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孤独症谱系障碍治疗的研究进展

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摘　要：孤独症谱系障碍又称自闭症，是一种常见的神经发育障碍，核心特征表现为社交互动的持续性障碍，以及行为、兴趣和日常活动的刻板重复行为。自闭症病因复杂，迄今为止，还没有能完全治愈的方案。该文概述了孤独症谱系障碍的定义、流行病学数据和临床表现，并介绍了常用的治疗方法，包括药物疗法、行为疗法和替代疗法等。此外，该文还总结了一些新兴的治疗方法，如干细胞疗法、动物辅助治疗和基因治疗等。最后，该文对自闭症的研究现状进行总结，对未来的研究方向进行了展望，呼吁进行更多的研究来探索自闭症的致病机制和诊断依据。

关键词：孤独症谱系障碍；自闭症；治疗；干预
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Research progress in the treatment of autism spectrum disorders

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Abstract: Autism spectrum disorder, also known as autism, is a common neurodevelopmental disorder characterized by persistent difficulties in social interaction and stereotypical repetition of behaviors, interests, and daily activities. The causes of autism are complex, and to date, there is no complete treatment for autism. This article summarizes the definition, epidemiological data, and clinical manifestations of autism spectrum disorders, and describes common treatment methods, including pharmacotherapy, behavioral therapy, and alternative therapy. In addition, the paper also summarizes some emerging therapeutic approaches, such as stem cell therapy, animal-assisted therapy, and gene therapy. Finally, this paper summarizes the current research status of autism, prospects the future research direction, and calls for more research to explore the pathogenesis and diagnostic basis of autism.

Key words: autism spectrum disorder; autism; treatment; intervention

孤独症谱系障碍 (autism spectrum disorder, ASD)，又称自闭症，是一种神经发育障碍，包括孤独症、阿斯伯格综合征和未分类的广泛性发育障碍，患者一般在 3 岁前即可表现出相关症状。过去 10 年，自闭症的患者人数迅速增加，美国疾病控制与预防中心 (Centers for Disease Control and Prevention, CDC) 关于自闭症发病率的最新一项估计表明：自闭症年发病率为 2.76%，并且男孩的患病率显著高于女孩 [1]。根据美国精神病学协会第五版《精神障碍诊断与统计手册》，自闭症患者有两个核心特征：社会沟通与人际交往的障碍以及行为模式受限、刻板行为和兴趣受限。此外，自闭症患者容易出现一系列神经系统并发症，例如癫痫、大头畸形、脑积水、脑瘫、偏头痛和神经系统先天性异常等症状 [2]。自闭症的发病机制尚不明确，遗传因素、父母精神类疾病、胎儿接触精神药物等因素都可能与其有关。临床上主要采用综合性治疗，包括药物治疗、行为矫正、教育训练和物理治疗等 [3-4] 手段，且更早的

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诊断和干预治疗可能对自闭症患者的康复更有利 [5]。

1 药物治疗

目前国际上还没有针对自闭症核心症状的批准药物，然而药物可能在治疗其并发症及相关症状方面发挥作用 [6]。临床上主要使用抗精神病药、抗抑郁药对自闭症患者进行治疗；另外，催产素或加压素受体拮抗剂及营养补充剂的使用似乎也对自闭症有一定的治疗作用。本文还调研了最新研发的自闭症治疗药物，这些药物在临床试验中已经显示能改善自闭症的某些症状；但值得注意的是，这些药物还未上市，临床研究还在进行中，其有效性和安全性仍需要进一步确定。

1.1 抗精神病药物

相对于一般人群，自闭症患者的情绪问题更加严重，主要表现为易怒和攻击性行为 [7]，这严重影响了患者的身体健康，并导致患者生活质量的下降和自杀死亡率的增加。目前临床上常用的抗精神病药物主要有利培酮(risperidone)、阿立哌唑(aripiprazole)、喹硫平 (quetiapine) 等。

利培酮、阿立哌唑是目前美国食品和药品管理局 (Food and Drug Administration, FDA) 批准用于自闭症相关症状治疗的仅有的两种药物 [8]。其中，利培酮是苯丙异噁唑类抗精神病药物，对多巴胺受体(D2)、5- 羟色胺 (5-hydroxytryptamine, 5-HT) 有阻断作用，能抑制血清素和去甲肾上腺素的再摄取；阿立哌唑是喹啉酮类抗精神病药，是 D2 和 5HT-1a 受体的部分激动剂以及 5HT-2a 受体的拮抗剂，阿立哌唑在细胞内信号通路中表现出功能选择性，要求D2 受体的占有率大于 90% 才能具有临床活性，因此不会产生那么多锥体外系症状。研究表明，对自闭症或多动症患者单独使用利培酮或阿立哌唑，或联合其他药物治疗，均能改善患者的核心体征和症状 [9-12]。其中利培酮最适合激越、攻击性、冲动症状，而阿立哌唑适合激动、烦躁症状；此外，对利培酮、阿立哌唑治疗无效的侵略性和情绪不稳定，可以使用喹硫平补充治疗 [13]。并且研究表明在患者的生命早期就开始进行药物干预，可以潜在地消除自闭症的核心体征和症状 [14]。

