齐拉西酮针剂治疗精神分裂症患者激越症状的Meta回归

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摘 要：【目的】基于已发表的齐拉西酮速效针剂对精神分裂症患者激越症状治疗的中英文文献，综合分析齐拉西酮针剂治疗激越症状的疗效及其相关影响因素。【方法】检索PubMed、EMBASE、Web of Knowledge、Cochrane Library、万方数据，中国期刊全文数据库，中国生物医学文献数据库(CBMdisc)和维普网，应用随机临床试验报告的声明(CONSORT)为参照标准进行入组和评价文献，采用STATA软件进行Meta分析，以疗效的效应值为因变量，性别、年龄、治疗前PANSS量表总分、是否合并口服抗精神病药物等为协变量，进行Meta回归模型分析。【结果】根据GRADE方法，主要结局指标的证据水平为“中度”。共有14项研究纳入Meta分析和Meta回归，其中英文5篇、中文9篇。治疗前后样本量分别为1 197和1 149。随机效应Meta分析结果显示齐拉西酮针剂疗效显著[SMD=2.04，95%CI(1.47，2.61)，P = 0.000]。Meta回归分析显示，疗效与基线PANSS分数(t = 5.57，P = 0.011)、合并使用口服抗精神病药物(t = 4.07，P = 0.027)有关，与文献发表语种(t = −0.57，P = 0.625)、年龄(t = 0.74，P = 0.539)无关，女性相对于男性有疗效更优的统计学差异趋势(t = −2.95，P = 0.060)。【结论】齐拉西酮速效针剂治疗精神分裂症患者激越症状疗效良好，Meta回归模型显示治疗前病情较重、合并口服抗精神病药物的患者疗效更好。

关键词：精神分裂症；激越；齐拉西酮；Meta分析；Meta回归
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Ziprasidone Injection for Agitation in Schizophrenic Patients: A Meta-Regression Analysis

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Abstract: 【Objective】To evaluate the efficacy of ziprasidone injection and the related influencing factors for treating agitation in schizophrenic patients based on published literature in English or Chinese. 【Methods】We searched PubMed, EMBASE, Web of Knowledge, Cochrane Library, Wanfang data, Chinese Journal Full-Text Database (CJFD), Chinese Biomedical Literature Database (CBMdisc) and VIP Chinese Technology Periodical Database (VIP). The Consolidated Standards of Reporting Trials (CONSORT) statement was used as a criterion for screening and assessing the literature. Meta-analysis and meta-regression were conducted by using STATA. With the effect size as the dependent variable and sex, age, baseline PANSS scale total score and oral antipsychotics as the covariates, the meta-regression model was analyzed. 【Results】The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was employed to rate the overall quality of evidence. A total of 14 studies (5 in English and 9 in Chinese) were included in meta analysis and meta regression. The samples were, respectively, 1 197 and 1 149 at baseline and after

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treatment. Random effect Meta analysis showed that ziprasidone injection had significant efficacy in the treatment of agitation symptoms [SMD=2.04, 95%CI (1.47, 2.61), P = 0.000]. Meta regression revealed that the efficacy was related to baseline PANSS scores (t = 5.57, P = 0.011) and oral antipsychotics (t = 4.07, P = 0.027), but irrelevant to age (t = 0.74, P = 0.539) and language published (t = −0.57, P = 0.625). The efficacy was better in female patients than that in male patients (t = 2.95, P = 0.060).【Conclusion】Ziprasidone injection has significant efficacy in schizophrenia patients with agitation symptoms and the efficacy may be enhanced in those patients with higher baseline PANSS score and added with oral antipsychotics.

Key words: schizophrenia; agitation; ziprasidone; meta-analysis; meta-regression

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精神分裂症患者急性期兴奋激越症状非常常见[1]，研究显示精神科新入院患者中伴有激越症状表现的患者中精神分裂症比例高达64.3%，其中严重激越患者为31.0%[2]。第二代抗精神药物中齐拉西酮速效针剂是临床上常用的快速控制激越症状的药物剂型，也是目前我国国内唯一的速效新型抗精神病药的针剂。我们曾对齐拉西酮、氟哌啶醇、氯硝西泮3种针剂治疗中国人群精神分裂症患者进行网络Meta分析，结果显示综合疗效和不良反应，在中国精神分裂症患者人群中，齐拉西酮针剂治疗急性期激越症状优于氟哌啶醇、氯硝西泮针剂[3]。但影响齐拉西酮针剂疗效的因素尚不清楚，故我们进行Meta回归以了解齐拉西酮针剂治疗精神分裂症患者激越症状的疗效、安全性及影响疗效的因素。

