Advances in Clinical Medicine 临床医学进展, 2026, 16(3), 3392-3404
Published Online March 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1631145

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肠－脑轴调控在苯二氮䓬类药物依赖与慢性失眠中的作用及治疗前景

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收稿日期：2026年2月16日；录用日期：2026年3月9日；发布日期：2026年3月19日

摘　要

慢性失眠是全球高发的睡眠障碍性疾病，苯二氮䓬类药物(BZDs)是临床治疗该疾病的一线药物，但长期使用易引发躯体与精神依赖，且停药后易出现戒断反应并加重失眠症状，形成恶性循环。肠－脑轴作为连接肠道与中枢的双向通讯网络，其功能异常不仅参与慢性失眠的病理过程，还与BZDs依赖的发生及戒断反应密切相关。本文从肠－脑轴的结构与功能基础出发，系统阐述肠－脑轴介导慢性失眠与BZDs依赖的相互作用机制，总结目前基于肠－脑轴调控的干预策略研究进展，并分析其临床应用前景与挑战，为探索慢性失眠合并BZDs依赖的新型治疗方案提供理论依据与研究方向。

关键词

肠－脑轴，苯二氮䓬类药物依赖，慢性失眠，肠道菌群，神经递质，干预策略

Regulation of the Gut-Brain Axis in Benzodiazepine Dependence and Chronic Insomnia: Mechanisms and Therapeutic Prospects

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Received: February 16, 2026; accepted: March 9, 2026; published: March 19, 2026

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文章引用: 冯勤, 尹泓. 肠-脑轴调控在苯二氮䓬类药物依赖与慢性失眠中的作用及治疗前景[J]. 临床医学进展, 2026, 16(3): 3392-3404. DOI: 10.12677/acm.2026.1631145

Abstract

Chronic insomnia is a widespread sleep disorder worldwide. Benzodiazepines (BZDs) are the first-line drugs for treating this disease. However, long-term use can lead to physical and mental dependence, and after discontinuation, withdrawal reactions occur, which further aggravate the insomnia symptoms, forming a vicious cycle. The gut-brain axis, as a bidirectional communication network connecting the gut and the central nervous system, has abnormal functions that not only participate in the pathological process of chronic insomnia but are also closely related to the occurrence of BZD dependence and withdrawal reactions. This article starts from the structural and functional basis of the gut-brain axis, systematically elaborates the interaction mechanism between the gut-brain axis and chronic insomnia and BZD dependence, summarizes the current research progress on intervention strategies based on the regulation of the gut-brain axis, and analyzes its clinical application prospects and challenges, providing theoretical basis and research directions for exploring new treatment schemes for chronic insomnia combined with BZD dependence.

Keywords

Gut-Brain Axis, Benzodiazepine Dependence, Chronic Insomnia, Gut Microbiota, Neurotranszmitter, Therapeutic Strategies

1. 引言

慢性失眠全球患病率高达 30%~35% [1]，且呈逐年上升趋势[2]。显著增加心血管病、认知衰退及精神疾病风险[1] [3]，严重影响患者生活质量。苯二氮䓬类药物(BZDs)因能增强 GABA 抑制，成为一线治疗药物[4]。但长期使用易致耐受性与依赖，停药后出现戒断反应，形成恶性循环[5] [6]。目前治疗以逐步减药为主，疗效有限[7]，亟需新靶点。

肠－脑轴是由肠道神经系统、肠道微生物群、神经内分泌通路、免疫系统共同构成的双向调控网络，其通过神经、免疫、内分泌及代谢途径实现肠道与中枢神经系统的信息传递[8] [9]。近年来研究发现，肠－脑轴功能紊乱是慢性失眠发生的重要机制[10] [11]，而 BZDs 的长期使用会进一步破坏肠道微生态平衡，加剧肠－脑轴通讯障碍，同时肠道菌群异常又会影响中枢神经递质代谢与药物敏感性，促进 BZDs 依赖的形成[12] [13]。肠－脑轴作为连接肠道与中枢的“隐形桥梁”，为慢性失眠合并 BZDs 依赖的治疗提供了全新的靶点[14] [15]。本文将围绕肠－脑轴与慢性失眠、BZDs 依赖的相互作用机制展开综述，总结基于肠－脑轴调控的干预手段，并展望其临床应用前景。

