·标准与规范·

中国痴呆与认知障碍诊治指南(五):痴呆治疗

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随着痴呆发病率的逐年增高,痴呆的治疗受到极大关注。痴呆治疗方法多样,包括药物治疗、免疫治疗、基因治疗及神经心理治疗等方法。其中药物治疗仍是现今痴呆治疗主体。近年来针对痴呆治疗药物疗效,除改善认知功能外,更加重视对痴呆患者全面生活质量管理,以最大限度的延缓痴呆的进程。为规范痴呆治疗,写作组参考了国内外近期发表的相关临床研究、荟萃分析和系统性综述,以循证医学结果为依据,并结合我国实际情况,编写了痴呆治疗指南,以便指导临床实践。文献证据级别和推荐强度标准参见本杂志刊载系列中的《中国痴呆与认知障碍指南(一):痴呆诊断流程》一文(见本刊 2011 年 91 卷第 9 期 577-581 页)。

一、痴呆的认知功能障碍治疗

(一)胆碱酯酶抑制剂

胆碱酯酶抑制剂临床应用主要包括:

1. 阿尔茨海默病(AD):胆碱酯酶抑制剂增加突触间隙乙酰胆碱含量,是改善痴呆认知功能最主要的作用机制,也是现今治疗轻、中度 AD 一线治疗药物。现有临床使用的胆碱酯酶抑制剂主要包括多奈哌齐、卡巴拉汀、加兰他敏和石杉碱甲。多奈哌齐、卡巴拉汀、加兰他敏治疗轻-中度 AD 患者,改善认知功能、总体印象和日常生活能力疗效确切[1-4](均Ⅰ级证据)。石杉碱甲治疗 AD 研究文献报道较少。胆碱酯酶抑制剂中,有部分研究证实多奈哌齐、卡巴拉汀对中-重度 AD 也有一定治疗效果[5](Ⅰ级证据)。此外,现有研究显示使用胆碱酯酶抑制剂 1~5年内,有延缓痴呆进程的作用,且延缓进程的作用与疗程呈正比[6-7]。但这一差别是否能在更长的时间内显示有效尚待进一步研究。胆碱酯酶抑制剂如多奈哌齐、卡巴拉汀、加兰他敏,除可改善 AD 患者认知功能、全面功能和日常功能外,对轻-中度、中-重度 AD 的早期精神行为异常治疗有效[8-9](均为Ⅰ级证据)。一项临床观察 24 周的多中心、随机、双盲对照研究,提示卡巴拉汀在改善轻-中度 AD 精神症状效果较多奈哌齐好,而多奈哌齐耐受性较卡巴拉汀好[10]。另一项荟萃分析结果也证实多奈哌齐在副反应方面较卡巴拉汀少[11]。

2. 血管性痴呆:多奈哌齐、卡巴拉汀、加兰他敏对改善血管性痴呆(VaD)患者认知功能、日常生活能力有一定效果[12]。其中,证据最充足,经过大规模、前瞻性的临床试验报道仅见于多奈哌齐的临床试验[13](Ⅰ级证据)。此外,也有研究证实加兰他敏对治疗血管性认知功能障碍和 AD 合并脑血管病也有一定效果[14],但基于队列研究的荟萃分析提示加兰他敏胃肠道副反应发生率较高,中途停药率高[15]。VaD 是一个异质性疾病,近年有研究对胆碱酯酶抑制剂治疗血管性痴呆亚型疗效和安全性进行探讨,有报道在多奈哌齐(10 mg/d)对伴有皮质下梗死和白质脑病的常染色体显性遗传脑动脉病(CADASIL)患者疗效和安全性观察中,对患者执行功能有改善[16](Ⅱ级证据)。另有一项小样本、多中心临床研究结果显示,多奈哌齐(5 mg/d)可改善 Binswanger 型皮质下血管性痴呆患者的认知功能[17](Ⅳ级证据)。

3. 帕金森病痴呆和路易体痴呆:路易体痴呆(dementia with Lewy bodies, DLB)和帕金森病痴呆

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(Parkinson disease dementia, PDD)均有胆碱能神经递质的不足。胆碱酯酶抑制剂多奈哌齐、卡巴拉汀及加兰他敏可改善 DLB、PDD 的认知功能,且能减轻淡漠、焦虑、幻觉、妄想及行为紊乱伴发精神症状,包括Ⅰ级证据[18-19]和Ⅱ级证据[20]。