1　材料与方法

1.1　文献检索

文献数据库和检索策略：英文分别为PubMed、Web of Knowledge、EMBASE、Cochrane Library等，检索词为schizophrenia, agitation, injection, intramuscular；中文数据库为万方数据资源系统，中国期刊全文数据库，中国生物医学文献数据库(CBMdisc)和维普网等，中文检索词包括：精神分裂症，激越，兴奋，针剂，注射液，肌注等。文献检索策略参考Cochrane协作网工作手册制定[4]，检索时均使用截词符以提高查全率；并从近半年精神科相关杂志(中华精神科杂志、中国神经精神疾病杂志、上海精神医学等)及检索后的相关文章的参考文献中进行手工回溯检索[5]。

1.2　检索结果

中英文文献数据库检索均不限定初始检索时间，最后的检索截止时间为2019年6月18日，第1和第2作者在4个外文数据库和4个中文数据库中共检索到研究文献14篇，英文和中文分别为5及9篇，其中Daniel等[6]报道了两个治疗剂量组均符合纳入标准。入组文献及筛查文献等情况见图1。

1.3　筛查文献

文献纳入和排除标准以随机临床试验报告的声明(CONSORT)为标准参照进行[7]。具体纳入标准为：①研究对象为精神分裂症的患者；②研究设计为随机对照研究或有明确盲法的自身对照研究；③统计方法正确；④数据完整，报告了可供Meta分析的疗效数据和/或不良反应数据等[8]。排除标准：①研究设计非随机对照研究；②缺乏可供Meta分析的统计数据；③综述文献、个案报道和动物实验等；④重复报道文献[8]。最终鉴定和筛选用于更详尽评价的全文文献(n=22)，最后排除8篇研究(个案报道3篇，研究对象为儿童1篇，缺乏Meta分析数据2篇，回顾性研究1篇，研究对象为急诊病人1篇)，最终有14篇可纳入Meta分析(图1)。

1.4　文献质量评估、分级及数据收集

对纳入的文献分别由两位评价者(Su, Xu)独立进行质量评价。如果两位评价者意见不一致时讨论解决，如仍存在分歧请第3位评价者(Lu或Shi)。根据Cochrane手册中偏倚风险量表(Risk of Bias, RoB)对各纳入研究进行相应的评估[4]。激越症状疗效指标数据、不良反应等数据提取，分别由两位评价者(Su, Xu)独立完成，录入数据库，

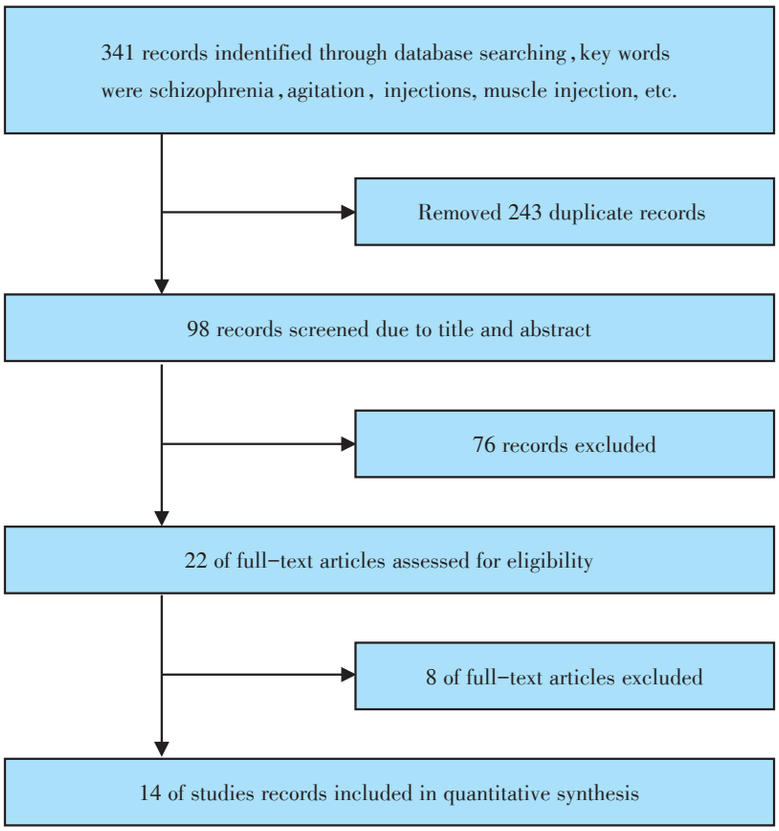


图1 研究入组流程图

Fig.1 Flowchart of included studies

并进行交叉核对。纳入Meta分析的研究情况详见表1。

1.5 统计学处理

使用统计软件Stata 14.1进行Meta分析和Meta回归:疗效指标为激越症状量表的治疗前后的变化,以疗效的效应值为应变量,性别、年龄、治疗前PANSS量表总分、是否合并口服抗精神病药物等为协变量,进行Meta回归模型分析[9]。发表性偏倚的分析采用漏斗图来评估所纳入文献的偏倚情况[10]。采用GRADE(Grades of Recommendation, Assessment, Development and Evaluation)方法判断主要结局指标的证据水平[11]。