在药物不良反应方面，多数临床试验研究表明抗精神病类药物的使用可能会导致患者的锥体外系反应，体重和食欲增加，甚至有时会囤积食物 [15]；利培酮和阿立哌唑的使用还可能增加骨折的风险 [16]。除此之外，利培酮的使用可能导致高催乳素血症，在母乳喂养期间需谨慎使用；阿立哌唑与较低的高胆固醇血症、葡萄糖失调、心血管异常和高催乳素血症的发生率相关；喹硫平的使用应考虑神经阻滞剂恶性综合征，嗜睡、直立性低血压和头晕是喹硫平最常见的副作用。因此，在临床上对受到自闭症严重损害的儿童和青少年使用此类抗精神病药物时，应当仔细监测其不良反应 [17]。

1.2 抗抑郁药

尽管抗抑郁药物改善自闭症核心症状的证据不足 [18]，但抗抑郁药物尤其是选择性血清素再摄取抑制剂 (selective serotonin reuptake inhibitors, SSRI)，正在临床上广泛使用以改善自闭症患者的焦虑抑郁、刻板行为。SSRI 能够阻断神经元再摄取血清素，将更多的血清素用于改善神经元之间的信息传递，目前临床上常用的 SSRI 主要有舍曲林、氟西汀和氟伏沙明等。Nanjappa 等 [19] 汇总相关研究指出，舍曲林能有效治疗自闭症人群中与过渡期和激越相关的焦虑，氟西汀对与自闭症相关的重复行为有效，氟伏沙明显示出在应对患者挑战性行为 (例如重复性自伤或攻击行为) 方面的疗效。然而抗抑郁药的使用可能会产生轻生念头，怀孕期间接触 SSRI 类药物还可能还会导致后代自闭症症状 [20]。

1.3 其他药物

1.3.1 催产素和加压素

催产素和加压素都是垂体分泌的肽激素，分别因其对分娩哺乳和血压及尿液浓度的外周内分泌作用而闻名。自闭症患者的社交障碍可能与催产素水平有关，自闭症患者唾液中催产素的水平较低 [21]，而催产素能促进社会学习，帮助自闭症患者发展新的关系 [22],但是催产素如何进一步与行为疗法配对，以增强学习和改善社会行为,还需要进一步研究 [23]。加压素与催产素的作用类似。如何寻求个性化的治疗方案仍需新一步研究 [24-25]。

1.3.2 营养补充剂

由于拒绝进食及消化不良，自闭症患者更容易出现营养缺乏及精神问题。虽然营养补充剂不能直接针对自闭症的核心症状，但是营养补充剂可以消除营养不良带来的副作用。Adams 等 [26] 汇总针对自闭症的临床试验，表明使用褪黑素、Omega-3 脂肪酸、维生素、叶酸、草药配方、谷胱甘肽等共 58 种营养补充剂对自闭症患者是有益处的；此外，无麸质和酪蛋白饮食、生酮饮食、益生元或益生菌等也同样显示出积极的结果 [27]，但仍需要更多的证据。

1.4 正在研发的新药

目前最新研发的自闭症治疗药物包括巴洛伐坦(balovaptan)、胰岛素样生长因子 1(insulin-like growth factor 1, IGF-1)、次大麻二酚 (cannabidivarin, CBDV)。

巴洛伐坦由瑞士罗氏制药公司研发，是一种靶向催产素受体 1a 的药物，耐受性良好，尚未出现过安全问题，在 2018 年年初获得了 FDA 授予的治疗自闭症的“突破性药物资格”，目前正在进行 III 期临床试验。在巴洛伐坦治疗成年自闭症的为期 12 周的临床 II 期研究中，它改善了患者的适应性行为量表综合评分，这表明该药有利于矫正自闭症患者的社会行为 [28]。然而，在后续两项 24 周的随机、双盲、安慰剂对照试验中，在儿童和成年人中均未发现巴洛伐普坦在改善社交沟通困难方面有效 [29-30]，这可能是安慰剂效应导致的 [31]。因此，巴洛伐坦具体的药效还需要进一步的临床试验加以确定。