4. 其他痴呆:额颞叶痴呆(FTD)也是一种常见的变性病性痴呆,占老年痴呆人群的 15% ~25%。有报道胆碱酯酶抑制剂治疗 FTD 无效(Ⅱ级证据)[21],甚至有研究提示部分 FTD 患者服用胆碱酯酶抑制剂后可能加重原有的精神行为症状[22]。其他类型痴呆还包括克-雅病性痴呆、梅毒晚期麻痹性痴呆、人类免疫缺陷病性痴呆等,或因感染病毒、细菌后引发的痴呆,以及亨廷顿病性痴呆、正常颅压脑积水和其他因缺乏维生素 B1、烟酸、维生素B12、叶酸的代谢性疾病并发痴呆(即特定疾病的痴呆)。这些痴呆中,尚无胆碱酯酶抑制剂治疗报道。

5. 用法及注意事项:现有的胆碱酯酶抑制剂治疗痴呆的作用机制不尽相同。多奈哌齐是选择性乙酰胆碱酯酶抑制剂,用法用量为:起始剂量 5 mg,1 次/d,服用 4 周后可增至 10 mg,1 次/d,晚上睡前服用。如患者有失眠等睡眠障碍,也可改为早餐前服用。卡巴拉汀为乙酰胆碱酯酶和丁酰胆碱酯酶双向抑制剂,用法用量为:起始剂量为 1.5 mg,2 次/d;如患者服用至少 4 周以后对此剂量耐受良好,可将剂量增至 3 mg,2 次/d;服用至少 4 周以后对此剂量耐受良好,可逐渐增加剂量至 4.5 mg,以至 6 mg,2 次/d。加兰他敏为乙酰胆碱酯酶抑制剂,并可使前烟碱受体发生变构。起始剂量为 5 mg,2 次/d,1 周后可改为一次 10 mg,2 次/d,餐后服用。4 种胆碱酯酶抑制剂间药物活性的差异也支持在 AD 治疗中,胆碱酯酶抑制剂药品间的转换治疗,如 AD 患者使用多奈哌齐治疗无效或不能耐受副作用停药的患者,换用卡巴拉汀继续治疗,约 56.2% 患者仍可获得较好疗效[23-24]。

胆碱酯酶抑制剂治疗痴呆较为安全,仅少数患者在服用过程中,可能出现恶心、食欲下降等胃肠道反应。不良反应发生与使用存在明确的量效关系,通常较高的剂量容易导致副反应发生。新近上市卡巴拉汀透皮贴剂和多奈哌齐口腔崩解片增加了 AD 患者服药依从性,一定程度上可减少药物副反应发生[25-26]。需要指出的是,倘若治疗中出现副作用(如恶心、呕吐、腹痛或食欲减退等)或体重下降,应将每日剂量减至患者能够耐受的剂量为止。

(二)兴奋性氨基酸受体拮抗剂

美金刚是一个对中、重度 AD 疗效确切的药物,可有效改善患者的认知功能、全面能力、日常生活能力[27-28](均Ⅰ级证据)。最新研究报道提示美金刚对轻度、轻-中度 AD 治疗也有一定效果[29](Ⅰ级证据)。一些总结先前队列研究资料荟萃分析显示,使用美金刚 6 个月内可显著抑制 AD 从中度向重度痴呆发展的进程,对延缓认知衰退有部分效果[30]。美金刚单独使用具有较好的耐受性[31],在研究中也有美金刚与多奈哌齐或卡巴拉汀合用减缓中-重度 AD 患者认知功能衰退[32-33](Ⅱ级证据)。针对轻度 AD,也有研究报道美金刚可与胆碱酯酶抑制剂联合治疗轻、中度 AD,但疗效尚无一致性结论[34-35](均Ⅰ级证据)。

美金刚可用于轻度到中度之间的 VaD 患者[36-37]。新近队列荟萃分析中,2 个研究显示美金刚对改善患者认知功能和精神行为效果较好,但对临床全面能力提高效果不明显[38]。美金刚有较好的耐受性,在这些研究的亚组分析研究中[39],认知功能的优点在具有小血管疾病患者亚群中更为突出。

美金刚也被用于治疗 DLB,但目前文献报道较少。有报道提示约 2/3 的 DLB 患者能耐受美金刚的治疗,并可改善临床症状,但少数患者可能加重激惹、妄想和视幻觉等精神症状[40]。针对美金刚治疗 PDD,已有几项基于小样本随机、双盲、安慰剂对照研究,结果证实美金刚治疗 PDD 患者疗效、安全性较好,可选择性提高患者的记忆、执行功能、日常生活能力、情绪障碍和运动功能以及全面功能[41-42]。美金刚治疗 PDD 的疗效和安全性有待大样本临床试验进一步验证。

