

中药复方对抗精神病药物所致女性精神分裂症患者闭经的疗效的 Meta 分析

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【摘要】 背景 精神疾病发病率不断升高, 而抗精神病药物容易引发女性患者药源性闭经, 使患者服药依从性降低, 疾病复发率增高。改善药物引起的女性患者闭经问题成为一个亟需解决的问题。目的 探讨中药复方治疗抗精神病药物所致闭经的效果和安全性, 为中药复方治疗抗精神病药物所致闭经提供参考。方法 于 2022 年 9 月 4 日, 计算机检索中国知网、维普数据库、万方数据库、中国生物医学文献数据库、PubMed、Cochrane Library、Embase, 收集中药复方治疗抗精神病药物所致闭经的随机对照试验(RCT)。采用 Cochrane 5.3 偏倚风险评估工具对纳入文献进行质量评价。采用 RevMan 5.3 对中药复方治疗抗精神病药物所致闭经的总有效率、治愈率、不良反应发生率和复发率进行 Meta 分析。结果 最终纳入 22 项 RCT 研究, 包括 1 879 例患者。Meta 分析结果显示, 中药复方或中药复方联合西药治疗抗精神病药物所致闭经的总有效率($RR=1.29, 95\% CI: 1.16\sim 1.44$)及治愈率($RR=1.62, 95\% CI: 1.45\sim 1.80$)均高于单纯西药治疗, 不良反应发生率($RR=0.56, 95\% CI: 0.41\sim 0.76$)和复发率($RR=0.16, 95\% CI: 0.06\sim 0.42$)均低于单纯西药治疗。结论 中药复方可能有助于改善抗精神病药物所致的闭经, 且安全性优于单纯西药治疗。

【关键词】 抗精神病药物所致闭经; 中药复方; 临床疗效; Meta 分析

开放科学(资源服务)标识码(OSID):



中图分类号: R749.053

文献标识码: A

doi: 10.11886/scjsws20230718001

Efficacy of traditional Chinese medicine compound on amenorrhea in female patients with schizophrenia caused by antipsychotic drugs: a Meta-analysis

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【Abstract】 **Background** The incidence of mental disorders is steadily increasing. However, antipsychotic medications, commonly used in treatment, can lead to drug-induced amenorrhea in female patients. This side effect significantly reduces medication adherence and increases the risk of disease recurrence. Therefore, addressing drug-induced amenorrhea in female patients has become an urgent problem requiring effective solutions. **Objective** To explore the efficacy and safety of traditional Chinese medicine compound in treating antipsychotic-induced amenorrhea, so as to provide guidance for the treatment of this condition using traditional Chinese medicine compound. **Methods** On September 4, 2022, a computerized search was conducted on across multiple databases, including China National Knowledge Infrastructure, VIP Database, Wanfang Database, China Biomedical Literature Database, PubMed, Cochrane Library and Embase, and randomized controlled trials (RCT) of traditional Chinese medicine compound in treating antipsychotic-induced amenorrhea were collected. The quality of the included literature was assessed using Cochrane 5.3 bias risk assessment tool. Meta-analysis was performed to assess the total effective rate, cure rate, incidence of adverse reactions and recurrence rate using RevMan 5.3. **Results** Ultimately, 22 RCT involving 1 879 patients were included. Meta-analysis results showed that the total effective rate ($RR=1.29, 95\% CI: 1.16\sim 1.44$) and cure rate ($RR=1.62, 95\% CI: 1.45\sim 1.80$) of traditional Chinese medicine compound or its combination with western medicine in treating antipsychotic-

induced amenorrhea were significantly higher compared to western medicine alone. Moreover, the incidence of adverse reactions ($RR=0.56$, $95\% CI: 0.41\sim 0.76$) and recurrence rate ($RR=0.16$, $95\% CI: 0.06\sim 0.42$) were significantly lower than those of western medicine alone. **Conclusion** Traditional Chinese medicine compound may offer benefits in ameliorating antipsychotic-induced amenorrhea and its safety is better than simple western medicine treatment.