IGF-1 是一种神经营养多肽，对中枢神经系统的生长、发育和成熟起着重要作用，在动物研究中已经表现出对社交行为和认知方面的增强作用，目前正在进行 II 期临床试验。临床试验发现，IGF-1 对神经发育障碍类疾病有潜在的治疗效果，对病理生理性行为异常有改善作用 [32]；进一步的研究表明，IGF-1 在自闭症儿童脑发育中起着重要的作用，在患病早期给予 IGF-1 治疗，可以降低神经元兴奋性 [33]。此外，近期在针对自闭症儿童的试验中，IGF-1 能显著改善刻板行为和多动症 [34]，然而该结果依赖于父母报告的结局测量，并且样本量较小。因此，对 IGF-1 的药效研究需要大样本量的进一步临床试验。

CBDV 是大麻提取物中的非精神活性成分之一，属于大麻二酚 (cannabidiol, CBD) 的结构类似物，由于其抗惊厥特性和治疗自闭症的潜力，近年来受到关注，目前正在进行 II 期临床试验。在动物实验中，CBDV 有逆转或预防产前暴露于丙戊酸的大鼠自闭症样行为的能力，并恢复改变的海马内源性大麻素系统和神经胶质 [35]；并且，CBDV 还抑制了已建立的转基因秀丽隐杆线虫中的 α- 突触核蛋白聚集 [36]。纹状体在发育过程中起着核心作用，其非典型功能连接可能导致多种自闭症症状，而 CBDV 改变了纹状体“兴奋性 - 抑制性”代谢物的平衡，这有助于调节功能连接区域 [37]。此外，CBDV 还调节了左基底神经节中的谷氨酸 - GABA 系统，这些可能是 CBDV 改善患者运动障碍和认知缺陷的潜在机制 [38]。

2 行为矫正

2.1 应用行为分析法

应用行为分析法 (applied behavior analysis, ABA) 是一种通过强化训练来教授技能和正确行为的疗法，是自闭症行为干预及康复治疗最安全有效的方法之一。ABA 强调将目标技能或者行为分解成小的步骤，通过强化和辅助反复训练每个步骤，直到孩子能独立完成目标。广义的 ABA 疗法包括离散试验训练 (discrete test training, DTT)、言语行为干预 (verbal behavior intervention, VBI)、早期强化行为干预 (early intensive behavioral intervention, EIBI)、早期启动丹佛模型 (early start Denver model, ESDM)、关键反应训练 (pivotal response treatment, PRT) 等不同类型。不同类型的操作和效果存在差异 [39]，但是它们的核心特征依旧是操作性条件反射原理，需要孩子在 3~4 岁时进行治疗，并保持高强度干预频率，每周训练时间应达到 20~40 h。Yu 等 [40] 的研究结果表明 ABA 干预对社交、交流和表达语言影响著性，并且长期、全面的基于 ABA 的干预措施更有益于自闭症儿童的终身发展。虽然 ABA 有较强的可操作性以及有效地加强自闭症患者的期望行为，然而也有很多学者觉得它试图控制自闭症患者的行为，不尊重自闭症患者的需求 [41]。

2.2 认知行为疗法

认知行为疗法 (cognitive-behavioral therapy, CBT) 将行为治疗和认知治疗相结合，通过认知和行为的理论和技术方法来建立理解他人的认知能力、互惠互利的社会行为。CBT 已经被证明对焦虑、抑郁和强迫症等一系列精神性疾病有效 [42-43]，尤其是对自闭症患者的焦虑 [44]。CBT 通过引导患者意识到自我的不适应的思维，并给予患者适宜的行为示范，在患者克服目标行为的同时给予反馈，如使用视频强化和开展研讨会 [45]。因此 CBT 要求患者具备一定的认知能力，并且有足够的意愿来参与治疗，故而 CBT 可能对成人有更好的治疗效果 [46]。

3 教育训练

3.1 音乐疗法

美国音乐治疗协会 (American Music Therapy Association, AMTA) 将音乐治疗定义为：由完成音乐治疗专业训练课程，并具有专业资格认证的音乐治疗师，在临床上以音乐治疗理论为基础，通过音乐的干预和与个体建立具有治疗性的关系，以实现