2. 肠－脑轴的结构与功能基础

肠－脑轴并非单一的神经通路，而是多系统协同作用的复杂网络，其核心组成包括肠道神经系统、肠道微生物群、迷走神经通路、下丘脑－垂体－肾上腺(HPA)轴及肠道黏膜免疫系统，各组分相互配合实现肠道与中枢神经系统的双向通讯[16] [17]。

肠道神经系统被称为“腹部小大脑”，包含约 5 亿个神经元，可独立处理肠道的感觉、运动信号，

同时通过迷走神经与脑干、下丘脑等中枢核团直接相连，是肠－脑轴神经通讯的结构基础[18]。迷走神经作为肠－脑轴的主要神经通路，负责将肠道菌群代谢信号、肠道黏膜的感觉信号传递至中枢，同时将中枢的调控信号反馈至肠道，调节肠道蠕动、分泌功能[9]。肠道微生物群是肠－脑轴的核心调控单元，人体肠道内定植着超 1000 种微生物，其总量达 10^{14} 个，不仅参与营养物质的消化吸收，还能合成多种神经活性物质，包括 90%的外周血清素、GABA、多巴胺、色氨酸等，这些物质可通过迷走神经或血液循环进入中枢，调节神经系统功能[19] [20]。

肠道黏膜免疫系统占人体免疫细胞总量的 70% [21]，肠道菌群通过调节肠道黏膜屏障完整性，控制炎症因子的释放与转运。正常情况下，肠道菌群可分泌短链脂肪酸(SCFAs)等代谢物，增强肠黏膜紧密连接，阻止菌群毒素与炎症因子入血[22] [23]；而当肠道菌群失衡时，肠黏膜屏障受损引发“肠漏”，脂多糖(LPS)、肿瘤坏死因子-α (TNF-α)、白细胞介素-6 (IL-6)等炎症因子进入血液循环，通过血脑屏障激活中枢小胶质细胞，引发神经炎症[24]。HPA 轴作为神经内分泌通路的核心，与肠－脑轴形成双向调控，肠道菌群代谢物可通过迷走神经调控 HPA 轴的活性，而应激状态下 HPA 轴过度激活释放的皮质醇，又会抑制肠道有益菌生长，破坏肠道微生态平衡[25] [26]。

此外，肠道菌群的代谢产物在肠－脑轴通讯中发挥着关键作用。SCFAs 作为肠道菌群发酵膳食纤维的主要产物，可通过血脑屏障进入中枢，调节神经胶质细胞的增殖与分化，增强 GABA 能神经抑制作用，同时还能抑制 HPA 轴的过度激活，降低皮质醇水平[27]。色氨酸是血清素合成的前体物质，肠道菌群可通过调节色氨酸代谢通路，影响中枢血清素的合成与释放，进而调节情绪与睡眠－觉醒周期[28] [29]。肠－脑轴的正常功能是维持睡眠稳态、中枢神经递质平衡及药物代谢的重要基础，其任一环节的功能异常均会引发神经系统的病理改变[30]。

3. 肠－脑轴介导慢性失眠与苯二氮䓬类药物依赖的相互作用机制

慢性失眠与 BZDs 依赖并非独立的病理过程，二者通过肠－脑轴形成恶性循环：慢性失眠引发肠－脑轴功能紊乱，导致肠道菌群失衡、神经递质代谢异常[28]，进而降低中枢对 BZDs 的敏感性，促进药物依赖的形成；而长期使用 BZDs 会进一步破坏肠道微生态平衡，加剧肠黏膜屏障损伤与神经炎症，加重失眠症状，同时肠道菌群异常又会影响药物的代谢与戒断反应，使依赖状态难以缓解[31] [32]。其核心作用机制主要涉及肠道菌群失衡、神经递质代谢紊乱、HPA 轴亢进、神经炎症激活及药物靶点敏感性改变五个方面[28] [29] [31] [33]。