【Keywords】 Antipsychotic-induced amenorrhea; Traditional Chinese medicine compound; Clinical efficacy; Meta-analysis

精神疾病是一种慢性疾病,抗精神病药物可有效控制患者的精神病性症状,但可能导致一定程度的不良反应。在年轻女性患者中,长期服用抗精神病药物容易引发药源性闭经,降低患者服药依从性,加重患者的心理负担,引起内分泌紊乱、加重闭经,进而增加精神疾病治疗的难度和社会经济负担。研究显示,部分女性患者服用抗精神病药物后血清催乳素水平升高,导致闭经^[1]。此现象已引起精神科医师的广泛关注,并寻求相应的预防和治疗措施。

对女性精神病患者而言,停用抗精神病药物 3~6 个月后基本可恢复正常月经周期,但停药会使患者精神疾病复发,增加后期治疗难度^[2]。现代医学已通过激素治疗、多巴胺受体激动剂治疗以及阿立哌唑治疗对月经周期进行调整,虽取得一定治疗效果,但可能会加重精神病性症状,降低患者治疗依从性,甚至引发新的不良反应^[3]。目前,临床常使用中药复方治疗抗精神病药物所致闭经,但其具体疗效有待进一步评估。本文通过对已发表的单一或联合使用中药复方治疗抗精神病药物所致闭经的随机对照试验(randomized controlled trial, RCT)进行 Meta 分析,以期对临床使用中药复方治疗抗精神病药物所致闭经问题提供参考。

1 资料与方法

1.1 资料来源与检索策略

1.1.1 资料来源

于 2022 年 9 月 4 日,由两名作者分别独立对中国知网、维普数据库、万方数据库、中国生物医学文献数据库、PubMed、Cochrane Library、Embase 进行检索,收集中药复方治疗抗精神病药物所致闭经的 RCT,检索时限为建库至 2022 年 9 月 4 日。

1.1.2 检索策略

采用主题词与自由词相结合进行检索。中文检索词:中药、中草药、抗精神病药物、舒必利、利培酮、氨磺必利、氯氮平、奥氮平、齐拉西酮、闭经。英文检索词:traditional Chinese medicine、herbal

formula、antipsychotics、sulpiride、risperidone、amisulpride、clozapine、olanzapine、ziprasidone、amenorrhea。

中文检索式(以中国知网为例):SU%=(‘中药’+‘中草药’)*(‘闭经’)*(‘抗精神病药物’+‘舒必利’+‘利培酮’+‘氨磺必利’+‘氯氮平’+‘奥氮平’+‘齐拉西酮’)。英文检索式(以 PubMed 为例):((traditional Chinese medicine) or (herbal formula)) and (amenorrhea) and ((antipsychotics) or (sulpiride) or (risperidone) or (amisulpride) or (clozapine) or (olanzapine) or (ziprasidone))。

1.2 文献纳入与排除标准

纳入标准:①研究设计为 RCT;②研究对象符合《中国精神障碍分类与诊断标准(第 3 版)》(Chinese Classification and Diagnostic Criteria of Mental Disease, third edition, CCMD-3)、《国际疾病分类(第 10 版)》(International Classification of Diseases, tenth edition, ICD-10)或《精神障碍诊断与统计手册(第 5 版)》(Diagnostic and Statistical Manual of Mental Disorders, fifth edition, DSM-5)中的精神分裂症诊断标准;③研究对象均接受抗精神病药物治疗;④研究对象为抗精神病药物所致闭经的女性患者,入组前停经>3 个月;⑤对照组接受单纯西药治疗,研究组接受中药复方或中药复方联合西药治疗;⑥结局指标包括总有效率、治愈率、不良反应发生率、复发率。排除标准:①非中英文文献;②由于阿立哌唑能够改善抗精神病药物引起的高催乳素血症,进而改善闭经症状^[4-5],故排除采用阿立哌唑进行治疗的文献;③内容不全、无法获取数据或质量相对较差的文献。

1.3 文献筛选与数据提取

由两名作者根据纳入与排除标准独立筛选文献并提取数据,交叉核对,若遇分歧,由第三名作者进行判定。采用 EndNote X7 管理文献。提取内容包括各文献的第一作者姓名、发表年份、样本量、干预措施、干预疗程和结局指标。