个体化的治疗目标。许多自闭症儿童对音乐反应敏感，拥有良好的短期和长期音高记忆[47]，部分患者甚至拥有绝对音高[48]，因而将音乐这种"全脑工作"、"无创伤"的教育训练用于自闭症的治疗有独特的效果。音乐能与自闭症患者的大脑功能相互作用并有助于其治疗，产生认知、心理社会、行为和运动益处[49]。Geretsegger等[50]和Applewhite等[51]的汇总研究发现，大多数基于音乐的干预措施有利于改善社会、情感和行为问题，并且音乐疗法与自闭症患者身体改善的概率增加可能存在关联，有助于改善自闭症患者的生活质量。

3.2 游戏疗法

游戏疗法作为一种特殊的治疗方法，广泛地用于自闭症儿童的教育训练[52]。游戏疗法主要包含沙盘游戏、剧本游戏、角色扮演等[53-54]，通过游戏中的动作进行感官刺激的感觉统合训练也是游戏疗法的一种[55]。与一般儿童相比，自闭症儿童想要口头表达自己的想法并不是一件容易的事情，在游戏疗法中孩子通过游戏来表达他们的情绪感受，孩子在游戏中的行为能翻译成他们沟通的"游戏语言"[56]。游戏疗法适用于自闭症儿童，能显著性地降低儿童的负面情绪和行为[57]，长时间高强度的游戏治疗更有利于降低自闭症的严重程度，改善互动、沟通和重复行为[58]。然而目前针对游戏治疗的研究较少，如何增加游戏的多样性以及疗效，仍需要进一步的研究[59]。

4 物理治疗

4.1 虚拟现实技术疗法

虚拟现实技术(virtual reality, VR)是指利用VR设备模拟(如高分辨率头戴式显示器)创建出逼真的完全交互式三维虚拟世界，为使用者提供存在感、沉浸感和交互性的体验技术[60]。近二十年来，VR在医学上得到广泛应用，并在临床认知康复运动中受到越来越多的关注[61]。自闭症患者能将在VR中习得的技能运用到现实生活中，而VR设备为自闭症患者提供了完全受控并且积极的学习环境或背景，并且可供患者在这种交互式的设备中重复练习[62]。Karami等[63]汇总相关研究发现，VR不仅对自闭症患者的生活技能有所改善，对认知技能、情绪调节和识别技能、社交和沟通技能也有提升。此外，有研究表明VR的联合干预措施可以提高利培酮反应的有效性，并能帮助儿童提前练习和学习一些社交互动的技能，从而增强他们在真实环境中的社交互动[64]。然而将VR用于自闭症患者的精神障碍诊断和治疗仍不够成熟[65]，VR设备技术和设计相关的限制也需要进一步解决[62]。

4.2 针灸

在美国，很少将针灸用作自闭症患者的治疗[66]；然而，在中国和其他亚洲国家，针灸以多种方式广泛用于自闭症的治疗，包括针刺、电针、火针、激光针灸、头皮针灸、手针和蜂毒针灸等[67]。针灸是一种有效治疗自闭症相关症状的方法[68]，它可以提升患者言语和社交互动能力[69]，缓解胃肠道症状等[70]，并对患者的情绪和睡眠也能起到良好的改善作用[71]。然而，由于针灸的不同流派和医生经验的差异，其疗效的异质性比其他治疗方法更为明显。因此，为了提高针灸治疗的疗效和安全性，需要逐步规范和标准化针灸操作[72]。此外，针灸治疗的机制也尚不明确，有学者认为可能与触发下丘脑催产素系统有关[73]，但仍需进一步研究。

5 其他治疗方法

5.1 运动疗法

据报道，运动疗法能改善自闭症患者的睡眠质量[74]，提升患者的敏捷性、平衡、反应时间、握力和柔韧性[75-76]，降低体重指数水平[77]。除了身体方面的益处外，运动疗法还能减少自闭症患者的刻板行为[78]，降低焦虑水平[79]；作为一种干预手段，运动疗法也被证明可以提升患者的执行功能、行为功能以及专注力，帮助调节患者不良情绪[80-84]。这可能是由于运动对患者前额叶氧合的急性影响和抑制性控制[85]，并可以改变患者的炎症特征，从而改善免疫系统激活相关的低度慢性炎症反应引起的中枢神经系统紊乱[86]。然而，因为患者的情绪以及行为问题，自闭症患者对运动治疗可能存在厌恶，要求自闭症患者锻炼有时是一件困难的事情，这需要孩子和父母共同努力[87-88]。

5.2 干细胞疗法

干细胞疗法一般选用脐带血干细胞、骨髓干细胞、间充质干细胞、神经干细胞或诱导多能干细胞移植到患者体内[89]。以往通常将干细胞疗法用于血液系统恶性肿瘤，然而近几十年来，研究发现干细胞疗法能给患者补充广泛缺失或异常的酶，合成和释放趋化因子、细胞因子和生长因子，有助于预防神经系统变性[90]，因此也被用于治疗由神经系统功能障碍引起的其他疾病，如自闭症。干细胞疗法可能通过减少炎症、恢复神经连接、促进血管生成、

