假刺激组或SSRIs组^[22]。因此,rTMS对PD抑郁的疗效仍需大样本RCT验证。

三、脑深部电刺激

近年来,脑深部电刺激(deep brain stimulation, DBS)治疗已成为PD患者全程管理中不可或缺的一环,而其对PD抑郁症状的影响,研究结果尚不一致。有研究报道老年人群DBS术后抑郁症状有短暂的改善,但疗效持续时间较短^[23]。另有文献报道,DBS术后患者出现焦虑、抑郁等精神症状,但多在短期内改善^[24]。而Meta分析提示结果的不一致,可能为手术靶点和研究方法的异质性导致^[25]。丘脑底核(subthalamic nucleus, STN)能否成为改善PD患者抑郁症状的有效靶点呢?近期两项STN-DBS术后研究,分别随访1个月及6个月和6个月及2年,发现均显著改善PD患者抑郁症状^[26-27]。然而,与苍白球内侧DBS(globus pallidus internus-DBS, GPi-DBS)比较,GPi-DBS虽然可能加重部分患者抑郁症状,但荟萃分析显示STN-DBS和GPi-DBS手术前后患者的抑郁量表评分改变,两组间比较差异无统计学意义^[23]。因此,DBS手术方法治疗PD抑郁的有效性仍需大样本验证,同时对手术靶点的进一步探索研究,将有助于提高手术疗效^[25]。

四、电休克疗法

电休克治疗(electroconvulsive therapy, ECT)是治疗难治性抑郁最有效的治疗形式,有研究表明ECT可改善PD患者的抑郁症状和运动功能,尤其可改善患者难治性精神症状^[28-29]。纳入43篇相关文献的Meta分析,结果ECT干预后93.1%的PD患者抑郁症状改善,83%的患者运动症状改善,94%的患者并未出现认知功能损害,提示ECT对PD患者的抑郁症状安全有效。最近,为避免ECT可能导致部分患者出现一过性精神错乱、短暂的意识模糊、跌倒、尿潴留等不良反应,Calderon等^[30]采用一种新ECT技术,即右侧超短脉冲ECT,进行一项开放性初步研究,结果显示其对PD患者运动、情绪等多方面有潜在疗效,并且对认知功能影响较小,安全、易行,但有效性和安全性仍需大样本RCT证实。总之,ECT对PD患者的抑郁症状和运动症状均有潜在疗效,有望成为治疗PD合并难治性抑郁的重要方法。

五、认知行为疗法

心理或行为干预包括认知行为疗法(cognitive behavioural therapy, CBT)、心理剧、教育、行为疗法和多学科康复锻炼等,其中CBT是目前研究热点。CBT通过促进PD患者心理健康和改善总体的生活质量帮助患者战胜生活中的各种挑战,强调放松锻炼、行为激活、解决问题和心理教育,进而改善抑郁

症状。CBT治疗包括个体、团队、远程等方式。有RCT证实个体CBT治疗,对PD抑郁、焦虑、社会功能、积极性、PD运动症状均显著改善,若照料者参与疗效可能更佳^[31-33]。团队CBT治疗仅有部分小样本的临床研究,但多数提示其有效易行,且具有较好的远期疗效,甚至优于心理教育干预治疗^[34-35]。应用现代技术进行网络远程CBT治疗PD抑郁,内容涉及心理教育、放松锻炼、活动安排和睡眠管理等,症状亦有显著性改善,但患者满意度较低^[31]。对于早期PD抑郁患者,非药物治疗如CBT和简易心理治疗等已成为首选,但要求患者需具备一定的认知和言语交流能力^[1]。而对于药物治疗或rTMS治疗疗效欠佳的患者,仍可以给予无明显不良反应的行为干预治疗,近期一项纳入20项RCT研究的Meta分析评估了药物、行为干预及rTMS治疗PD抑郁的疗效,结果提示CBT和SSRIs能显著改善PD患者的抑郁症状^[36]。此外,还有其他的物理治疗手段如强光疗法、有氧运动如太极等对PD抑郁可能具有潜在疗效^[37-38],但仍需进一步研究证实。

综上,虽然PD抑郁的治疗尚缺乏高质量的循证医学证据,但不乏可选择药物和方法,临床医生需要分析患者抑郁的严重程度、临床表型,遵从个体化原则,权衡利弊,多学科合作,综合治疗。

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