3.1. 肠道菌群失衡：核心始动因素

肠道菌群平衡是肠－脑轴功能正常的基础，慢性失眠与 BZDs 依赖均会引发肠道菌群结构的显著改变，而菌群失衡又会进一步加剧二者的病理状态[34] [35]。研究显示，仅一周的睡眠不规律即可导致肠道内双歧杆菌、乳杆菌等有益菌减少 40%，大肠杆菌、梭状芽孢杆菌等致病菌大量繁殖，使肠道菌群多样性显著降低[36] [37]。慢性失眠患者因睡眠－觉醒周期紊乱，会导致肠道菌群的昼夜节律失调，而菌群昼夜节律的破坏又会影响中枢时钟基因的表达，进一步抑制褪黑素的合成与释放，加重失眠[38]。

长期使用 BZDs 会对肠道菌群产生直接的抑制作用，研究发现，BZDs 可通过血液循环进入肠道，抑制有益菌的增殖，同时促进致病菌的生长，导致肠道微生态平衡被打破[12] [39]。BZDs 依赖患者的肠道菌群检测结果显示，其双歧杆菌、罗伊氏乳杆菌丰度显著低于健康人群，而促炎菌丰度显著升高，且菌群失衡程度与药物依赖程度、戒断症状严重程度呈正相关[35] [40]。此外，肠道菌群失衡还会影响药物的代谢效率，肠道菌群可通过产生 β-葡萄糖醛酸酶等代谢酶，调节 BZDs 在肠道的吸收与生物利用度，菌群失衡会导致药物代谢紊乱，使中枢药物浓度波动，进而引发耐受性与依赖[39] [41]。

3.2. 神经递质代谢紊乱：关键介导环节

肠–脑轴通过调控中枢与外周神经递质的合成、释放及代谢参与睡眠调节与药物依赖的形成，核心调控递质包括 GABA、血清素与多巴胺[42] [43]。

GABA 是中枢神经系统主要的抑制性神经递质，BZDs 通过作用于 GABAA 受体增强 GABA 能神经抑制，从而发挥催眠镇静效应。肠道菌群可合成外周 GABA，并调节中枢 GABAA 受体的表达与敏感性，影响 GABA 功能[42] [44]。慢性失眠患者因肠道菌群失衡，肠道 GABA 合成减少，中枢 GABAA 受体表达下调，GABA 能抑制作用减弱，大脑兴奋性增高，导致入睡困难与睡眠维持障碍[37]。长期使用 BZDs 可致中枢 GABAA 受体脱敏，需更高剂量才能激活受体；同时肠道菌群失衡进一步削弱 GABA 合成能力，形成药物耐受[12] [42]。

血清素参与睡眠–觉醒周期与情绪调节，其合成前体色氨酸的代谢受肠道菌群调控[45]。慢性失眠患者肠道有益菌减少，色氨酸代谢紊乱，中枢血清素水平下降，不仅影响睡眠启动，还诱发焦虑，形成恶性循环[37] [43]。BZDs 依赖患者血清素能系统功能失衡，5-HT1A 受体系统功能异常，情绪调节能力减弱[46]；血清素水平降低可增强心理依赖，增加戒断难度。此外，肠道菌群还能合成多巴胺等兴奋性递质，其代谢异常可影响中枢奖赏回路，促进药物依赖形成[47]。

3.3. HPA 轴亢进：重要调控通路

HPA 轴作为神经内分泌的核心通路，与肠–脑轴形成双向调控，其过度激活是慢性失眠与 BZDs 依赖的共同病理特征[48]。慢性失眠患者因睡眠紊乱，中枢应激信号增强，导致 HPA 轴亢进，皮质醇分泌节律紊乱，表现为夜间皮质醇水平升高，抑制褪黑素合成，进一步加重失眠；而皮质醇的持续升高会抑制肠道有益菌生长，破坏肠黏膜屏障完整性，引发肠道菌群失衡与“肠漏”[49] [50]。肠黏膜屏障受损后，炎症因子入血激活中枢应激信号，再次加剧 HPA 轴亢进，形成“睡眠紊乱–HPA 轴亢进–肠道菌群失衡–睡眠紊乱”的闭环[51] [52]。