增加抗氧化活性等来帮助自闭症患者恢复功能和重组结构 [91]。Villarreal-Martínez 等 [92] 的总结性研究表明，干细胞疗法能显著改善自闭症患者的量表，促进其病症恢复。然而，干细胞疗法可能会导致发烧、头痛、呕吐、多动和攻击性等不良反应 [92]，并且当前临床治疗后的随访期通常很短，因此对干细胞治疗的长期安全性和有效性需要进一步评估 [91]。

5.3 动物辅助治疗

动物辅助治疗是一种不断发展的替代和补充疗法，通过训练有素的动物结合常规治疗来帮助缓解患者的身体和情感需求 [93]。动物辅助治疗对不同的神经系统疾病有益，包括运动和身体能力以及心理和行为健康方面 [94]。Rehn 等 [95] 在自闭症动物辅助治疗研究中证明，动物辅助疗法对患者的认知、社会、情感、行为和身体领域产生了积极的影响。相比于其他动物的辅助治疗，狗和马是自闭症辅助治疗中最常用的动物 [96-98]；狗能区分人类积极和消极的情绪并发展与人类共享的技能 [99]，当自闭症患者与治疗犬玩耍时，会表现出更多的交流互动和注意力迹象，给患者提供互动体验，改善社交障碍 [100]；类似地，马的辅助治疗能通过改善平衡和矫直反应来改善姿势控制，促使患者步态的正常化或者标准化肌肉张力 [94]，帮助改善患者社会沟通交流以及减少易怒行为和多动症状 [101]。然而，使用动物辅助治疗也存在一定的安全问题，比如治疗犬可能携带病菌或者对患者进行攻击，因此选择合适的治疗犬和治疗课程至关重要 [102]；一些患者也可以考虑使用简单机器人或动物机器人替代动物辅助治疗 [103]。

6 总结与展望

随着科技的不断发展进步，有越来越多的方法应用于自闭症治疗，除了上述方法外，一些治疗方法也被用于自闭症的干预，比如患者父母有空余时间还可通过培训尝试使用地板时光 (floor time, FT)、人际关系发展干预疗法 (relationship development intervention, RDI)、亲子互动疗法 (parent-child interaction therapy, PCIT) 等 [104-106] 来与孩子建立联系，帮助改善症状；而另一些方法，诸如图式疗法、颅磁刺激、电休克疗法、高压氧疗法等 [107-109] 因为样本量不足、存在一定危险性、治疗效果不明确等原因，因而在此未做详尽描述；此外，使用哌醋甲酯、大麻等 [110-111] 兴奋类药物对自闭症存在一定的治疗作用，然而由于成瘾性，这些药物的使用必须受到严格的控制。

由于自闭症病因和症状的多样性，上述治疗方案只对自闭症患者某些方面有针对性作用，而要完全治愈自闭症，基因治疗可能是未来的主要研究方向。因为自闭症似乎主要是由遗传驱动的，并且可能在出生后是可逆的，这一事实为使用基因疗法治疗自闭症提供了可能 [112]。在过去几十年，基因编辑技术一直是探索自闭症的致病机制的重要工具 [113]。未来，基因治疗有望展示出根治自闭症的潜力：目前已经发现大量与自闭症相关的基因，并且随时间数量还在不断增加 [114]，其中包括神经可塑性、睡眠缺陷、行为异常等高置信度自闭症基因 [115]。针对这些自闭症基因的治疗可以改善相应的症状，如最新的研究表明，脆性 X 综合征 (fragile x syndrome, FXS) 与自闭症在发病机制上存在重叠，FXS 是一种常染色体显性遗传疾病，大约 15%~60% 的 FXS 患者也会同时被诊断为自闭症，针对 FXS 的基因治疗可能改善自闭症患者的行为异常 [116]。

然而，目前的基因治疗技术主要集中在设计精确的病毒载体、质粒转染、纳米技术、microRNA 和体内簇调节间隔短回文重复序列 (clustered regularly interspaced short palindromic repeats, CRISPR) 等疗法，但这些递送方法都有其局限性，包括免疫原性反应、脱靶效应以及缺乏有效的生物标志物来确定治疗的有效性 [117]，因此需要进一步探索自闭症的致病机制和诊断依据。即便如此，基于基因疗法在解决自闭症致病根源方面的巨大潜力，其在未来依旧是主流的研究方向。

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