现有小样本、对照研究美金刚治疗 Wernenick 脑病,结果显示对患者全面功能有一定改善,且安全性和耐受性好(Ⅳ级证据)[43]。但试验样本少(仅 10 例),其结果尚待进一步探讨。

美金刚每日最大剂量 20 mg,用法用量为:为了减少副作用发生,起始剂量 5 mg,1 次/d,晨服;第 2 周增加至每次 5 mg,2 次/d;第 3 周早 10 mg,下午服 5 mg;第 4 周开始服用推荐的维持剂量每次 10 mg,2 次/d。可空腹服用,也可随食物同服。美金刚治疗痴呆安全,偶有幻觉、意识混沌、头晕、头痛和疲倦,以及焦虑、肌张力增高、呕吐、膀胱炎和性欲增加。

(三)中药干预

现有治疗痴呆中药为银杏叶提取物(EGb 761)

和鼠尾草提取物(Sage)。关于银杏叶对 AD 防治效果尚存争议,先前大部分研究均报道银杏叶对 AD 有轻微治疗作用,可改善患者出现的神经精神症状,延缓痴呆病程[44](Ⅱ级证据)。但另一些试验则对银杏叶提取物改善 AD 认知功能等疗效提出相反的结论,且有研究者认为先前临床研究在研究方法方面存在不足。而美国从 2000 至 2009 年间开展的一项纵向随访 6 年的随机、双盲、安慰剂对照试验的结果显示,银杏叶提取物不能有效降低正常老人或轻度认知功能损害患者出现 AD 概率[45](Ⅱ级证据)。因此对银杏叶是否防治 AD 尚无定论。

有报道中药鼠尾草提取物可改善轻、中度 AD 认知功能,并能一定程度缓解患者激越症状[46](Ⅱ级证据)。此外,新近有研究提示一种含有何首乌磷脂前体、维生素 B6、维生素 C 和叶酸等成分保健食品对改善轻度 AD 患者记忆,尤其是单词延迟回忆和全面功能有效[47](Ⅱ级证据)。但上述研究结果文献报道少,且样本量小,结论尚待验证。在我国有关中药和针灸的研究也有很多报道,但终因缺乏随机对照试验而不能进行评估并做出推荐[48-49]。因此,中药提取物作为 AD 治疗药物尚缺少足够的循证医学证据。

(四)脑代谢赋活剂

脑代谢增强剂对痴呆治疗效果,现有报道中阴性结果较多,仅有几个小样本试验提示奥拉西坦和茴拉西坦治疗 AD 研究可能有效。但一项较为有力的基于随机、安慰剂对照研究的荟萃分析提示,没有充足的证据证实西坦类对 AD 有效[50]。

(五)影响自由基代谢的药物

自由基对膜的脂质过氧化作用以及对蛋白质、DNA 的氧化作用,可导致细胞衰老死亡。抗氧化剂中主要包括维生素 E、雌激素等。AD 和 VaD 患者血浆中存在维生素 E 含量低。维生素 E 在数量上是大脑最主要的亲脂抗氧化剂,先前曾有研究中认为维生素 E 可以有效地抑制脑脊液脂蛋白和大脑脂质的氧化,延迟 AD 患者的进程。但随后研究则认为没有充足的证据来说明维生素 E 治疗 AD 有效[51]。甚至有部分前瞻性研究显示雌激素加孕激素在绝经后的妇女,随访 4 年发现有增加痴呆危险[52]。因此,抗氧化对痴呆防治作用仍是一个尚待探讨的问题。

(六)其他

一些基于随机对照试验的荟萃分析结果显示尼麦角林、尼莫地平、包括麦角碱类等扩血管药物,均无足够的证据证实对 AD、VaD 有治疗作用[53-54]。但有研究提示尼莫地平可能对预防皮质下型 VaD 心血管事件发生有一定益处[55](Ⅱ级证据)。

他汀类是治疗高脂血症的药物,先前曾有一些回顾性或横断面研究发现其能降低 AD 发病率。但一些大型研究和临床荟萃分析显示,普伐他汀[56]、阿托伐他汀[57]等他汀类药物均不能有效改善痴呆认知功能障碍,也不能降低 AD 发病风险[58]。