1.4 质量评价

由三名作者采用 Cochrane 5.3 手册推荐的偏倚风险评估工具独立对纳入文献的偏倚风险进行评价,对评价结果交叉核对,若遇分歧,由第四位作者判定。评价内容包括随机方法、分配隐藏、盲法、结果数据的完整性、选择性报告研究结果和其他偏倚来源 6 个条目。各条目均用“低偏倚风险”“高偏倚风险”或“不清楚”评价。所有指标均评定为“低偏倚风险”,则该文献偏倚风险低;如果有一个或多个指标评定为“高偏倚风险”,则该文献偏倚风险高;如果有一个或多个指标评定为“不清楚”,则该文献偏倚风险不确定。

1.5 统计方法

采用 RevMan 5.3 进行数据分析。通过 I^2 值判断纳入文献间的异质性。若 $P>0.10$ 、 $I^2<50\%$,表示各研究间异质性较小,采用固定效应模型。若 $P\leq 0.10$ 、 $I^2\geq 50\%$,表示各研究间异质性较大,采用随机效应模型。 $I^2\geq 90\%$ 或无法判断异质性来源时,则不进行 Meta 分析,采用描述性分析。通过亚组分析和敏感性分析,寻找导致异质性的可能原因。计数资料采用相对危险度(Relative Risk, RR)为效应量,所有效应量均采用 95% CI 表示。检验水准 $\alpha=0.05$ 。

2 结 果

2.1 纳入文献的基本情况

初步检索共获取文献 977 篇,剔除 679 篇重复文献后,获得文献 298 篇;阅读文献标题、摘要和全文后,排除 276 篇,最终纳入文献 22 篇。文献筛选流程见图 1。

2.2 纳入文献基本特征

纳入的 22 篇文献包含 1 879 例患者,其中研究组 954 例,对照组 925 例。22 篇文献^[6-27]均报告了总有效率,21 篇文献^[6-20,22-27]报告了治愈率,11 篇文献^[7,13-16,18-20,22,26-27]报告了不良反应发生率,4 篇文献^[9,16,26-27]报告了复发率。微信扫 OSID 二维码获取纳入文献基本特征信息。

2.3 纳入文献质量评价

在纳入的 22 篇文献中,2 篇文献^[10,24]评为“低偏倚风险”;20 篇文献^[6-9,11-23,25-27]评为“不清楚”。微信扫 OSID 二维码获取纳入文献质量评价信息。

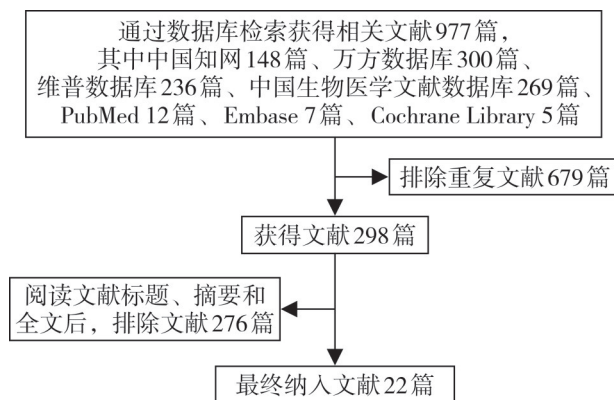


图1 文献筛选流程图

Figure 1 Flow chart of literature screening

2.4 Meta 分析结果

2.4.1 总有效率

22 篇文献^[6-27]均报告了总有效率,各文献存在异质性($I^2=84\%$, $P<0.01$),故采用随机效应模型。Meta 分析结果显示,两组总有效率比较,差异有统计学意义($RR=1.29$, 95% CI: 1.16~1.44)。亚组分析显示,中药复方组合并效应量($RR=1.50$, 95% CI: 1.14~1.98)与中药复方联合用药组合并效应量($RR=1.22$, 95% CI: 1.15~1.30)的置信区间存在重叠,差异无统计学意义($P=0.15$)。见图 2。