BZDs 可通过拮抗促肾上腺皮质激素释放因子(CRF)的作用，短暂抑制 HPA 轴的活性，发挥抗焦虑、镇静效果[53]。但长期使用 BZDs 会导致 HPA 轴产生适应性改变，CRF 表达上调，使机体对药物的抑制作用产生耐受，同时 NPY、CCK 等神经肽的分泌紊乱，进一步增强 HPA 轴的活性[54]。停药后，HPA 轴的抑制作用解除，出现过度亢进，表现为皮质醇水平骤升，引发焦虑、失眠反跳、自主神经功能紊乱等戒断症状[55]。而肠道菌群失衡会通过迷走神经与炎症通路[56] [57]，持续激活 HPA 轴，使戒断症状难以缓解，同时加重患者的心理依赖，增加复药风险[58]。

3.4. 神经炎症激活：重要病理环节

肠–脑轴介导的神经炎症激活是连接慢性失眠与 BZDs 依赖的重要病理环节，其核心机制为肠道菌群失衡引发的肠黏膜屏障损伤与外周炎症因子的中枢转运[12]。正常情况下，肠道黏膜屏障可阻止菌群毒素与炎症因子入血，而慢性失眠患者因睡眠紊乱与 HPA 轴亢进，肠黏膜紧密连接受损，引发“肠漏”，导致 LPS、TNF-α、IL-6 等促炎因子进入血液循环[59]-[61]。这些炎症因子可通过血脑屏障进入中枢，激活下丘脑、海马体、杏仁核等区域的小胶质细胞，引发中枢神经炎症，导致神经元损伤与神经递质代谢紊乱，进而加重失眠与焦虑症状[32]。

长期使用 BZDs 会进一步加剧肠道菌群失衡，使促炎菌丰度升高，外周炎症因子水平持续增加，中枢神经炎症处于慢性激活状态[12]。慢性神经炎症会降低中枢 GABAA 受体的敏感性，同时破坏多巴胺奖赏回路与血清素能系统，促进药物耐受性与依赖的形成[62]。此外，BZDs 戒断过程中，中枢神经炎症会进一步加重，导致神经元兴奋性增高，引发惊厥、震颤等严重戒断症状，同时神经炎症会增强患者的焦

虑与痛苦体验，增加复药概率[63]。

3.5. GABAA 受体敏感性改变：药物依赖的分子基础

GABAA 受体是 BZDs 的作用靶点，其表达与敏感性的改变是 BZDs 依赖形成的核心分子机制，而肠－脑轴功能紊乱会通过多种途径调控 GABAA 受体的功能[32]。GABAA 受体是由 α、β、γ 亚基组成的离子通道受体，其中 α1 亚基与镇静、催眠效果密切相关，BZDs 通过结合 $\alpha1\beta x\gamma2$ 型 GABAA 受体，增强 GABA 的抑制作用[64]。研究发现，肠道菌群代谢产生的 SCFAs 可通过血脑屏障，调节中枢 GABAA 受体的表达与组装，有益菌丰度降低会导致 SCFAs 合成减少，GABAA 受体 α1 亚基表达下调，受体敏感性降低[65] [66]。

慢性失眠患者因肠道菌群失衡，GABAA 受体敏感性下降，需增加 BZDs 剂量才能达到相同的催眠效果，进而引发药物耐受性[67]。长期使用 BZDs 会导致 GABAA 受体发生内吞与脱敏，同时肠道菌群失衡引发的神经炎症会进一步抑制 GABAA 受体的表达，形成恶性循环，最终导致药物依赖[68]。此外，肠道菌群还能通过调节外周 GABA 的水平，影响中枢 GABA 的反馈调节，进一步改变 GABAA 受体的功能状态，促进依赖的形成[65]。

4. 基于肠－脑轴调控的苯二氮䓬类药物依赖与慢性失眠干预策略

基于肠－脑轴的调控机制，目前临床与基础研究中针对慢性失眠合并 BZDs 依赖的干预策略主要集中在肠道菌群靶向调节、肠－脑神经通路调控、免疫炎症抑制及生活方式干预等方面，其中肠道菌群靶向调节是研究的热点，且已取得初步的临床效果。

4.1. 肠道菌群靶向调节

肠道菌群是肠－脑轴的核心调控单元，通过调节肠道菌群结构、恢复微生态平衡，可从根本上改善肠－脑轴通讯障碍，进而缓解慢性失眠症状、降低 BZDs 依赖程度，主要干预手段包括益生菌补充、益生元使用及粪菌移植[15] [17] [43]。

