

早期改善在抗抑郁药治疗重度抑郁症(MDD)中的研究进展

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【摘要】 在第2周末达到早期改善(early improvement)的重度抑郁症(major depressive disorder, MDD)患者继续维持原治疗方案只有3%能达到临床治愈,但尽管早期改善有较高的阴性预测值,阳性预测值却不理想。本综述整理现有的研究中除了17项汉密尔顿抑郁量表总分的减分率外,还有哪些指标能判断早期改善,早期改善的预测效果受到什么因素影响,能否协同这些因素提高早期改善的预测效果。用以指导早期换药,降低患者接受无效治疗的时间,降低治疗费用,增加患者对治疗的信心。

【关键词】 早期改善; 抗抑郁药; 重度抑郁症(MDD)

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Advances in early improvement of antidepressants for treating major depressive disorder (MDD)

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【Abstract】 Early improvement in the first 2 weeks can only predict 3% non-remission in major depressive disorder (MDD) patients who continued the original treatment. However, the positive predictive value of early improvement was unsatisfactory despite of higher negative predictive value. This report provides an updated review about the indicators of early improvement and the influence factor of the predictive value of early improvement.

【Key words】 early improvement; antidepressants; major depressive disorder (MDD)

抗抑郁药治疗的早期改善广义指所有在抗抑郁药物治疗抑郁症起效前能预测抗抑郁药疗效的指标变化^[1],目前纳入指南的定义为治疗2周后汉密尔顿抑郁量表17项版本^[2](17 items of the Hamilton Scale for Depression, HAMD-17)总分的减分率为20%^[1-3]。最初的抗抑郁药单药治疗只有一半的患者在2个月后能出现疗效,若最初的治疗效果不佳

会伴随治疗费用增加,门诊患者可能增加自杀风险,患者的负性认知可进一步被巩固,对治疗失去信心进而影响治疗效果^[4-5],因此许多研究使用早期改善这个概念以尽早识别疗效,指导调整治疗方案^[6]。为了进一步提升第2周预测疗效,除HAMD-17的总分研究外,本文还综述了还有哪些指标能判断早期改善,早期改善的预测效果受到什么因素影响,为

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临床制定重度抑郁症(major depressive disorder, MDD)早期优化治疗的策略提供参考。

判断 MDD 早期改善的指标

抑郁量表总分 使用抑郁量表评估早期改善的研究起源于 1990 年代,在当时延迟起效假说的背景下,为了更准确地评判抗抑郁药起效的时间,Stassen 等^[7],Nobler 等^[8],Derivan 等^[9]尝试生存分析、模式分析等方法,测定多种量表的多个阈值在治疗早期的判断疗效。80 年代用作主流的 HAMD-21 以及 CGI 在判断早期疗效中灵敏度不足,蒙哥马利抑郁量表(Montgomery Asberg Depression Rating Scale, MADRS)被认为比 HAMD-17 有更好的特异性,而 HAMD-17 的灵敏度较高^[10-11],抑郁的自评量表如 16 条目简易抑郁症自评量表(the 16-item Quick Inventory of Depressive Symptomatology, QIDRS)常在同时有 HAMD-17 或是 MADRS 的前提下用以判断早期改善的疗效,较少单独使用。

有了上述基础,Nierenberg 等^[12-13]研究氟西汀治疗 MDD 患者测定了第 2 周 HAMD-17 总分减分率 20% 的阳性与阴性预测值均较 30% 高,Szegedi 等^[14]认为米氮平治疗组疗程的第 2 周以及使用帕罗西汀组疗程的第 3 周, HAMD-17 总分减分率 20% 预测痊愈的阴性预测值达到最大值。前述研究对于指导早期换药的不足之处在于,阴性预测值不足以成为支持早期换药的证据^[15]。

目前抗抑郁药物治疗的第 2 周 HAMD-17 总分减分率 20% 这个阈值大多引自 2007 年 Stassen 等^[16]的随机对照试验与另一项 Meta 分析^[17]。Szegedi 基于前述研究结果,选择了第 2 周 HAMD-17 减分率 20% 这个值,证实早期改善对抗抑郁药的疗效有较好的阴性预测值^[1],并且受后续的系统综述支持^[6,17],但是也有部分研究认为第 2 周早期改善的阴性与阳性预测值不足^[18],且未达到早期改善者调整治疗方案后大部分能达到的疗效^[19],仍缺乏为早期改善如何指导换药提供证据的研究^[20]。

早期症状改善 2004 年 Katz 等^[21]提出应进一步细分不同药物所对应不同的 MDD 早期症状改善,以帕罗西汀为例,在第 2 周对焦虑的改善较抑郁的改善更能说明药物的起效,但是后续对早期症状改善的研究之间结果差异大。Harada 等^[22]认为早期焦虑改善预测效果不显著,Katz 等^[23]认为除了睡眠相关的条目之外,大多数条目的减分均能促进临