2.4.2 治愈率

21 篇文献^[6-20,22-27]报告了治愈率,各文献之间异质性较小($I^2=30\%$, $P=0.09$),故采用固定效应模型。Meta 分析结果显示,研究组治愈率高于对照组,差异有统计学意义($RR=1.62$, 95% CI: 1.45~1.80)。亚组分析结果显示,中药复方组合并效应量($RR=1.83$, 95% CI: 1.53~2.18)与联合用药组合并效应量($RR=1.49$, 95% CI: 1.30~1.70)的置信区间存在重叠,差异无统计学意义($P=0.07$)。见图 3。

2.4.3 不良反应发生率

11 篇文献^[7,13-16,18-20,22,26-27]报告了不良反应发生率,各文献之间无异质性($I^2=0\%$, $P=0.78$),故采用固定效应模型。Meta 分析结果显示,研究组不良反应发生率低于对照组,差异有统计学意义($RR=0.56$, 95% CI: 0.41~0.76)。亚组分析结果显示,中药复方组合并效应量($RR=0.38$, 95% CI: 0.23~0.65, $P<0.01$)与联合用药组合并效应量($RR=0.71$, 95% CI: 0.48~1.04)的置信区间有重叠,差异无统计学意义($P=0.06$)。见图 4。

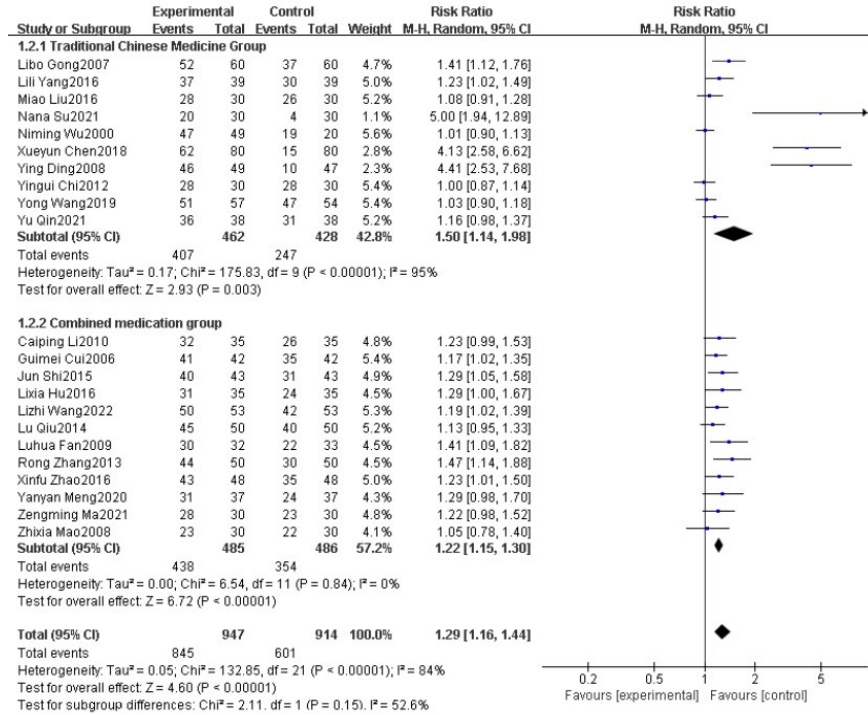


图2 两组总有效率比较的Meta分析森林图

Figure 2 Meta-analysis forest diagram of comparing the total effective rate between two groups