乳杆菌属、双歧杆菌属等“精神益生菌”是调节肠－脑轴的核心菌株。多项研究证实其改善睡眠的作用：长双歧杆菌 1714 可改善应激状态下的睡眠质量[46]。Wang 等证实，该菌株能调节静息态脑神经活动，直接影响与情绪相关的大脑处理过程[69]。Cheon 植物乳杆菌 P72 上调 GABA 表达，改善失眠焦虑[70]。Tian 等研究显示，短双歧杆菌 CCFM1025 改善昼夜节律紊乱[34]。Bongiovanni 等(2025)的 RCT 研究显示，多菌株乳杆菌使 PSQI 改善 69%，能量提升 31% [71]。

低聚果糖、低聚半乳糖等可促进有益菌增殖。Wong 等动物实验发现，色氨酸联合低聚果糖干预可使睡眠剥夺小鼠的睡眠时长增加 50.8%~81.0%，血浆 TNF-α 降低 38%、IL-6 降低 26%，同时乳酸杆菌和双歧杆菌丰度显著升高[72]。Chung 等研究证实，补充短链低聚半乳糖与长链低聚果糖混合物可恢复睡眠剥夺小鼠的肠道紧密连接基因表达，调节下丘脑时钟基因(BMAL1、CLOCK)及 CRF 受体表达，缓解焦虑与抑郁样行为[73]。

Zhang 等临床观察显示，洗涤菌群移植可显著改善自闭症合并失眠儿童的睡眠障碍评分，且睡眠改善与粪便形态改善同步，无明显不良反应[74]。山东省立第三医院的临床案例报道，粪菌移植治疗可使慢性失眠患者的入睡困难显著改善，镇静药物顺利减量。

4.2. 肠－脑神经通路调控

肠－脑轴的神经通讯主要依赖迷走神经通路，通过调控迷走神经的活性，可增强肠－脑正向通讯，改善睡眠稳态与神经递质平衡，降低 BZDs 依赖程度。非侵入性迷走神经调控是目前研究的热点，包括

迷走神经按摩、经皮迷走神经电刺激等，其具有操作简便、安全性高的特点。

Wu 等发现，经皮耳迷走神经电刺激(taVNS)可显著改善原发性失眠患者的睡眠质量，其机制与调节默认网络、视觉网络等脑功能活动有关[75]。Srinivasan 等证实，taVNS 治疗 4 周可显著降低 PSQI 及焦虑评分[76]。de Oliveira 等的 Meta 分析综合 6 项临床研究(336 例)证实，taVNS 可显著改善失眠患者的 PSQI (MD = −3.60)和 ISI 评分(MD = −5.24)，安全性良好[77]。Doerr 等发现，tVNS 可调节 HPA 轴活性，使唾液皮质醇下降曲线趋于平缓[78]。

4.3. 免疫炎症抑制

肠－脑轴介导的神经炎症是慢性失眠与 BZDs 依赖的重要病理环节，通过抑制外周与中枢炎症，可改善肠－脑轴功能，缓解症状。肠道黏膜屏障损伤是外周炎症产生的核心原因，除益生菌、益生元外，黏膜保护剂如谷氨酰胺可修复肠黏膜紧密连接，减少“肠漏”。Wang 等(2015)的动物实验证实，谷氨酰胺补充可显著上调肠黏膜紧密连接蛋白 Occludin 和 ZO-1 的表达，减轻 LPS 诱导的肠屏障损伤[79]。中枢炎症的抑制主要依赖抗炎药物。Ahmed 等(2021)研究发现，小剂量米诺环素可抑制睡眠剥夺诱导的海马小胶质细胞激活，恢复 Keap1-Nrf2 抗氧化通路，改善焦虑抑郁样行为[80]。Vicente 等(2023)进一步证实，米诺环素可减少蓝斑核小胶质细胞密度，恢复睡眠－觉醒周期[81]。Manosso 等(2024)综述指出，抗炎、抗氧化及 HPA 轴调节是改善睡眠障碍的潜在靶点。但抗炎药物长期使用需严格控制剂量与用药时间[82]。

4.4. 生活方式优化

生活方式的优化可通过调节肠道菌群的昼夜节律、改善肠－脑轴功能，辅助缓解慢性失眠与 BZDs 依赖症状，是基础且重要的干预手段，主要包括作息调节、饮食干预与规律运动。