床治愈,尤其以焦虑、自杀观念以及阻滞这些条目的减分的预测效果更加明显;日本学者同样提出兴趣减退条目的改善能较好地预测第 8 周的痊愈,罪恶感与躯体症状的改善与疗效相关^[24-25];Farabaugh 等^[26]则认为对于氟西汀治疗的患者,治疗早期食欲的改善能预测痊愈。我国几个小样本研究之间结果各异,张美霞等^[27]基于帕罗西汀的研究认为汉密尔顿量表之中各个症状的早期改善均能预测,其中预测值依次排序为情绪、睡眠、精神焦虑、认知以及躯体焦虑。程文桃等^[28]基于米氮平的研究同样认为情绪因子较精神与躯体焦虑有较好的预测效果。治疗早期的症状改善受到文化、人格、抑郁的分型等多种因素影响,在讨论个别症状的同时值得探讨与控制各个症状的影响因素。

功能改善 抑郁症具有较高的致残率,在抗抑郁药物治疗的过程中,语言能力、工作能力与社会功能的改善也预示着治疗的效果。Wagner 等^[29]发现治疗效果较好的患者可以观察到在治疗 2 周后语言流畅性明显的提升。Jha 等^[30]认为治疗后第 6 周前工作能力自评结果的早期改善能够预测未来的抗抑郁药疗效,他们将工作能力的改善分为显著改善、微小改善和无改善 3 种,显著改善组在治疗后的 3 个月以及 7 个月均有较高的临床痊愈比例。Jha 等^[31]同时基于 Uher 的抑郁症治疗轨迹理论,测试心理社会功能是否为区别不同治疗轨迹的潜在因子,他们发现第 6 周时的心理社会功能改善能预测第 3 个月与 7 个月均有较高的临床痊愈比例,心理社会功能比抑郁症状更能预测远期疗效。

脑电图 脑电图的早期改善是各种辅助检查中研究最成熟的,在前额叶可观测到前扣带回以及眶额叶皮层^[32],这些脑区活动产生的投影的 θ 波段^[33]活动被认为与抗抑郁药疗效相关^[34]。在 Iosifescu^[35]的推动下, θ Cordance 值与抗抑郁药反应指数已是预测抗抑郁药疗效较成熟的技术。Iosifescu 等^[35-36]发现在药物治疗开始 1 周后, MDD 患者额颞部 θ 波段相对功率显著低于无效者,预测 HAMD-17 减分率 50% 具有 76% 的灵敏度和 93% 的特异性,其他的研究也得到了 65%~75% 的精准度^[37-38],但是这并非脑电图技师常规掌握的技术,涉及到与脑电图跨学科的合作,在临床使用上难以普及。

功能影像学 使用功能影像学能够进一步研究脑电变化背后神经元活动的全貌,但是由于功能影

像学价格昂贵、预约时间长、难以频繁进行检查以及个体化诊断技术仍旧不成熟的特点,尚不能辅助临床诊断。尽管如此,功能影像学能够辅助我们了解早期改善背后的机制,Spies等^[39]发现早期改善与默认模式网络有关,研究认为抗抑郁药早期改善主要相关的脑区在默认模式网络,基线时在静息态转为任务态时,默认模式网络被抑制得越多,越能预示早期改善的发生。Hou等^[40]发现在基线时左侧苍白球的时间变异性较高者,较易达到早期改善。目前涉及早期改善的功能影像学研究较少,研究异质性大,治疗前的扫描仅仅能解释存在什么特征者较容易达到早期改善,而不能解释药物治疗早期脑影像的改变。

认知心理试验 Harmer等^[41]在患者服药后3h做认知心理学的试验,服用瑞博西汀的抑郁病患表现出对于乐观表情较好的反应,对于乐观的形容词有较快的反应速度以及和记忆力。他们提出抗抑郁药早期服用后即可立即调节抑郁患者的情绪处理。这些乐观的认知改变可能导致将社交信息赋予较正面的信号,对正面信号的叠加数天后才会产生认知的改变,以此提出了抗抑郁药的效果叠加假说。Tranter等^[42]基于西酞普兰的研究同样认为在服药后效果即可观测到,并认为在治疗的第2周愉快表情的增加可以有效预测第6周的治疗反应。