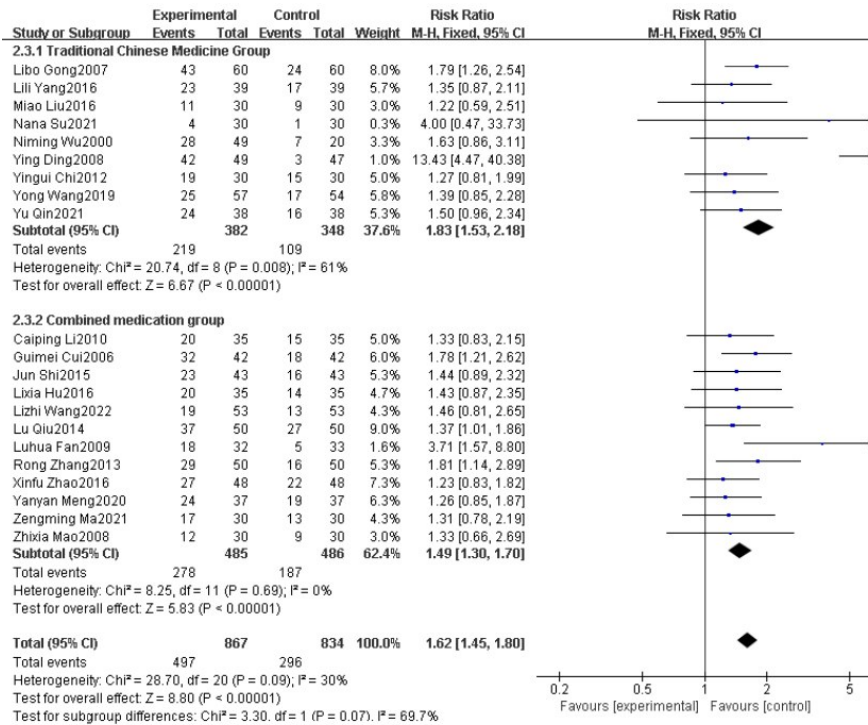


图3 两组治愈率比较的Meta分析森林图

Figure 3 Meta-analysis forest diagram of comparing the cure rate between two groups

2.4.4 复发率

4 篇文献^[9, 16, 26-27] 报告了复发率,各文献之间无异质性 ($I^2=0\%$, $P=0.52$), 故采用固定效应模型。Meta 分析结果显示, 研究组复发率低于对照组, 差异有统计学意义 ($RR=0.16$, $95\% CI: 0.06\sim 0.42$)。由于只有一篇文献报告了单纯中药复方的干预措

施, 故未进行亚组分析。见图 5。

2.5 敏感性分析

采用逐一剔除法, 分别对 22 篇文献依次剔除, 剩余文献进行 Meta 分析合并, 重新统计 Meta 分析结果未发生显著改变。

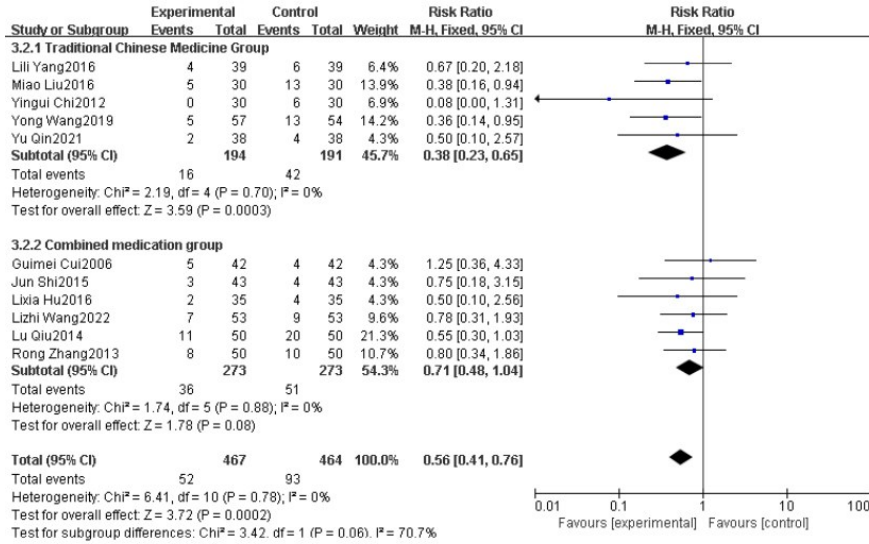


图 4 两组不良反应发生率比较的 Meta 分析森林图

Figure 4 Meta-analysis forest diagram of comparing the adverse reactions rate between two groups