固定的睡眠－觉醒作息可同步肠道菌群的昼夜节律与中枢时钟基因的表达，促进褪黑素的规律分泌。Liu 等(2020)研究发现，急性睡眠－觉醒周期改变可导致人体肠道菌群群落结构的显著变化[83]。Matenchuk 等(2020)综述指出，睡眠、昼夜节律与肠道菌群之间存在双向调控关系，稳定的作息可提升菌群多样性并改善睡眠质量[84]。

地中海饮食富含全谷物、深海鱼、蔬菜水果、橄榄油等，可提供丰富的膳食纤维与不饱和脂肪酸，促进肠道有益菌增殖。Abou-Khalil (2025)综述指出，富含抗炎和抗氧化化合物的膳食模式(如地中海饮食)可显著改善睡眠结局[85]。Lin 等(2024)综述强调，饮食是调节肠道菌群与睡眠关系的关键因素，膳食纤维促进短链脂肪酸合成，进而改善睡眠。减少高糖、高脂、精加工食品的摄入，可避免肠道菌群失衡，保护肠黏膜屏障功能[86]。

规律的中等强度运动可调节自主神经功能，改善肠道蠕动与菌群结构，同时抑制 HPA 轴过度激活。Psarianos 等(2025)的随机对照试验证实运动能促进中枢内啡肽的释放，缓解戒断过程中的焦虑症状，提高戒断成功率[87]。

4.5. 优先推荐的多靶点组合干预方案

基于现有循证医学证据及本团队最新完成的随机对照试验结果，本文提出两种优先级高、风险可控的肠－脑轴靶向干预方案，旨在为临床减停 BZDs 提供可操作的综合治疗路径：

方案一：逐步减量 ＋CBT-I＋ 直肠三氧灌注

本团队 RCT 研究(n = 88)显示，该方案可使 BZDs 完全停药率达 77.3%，显著高于对照组的 65.9% (P = 0.039)，PSQI 显著改善(5.45 ± 0.73 vs. 6.82 ± 0.62, P < 0.01) (本团队未发表数据，2026)。直肠三氧灌注

可修复肠道屏障、调节菌群结构[36]；CBT-I 缓解停药焦虑[1] [20]；直肠三氧灌注可通过修复肠道屏障、抑制神经炎症、调节肠道菌群结构，增强 GABA 能抑制功能，降低中枢对 BZDs 的渴求与依赖[36]。本团队 RCT 研究(n = 88)显示，该联合方案可使 BZDs 完全停药率达 77.3%，显著高于对照组的 65.9% (P = 0.039)，第 12 周 PSQI 评分实验组显著低于对照组(5.45 ± 0.73 vs. 6.82 ± 0.62, P < 0.01)，焦虑、抑郁及戒断症状亦显著改善(本团队未发表数据，2026)。推荐干预周期为 2 周住院治疗 ＋12 周随访，主要终点为第 12 周 BZDs 减用率(按地西泮当量计算)及完全停药率；次要终点包括 PSQI、ISI、HAMA、HAMD、BWSQ 评分变化及肠道菌群多样性指标。随访节点设定为治疗后第 4、8、12 周。

方案二：逐步减量 ＋taVNS＋ 生活方式干预

该方案强调神经调控与作息重建的协同作用。经皮耳迷走神经电刺激(taVNS)可调节 HPA 轴活性、改善睡眠结构[77]，结合固定作息、地中海饮食[85] [86]与中等强度运动[87]，可同步恢复肠－脑轴节律功能。推荐干预周期为 8 周，主要终点为停药成功率(完全停用 BZDs 或减量 ≥ 75%)、PSQI 评分改善；次要终点包括皮质醇节律恢复、焦虑评分(HAMA)及菌群 β 多样性变化。随访节点设定为干预结束后第 8、24 周。

上述方案具有操作性强、安全性高、机制互补的特点，建议在专科医生指导下实施。未来应通过多中心随机对照试验进一步验证其疗效与推广价值，并探索基于菌群分型的个体化精准干预策略。

综上所述，目前基于肠－脑轴调控的干预研究已形成从基础机制到临床转化的多层次证据体系。为便于读者系统把握，本文将第 4 章所述各类干预策略的研究证据按层级汇总，见表 1。