血清学 血清脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的早期改善对疗效有预测价值。沈仲夏等^[43]在基线及第2周测定BDNF,发现早期改善组与非早期改善组2周内BDNF的增加值有统计学意义。2017年Bare等^[44]结合脑电图、血清学、量表等指标在治疗第1周建立抗抑郁药的预测模型,模型中第1周血清BDNF水平联合第2周的抑郁症状早期改善可预测抗抑郁药的疗效。C反应蛋白、IL-6或皮质醇的研究仅涉及以基线的血清水平对起效进行预测,未涉及起效前这些指标的改善是否与抗抑郁药的疗效有关。

影响MDD早期改善的因素

性别 去甲肾上腺素药物如度洛西汀等对MDD男性患者早期改善的效果较女性好,女性的早期症状改善不能预测第8周的痊愈^[45-46],但是对于伴随躯体疼痛的女性,度洛西汀治疗第2周躯体疼痛的改善能够预测第8周的痊愈^[47]。对于5-羟色胺再摄取抑制剂,女性的早期改善有较好的预测效果^[48-49]。

年龄 许多文献报导年龄较大者较容易达到早

期改善^[50-51],但是仅止于将年龄罗列在结果部分,未在讨论部分以及摘要部分提及。目前尚未有研究系统性描述年龄与早期改善的关系。抑郁症患者入组的年龄为30岁以下有较高的双相抑郁的风险,然而纳入年龄大于40岁的女性抑郁者可能受到绝经期的内分泌紊乱、脑部血管硬化等因素影响,需要纳入多种因素综合分析,目前尚未有研究涉及。

抗抑郁药种类 Katz等^[21]认为应该用每个药物不同的症状群作为起效的判断,研究中以帕罗西汀为例,在第2周焦虑的改善较抑郁的改善更能说明药物的起效;米氮平被认为是起效较快的抗抑郁药^[52]。但是大部分的研究否认不同的抗抑郁药存在早期起效时间的区别,从Quitkin等^[53]到Stassen等^[7]均报导单药抗抑郁治疗(丙米嗪,吗氯贝胺,阿米替林,氟西汀,氧奈帕明,米氮平和帕罗西汀等药物)未发现药物之间有明显的差异,大型临床试验如抑郁症的序贯治疗研究(Sequenced Treatment Alternatives to Relieve Depression, STARD)否认早期起效以及不同药物之间起效时间的差异^[54-55]。

剂量 剂量与早期改善的关系仍不明确,大部分研究均使用个体化的治疗剂量,未着重报导剂量对早期改善的影响。一项大型回顾性研究调查了文拉法辛剂量与早期改善的关系,发现较小剂量比大剂量的治疗更容易达到早期改善,但是这个结果与种族有关,亚洲人用药的剂量较小,较易达到早期改善,而其他种人用药的剂量较大,较难达到早期改善^[51]。

治疗前的阈值下症状 焦虑对于早期改善的关系目前仍有争议,治疗前焦虑症状明显的患者治疗效果差^[56]。躯体症状可能在不同地区具有文化差异,其在欧美被认为是炎症因子所致,预示着疾病治疗周期长、效果较差^[57]、改善较慢^[58]。躯体疼痛是抑郁患者预后较差的因素^[59],存在躯体症状的患者即使在第2周达到早期改善的标准,但是往往难以在第8周达到痊愈^[60]。在东亚的研究中,躯体症状与罪恶感和焦虑情绪相比反而属于改善快且对于预后较好预测效果的症状^[25]。

基因组 基因组可作为临床症状和疗效预测的辅助指标,增加临床症状的变化预测末了疗效的可信度。Ramasubbu等^[61]发现5-HTTLPR L-等位基因纯合子的患者对艾斯西酞普兰或喹硫平有良好的反应,在治疗第1周即可发现杏仁核的过度激活的改善,能预测第8周的缓解。Su等^[62]纳入ADCY9、HTR1B、GNB3、HTR2A、TPH2和

SLC6A4 6 个候选血清素能基因,其中 TPH2 rs4570625 GG 携带者更容易达到抑郁和焦虑症状的缓解,与 TT 基因型携带者相比,GT 或 GG 基因型患者表现出更有利的抑郁症状严重程度。ADCY9、HTR1B 和 HTR2A 关系较弱。

展望 以 HAMD-17 减分率 20% 作为判断早期改善的依据已获得较多认可,也有许多研究致力于阈值下症状、辅助检查等多方面判断早期改善,但是这些研究成果无足够证据能结合临床的治疗方案调整以提升疗效。第一,这些影响因素与指标在这几年被分别报道,但尚无研究整合这些因素并制作在第 2 周预测未来疗效的模型;第二,目前仍少有对不同治疗剂量、年龄、人格、抑郁症的亚型、种族、童年创伤等可能对早期改善有影响的重要临床因素进行深入的探讨,明确这些因素对早期改善的影响可在早期优化治疗中给予更具可操作性的建议。

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