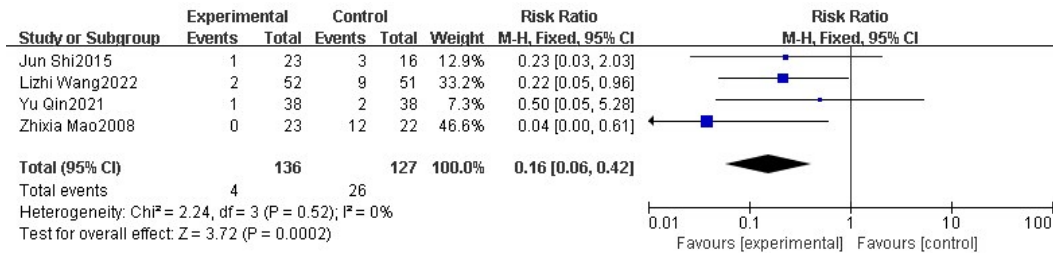


图 5 两组复发率比较的 Meta 分析森林图

Figure 5 Meta-analysis forest diagram of comparing the recurrence rate between two groups

2.6 发表偏倚

通过总有效率的散点图分析发表偏倚。漏斗图的对称性较低,表明样本量较小和可能存在发表偏倚。见图 6。

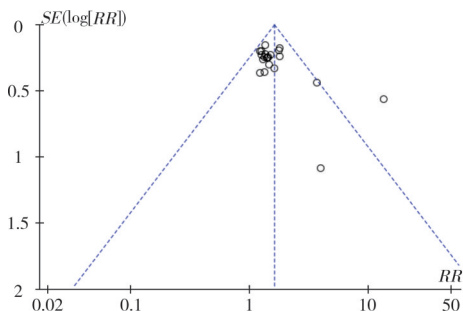


图 6 纳入文献发表偏倚漏斗图

Figure 6 Funnel diagram of publication bias of included studies

3 讨 论

本研究结果显示,与单纯西药相比,中药复方或中药复方联合西药治疗抗精神病药物所致闭经的总有效率和治愈率均高于单纯西药治疗,不良反应发生率和复发率均低于单纯西药治疗,提示中药复方可能有助于改善抗精神病药物所致闭经症状。

但由于纳入的 RCT 质量较低,偏倚控制存在一定问题,且各文献存在样本量较少、用药存在差异等问题,故还需要高质量的 RCT 进行深入分析和讨论。抗精神病药物普遍对 D₂ 受体表现出很强的亲和力,一旦与 D₂ 受体结合,导致催乳素水平升高;同时抗精神病药物可直接阻断多巴胺 D₂ 受体,从而削弱多巴胺对促黄体激素分泌的抑制作用,引起催乳素水平升高,从而导致月经出现异常^[28]。

中医治病谨守“观其脉证、知犯何逆、随证治之”的辨证论治学术思想,周小波等^[29]将抗精神病药物所致闭经分为肝郁气滞、阴虚火旺、脾虚湿盛及肝肾阴虚四种证型,辨证论治均取得一定效果。在本研究纳入的文献中,中药复方多为桃红四物汤加减。桃红四物汤为祛瘀血的基础方,在方中以祛瘀为核心,辅以养血行气。方中以桃仁、红花强劲破血,以熟地、当归滋阴养血,芍药养血和营,以增补血之力,川芎行气活血,以助活血之功。全方配伍,使瘀血祛、新血生、气机畅。桃红四物汤还可调节患者血脂水平,降低患者体质量指数,并改善卵巢局部血流动力学情况,增加子宫内膜厚度^[30]。而西医多采用激素治疗,通过模拟正常月经的周期调

节雌孕激素分泌,但部分患者疗效较差,甚至出现不良反应,复发率较高。

综上所述,中药复方或中药复方联合西药治疗可能有助于改善抗精神病药物所致闭经,且安全性优于单纯西药治疗。本研究局限性:①纳入文献未对抗精神病药物所致闭经的症状进行分类;②纳入文献样本量较小且质量偏低;③大部分研究未具体描述随机方法,可能导致潜在的选择性偏倚;④中药复方汤剂在具体的方药配伍、剂型、服用时间等方面未统一,结果存在一定偏倚。未来需要更多的多中心、大样本、高质量的 RCT 进一步探索中药复方治疗抗精神病药物所致闭经的效果和安全性。

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(收稿日期:2023-07-18)

(本文编辑:吴俊林)