阿司匹林对 VaD 的疗效却尚存争议。早期小规模试验、空白对照试验观察阿司匹林可改善 VaD 认知功能[59](Ⅲ级证据)。但荟萃分析结果则显示,阿司匹林对 VaD 无效[60]。与阿司匹林研究结果略不同,针对己酮可可碱的双盲随机对照试验显示,较安慰剂组能显著地改善血管性痴呆整体和认知功能[61]。基于 4 项双盲随机对照试验的系统回顾提示有改善认知功能的趋势[62](Ⅰ级证据)。

应该指出的是,虽然现有临床研究未显示治疗血管危险因素药物对改善 VaD 认知功能损害的效果,但是有效地控制各种血管性危险因素(抗高血压、抗血小板、控制糖尿病及调血脂等)仍是 VaD 治疗中一项重要措施。

【推荐】

必须与患者或知情人充分地讨论治疗益处及其可能出现的不良反应【专家共识】。

明确诊断为轻-中度 AD 患者可以选用胆碱酯酶抑制剂(多奈哌齐、卡巴拉汀、加兰他敏)治疗【A 级】。

胆碱酯酶抑制剂(多奈哌齐)可用于治疗轻-中度 VaD 患者【B 级】。

胆碱酯酶抑制剂可用于路易体痴呆和帕金森病痴呆的治疗【A 级】。

明确诊断为中-重度 AD、VaD 患者可以选用美金刚或美金刚与多奈哌齐、卡巴拉汀联合治疗【A 级】。

应用某一胆碱酯酶抑制剂治疗无效或因不良反应不能耐受时,可根据患者病情及出现不良反应程度,选择停药或调换其他胆碱酯酶抑制剂进行治疗,治疗过程中严密观察患者可能出现的不良反应【B 级】。

银杏叶制剂或鼠尾草提取物可能对治疗 AD 有效,尚待进一步验证【专家共识】。

轻-中度 AD 患者可以选用尼麦角林、尼莫地平、吡拉西坦或奥拉西坦、维生素 E 等作为胆碱酯酶抑制剂、兴奋性氨基酸受体拮抗剂的协同治疗药物【专家共识】。

在VaD治疗中应有效地控制各种血管性危险因素(抗高血压、抗血小板、控制糖尿病及调血脂等)【专家共识】。

二、痴呆精神行为症状治疗

(一)痴呆精神药物的使用原则及注意事项

1. 痴呆患者精神药物的使用原则:(1)评估用药的必要性,权衡用药的利弊,谨慎调整剂量;(2)坚持个体化用药原则,首选口服药物,并参考药物副作用,选择合适药物;(3)低起始剂量,缓慢增量,直至症状改善。(4)精神症状首选非典型抗精神病药,例如利培酮、奥氮平、思瑞康等;改善抑郁症状首选SSRI类抗抑郁药,例如西酞普兰、舍曲林等;存在焦虑症状者若应用SSRIs类效果不佳,可选择苯二氮䓬类药物。

2. 痴呆患者的用药注意事项:(1)肾脏排泄能力减退、肝脏代谢缓慢,密切观察药物不良反应,防止药物蓄积;(2)注意躯体疾病和药物的相互影响;(3)锥体外系副作用可加重运动障碍、跌倒;(4)抗胆碱能副作用,加重认知损害,导致谵妄,加重心血管和前列腺疾病;(5)直立性低血压可导致跌倒;(6)镇静作用可导致呼吸抑制;(7)尽量避免多种药物联用。此外,在精神药物治疗前应明确症状类型,以便选择合适的药物。并且随着痴呆的进展,精神行为症状(behavioral and psychological symptoms of dementia, BPSD)可能加重或减轻,应相应调整剂量、更换药物或停药。使用过程中必须对疗效进行认真评价并根据病情变化调整治疗方案,以防止精神药物副反应的发生。

(二)痴呆精神行为症状治疗药物

治疗BPSD的目的是为了减轻患者症状,提高患者、家属或照料者生活的安全性和舒适性。如果症状为轻度,危险程度很小,尽可能以非药物治疗(心理治疗)来改善症状。非药物治疗以支持性心理治疗为主,医生通过语言、情感和行为来影响患者的心理和行为,进而改善或解除症状。