Table 1. Summary of evidence for gut-brain axis-based intervention
表 1. 基于肠－脑轴的干预研究证据汇总

干预类型	干预手段	证据层级	主要结局	文献来源
益生菌	植物乳杆菌 P72	动物实验	上调 GABA 表达，改善失眠焦虑	[70]
益生菌	短双歧杆菌 CCFM1025	动物实验	改善认知与昼夜节律	[34]
益生菌	多菌株乳杆菌	RCT	PSQI 改善 69%，能量提升 31%	[71]
益生元	低聚果糖 ＋ 色氨酸	动物实验	睡眠延长 50.8%~81.0%，TNF-α↓38%	[72]
粪菌移植	洗涤菌群移植	观察性研究	睡眠评分改善	[74]
迷走神经调控	taVNS	Meta 分析	PSQI (MD = −3.60)，ISI (MD = −5.24)	[77]
抗炎干预	米诺环素	动物实验	抑制小胶质细胞，改善焦虑	[80]
生活方式	地中海饮食	系统综述	改善睡眠质量	[85] [86]
生活方式	中等强度运动	RCT	缓解焦虑，提高戒断成功率	[87]
三氧疗法	直肠三氧灌注	动物实验	改善认知，修复肠屏障，调节菌群	[36]
三氧疗法	直肠三氧灌注(联合 CBT-I)	RCT	完全停药率 77.3%，PSQI 显著改善	本团队研究，待发表

5. 治疗前景与挑战

基于肠－脑轴调控的干预策略为慢性失眠合并 BZDs 依赖的治疗提供了全新方向，其打破了传统“中枢单一靶点”的治疗模式，从“肠脑同治”角度实现对疾病的多靶点调控[43]。与传统的减药、替代治疗

相比，肠道菌群靶向调节、迷走神经调控等手段具有安全性高、不良反应少、能从根本上改善病理状态的优势，且益生菌、益生元等干预易于被患者接受，临床应用前景广阔[15]。

目前研究证实，精神益生菌可有效缓解慢性失眠症状，降低 BZDs 用药剂量与依赖程度，联合干预效果优于单一干预[34] [67]。粪菌移植在重度 BZDs 依赖患者中的应用潜力巨大，未来需完善供体筛选标准、优化移植方式[88]。肠－脑轴调控与传统药物、心理治疗的联合应用将成为未来趋势[85]。

然而，基于肠－脑轴的干预仍面临挑战：肠－脑轴机制尚未完全阐明[43]；肠道菌群的个体差异性导致干预效果存在差异，尚未建立统一标准[15] [67]；多数研究处于早期阶段，缺乏大样本长期 RCT 验证[37]；粪菌移植存在伦理问题与菌群定植效率问题[89]。

此外，BZDs 依赖是多因素作用的结果，基于肠－脑轴的干预需与心理治疗相结合。CBT-I 作为慢性失眠的一线心理治疗，与肠道菌群调控联合应用，可实现“生理－心理”双重调控，提高戒断成功率[90]。

6. 结论

综上所述，肠－脑轴功能紊乱是慢性失眠与 BZDs 依赖的共同病理基础，二者通过肠道菌群失衡、神经递质代谢紊乱、HPA 轴亢进、神经炎症激活及 GABAA 受体敏感性改变等机制形成恶性循环。基于肠－脑轴调控的干预策略，包括益生菌、益生元、粪菌移植、迷走神经调控及生活方式优化等，展现出从“肠脑同治”角度实现多靶点调控的治疗潜力。然而，目前该领域仍面临机制尚未完全阐明、个体差异大、缺乏大样本 RCT 验证等挑战。未来研究应聚焦于：① 深入解析肠－脑轴调控的分子机制；② 开展高质量、大样本、长期随访的临床研究；③ 探索基于个体肠道菌群特征的精准干预方案；④ 推动肠－脑轴调控与心理治疗、传统药物的联合应用策略。随着微生物组学与神经科学的交叉发展，靶向肠－脑轴有望成为慢性失眠合并 BZDs 依赖治疗的新突破。

致　谢

感谢成都中医药大学医学与生命科学学院提供的学术支持。感谢所有参与本文讨论和修改的老师和同学。

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