有研究都表明,胆碱酯酶抑制剂和谷氨酸受体拮抗剂具有显著改善BPSD的效果[63],如美金刚对中-重度AD的精神症状如妄想、激越等效果明显[64]。因此,促认知药可作为痴呆患者治疗BPSD的基础用药(Ⅰ级证据)。严重的BPSD需使用精神药物治疗。如果BPSD症状使患者痛苦或伴随的激越、冲动、攻击行为,使患者或他人处于危险之中,则是精神药物治疗的适应证。治疗痴呆精神行为症状的药物主要有抗精神病药、抗抑郁药、抗焦虑药。

1. 抗精神病药:抗精神病药对幻觉、妄想等严重精神病性症状具有肯定疗效。但是抗精神病药可能增加心脑血管事件、肺部感染等严重不良事件发生率,使痴呆患者死亡率增高。因此,对于严重的精神病性症状,临床医师应在权衡利弊的情况下谨慎使用。在抗精神病药中,利培酮、奥氮平和喹硫平,是近10年来才用于临床的新药,副作用相对较少,安全性好[65-67](Ⅰ级证据),适用于老年痴呆治疗。

2. 抗抑郁药:选择性5-羟色胺再摄取抑制剂(SSRIs)的副作用比三环和四环类抗抑郁药少,且服用方便,比较适合老年痴呆患者使用。不同SSRIs类药物在作用机制方面有不同,如帕罗西汀、氟伏沙明具有一定的镇静作用,可在一定程度上改善睡眠;氟西汀引起失眠、激越的可能性较大,适合用于伴有淡漠、思睡的患者。舍曲林和西酞普兰对肝脏P450酶的影响较小,安全性好。万拉法新(又名文拉法辛),对抗胆碱及心血管系统的不良反应小,耐受性也比较好,起效比较快。米氮平又名瑞美隆,抑郁作用强,为新一代的抗抑郁药,不过用于老年人的临床研究还比较少。SSRIs的有效治疗剂量分别为:氟西汀20 mg/d,帕罗西汀10~20 mg/d,舍曲林25~50 mg/d,氟伏沙明25~50 mg/d,西酞普兰10~20 mg/d。少数疗效欠佳者,剂量可适当增加。SSRIs类药较为安全,副反应较小,主要有恶心、呕吐、腹泻、激越、失眠、静坐不能、震颤、性功能障碍和体重减轻等。各种SSRIs引起的上述副作用的严重程度和频率可有不同。

3. 抗焦虑及镇静催眠药:主要是苯二氮䓬类药,用于治疗痴呆患者焦虑、激惹和睡眠障碍。苯二氮䓬类药根据半衰期的长短和镇静作用的强弱,一般可分为长效制剂(半衰期20 h左右)如地西泮、氯硝西泮、氟西泮等;中效制剂(半衰期10 h左右)如阿普唑仑、氧西泮、劳拉西泮等;短效制剂(半衰期3 h左右)如三唑仑、速眠安等。半衰期较短的药物多用于入睡困难,半衰期较长的药物适合焦虑、激惹和睡眠的维持治疗。苯二氮䓬类药的常见副作用有思睡、头晕、共济失调、记忆障碍、呼吸抑制、耐药、成瘾、撤药综合征等。苯二氮䓬类药能增强酒精和抗精神病药的镇静作用,突然停药可致抽搐,使用时应加以注意。半衰期短的药物记忆障碍、撤药综合征较多,半衰期长的药物,思睡、运动损害较重。治疗痴呆患者的睡眠障碍是为了减少或减轻失眠、易醒和夜间模糊,以增加患者的舒适,减轻家属和照料者的痛苦。药品的选择一般是根据除睡眠障碍外是否

还存在其他症状而定，例如：如果患者同时有精神病性症状和睡眠障碍，一般在睡前给予抗精神病药，如无禁忌证，可选镇静作用相对较强的抗精神病药如奥氮平、喹硫平等；如果抑郁和睡眠障碍并存，可在睡前给予具有镇静作用的抗抑郁药，如三唑酮、米氮平等。如患者只有睡眠障碍或焦虑激越，才考虑使用苯二氮䓬类药。

【推荐】

在使用促认知药物后，精神行为症状无改善时可酌情使用精神药物【A级】。

使用药物前应与知情人商讨精神药物作用及可能出现的不良反应，并权衡用药的利弊，谨慎调整剂量【A级】。

精神药物使用应遵循低起始剂量、缓慢增量，直至症状改善【A级】。

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中国痴呆与认知障碍诊治指南(五):痴呆治疗

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