2 结 果

2.1 纳入研究特征

共有14篇文献纳入最终的Meta分析和Meta回归模型,其中英文5篇,中文9篇;齐拉西酮针剂治疗前后样本量分别为1 197和1 149,患者平均年龄26~39.9岁,基线PANSS量表总分的均值介于78~106之间,多数研究中男性居多(表1)。其中4项研究的偏倚风险为"低风险",10项研究的偏倚风险为"高风险"。根据GRADE方法[11],主要结局指标的证据水平为"中度"。其中1项研究纳入了两个剂量组的齐拉西酮针剂的比较(Daniel 2004[6]),两组齐拉西酮针剂治疗的剂量分别为10 mg每日四次和20 mg每日四次。所有入组研究中14项研究为随机对照研究;各纳入研究的入组样本的平均年龄、性别构成、具体治疗实施方案等详见表1。

2.2 齐拉西酮针剂治疗前后激越症状的疗效

对入选的14篇文献15个比较进行异质性检验,精神分裂症患者激越症状齐拉西酮针剂治疗前后比较存在异质性[Heterogeneity: $Tau^2 = 1.19$; $I^2 = 96.5\%$, $df = 37$ ($P = 0.000$)],故采用随机效应模型进行汇总分析(图2),并进行亚组分层分

表1　纳入Meta分析和Meta回归的14个研究概括

Table 1　summaries of included studies in Meta analysis and Meta regression

Studies	Author	Year	Age	Duration	Baseline Sample	Endpoint Sample	Ratio of male patients	Baseline PANSS total scores
1	Wang[12]	2007	29	–	16	15	38%	105.9
2	Jiang[13]	2008	33	4.8 years	36	36	58%	–
3	Wang[14]	2005	27.4	–	30	30	63%	–
4	Ye[15]	2009	27.4	–	30	30	63%	103.5
5	Li[16]	2006	34	18 months	115	115	65%	103.96
6	Hu[17]	2014	28.4	–	43	43	60%	89.05
7	Zhang[18]	2015	28.1	1–10 year	47	47	60%	98.64
8	Chen[19]	2008	32.7	31.3 months	32	32	0%	91.2
9	Chen[20]	2010	31	64.5 months	40	39	60%	78.21
10	Zhang[21]	2013	32	3.2 days[1)]	189	167	48%	–
11	Daniel[22]	2001	39.9	–	78	41	78%	86.65
12	Daniel[6]	2004	38	–	71 and 66	59 and 56	93% and 86%	–
13	Brook[23]	2000	26	–	12	12	100%	–
14	Brook[24]	2005	34	–	429	427	67%	–

析。发表性偏倚的不对称性检验显示治疗前后比较无发表性偏倚(Begg′s Test，Number of Studies = 15，Z = 1.29，P =0.198，图3)。随机效应模型合并分析的结果显示，精神分裂症患者经过齐拉西酮针剂治疗后激越症状明显好转，[合并SMD=2.04，95%CI(1.47，2.61)，P = 0.000]；根据PANSS分数进行亚组分析显示两组疗效均显著(SMD分别为1.21和2.92)，但低分组异质性较大(两组I^2分别为87.4%和53.3%，图2)。敏感性分析的结果显示合并效应受单个研究的影响均较小，纳入或排除某个研究对合并效应的影响很小，合并效应的结果稳定性较好(图4)。

2.3　齐拉西酮针剂的不良反应发生率

齐拉西酮针剂治疗的不良反应发生率主要包括：头昏(发生率约10.4%，下同)，嗜睡(约13.1%)，心动过速(约12.2%)，心电图异常(约9.5%)和锥体外系反应(约24.3%)等，报道的总体不良事件发生率约28.1%~55%，只有一项研究报道了临床意义的QTc延长，但未报道具体值[20]。

2.4　疗效影响因素的Meta回归

齐拉西酮针剂治疗精神分裂症患者激越症状的Meta回归分析显示，疗效与基线PANSS分数(t = 5.57，P = 0.011)、合并使用口服抗精神病药物(t = 4.07，P = 0.027)有关，与文献发表语种(t = −0.57，P = 0.625)、年龄(t = 0.74，P = 0.539)无关，女性相对于男性有疗效更优的统计学差异趋势(t = −2.95，P = 0.060)。

3　讨　论

3.1　主要发现

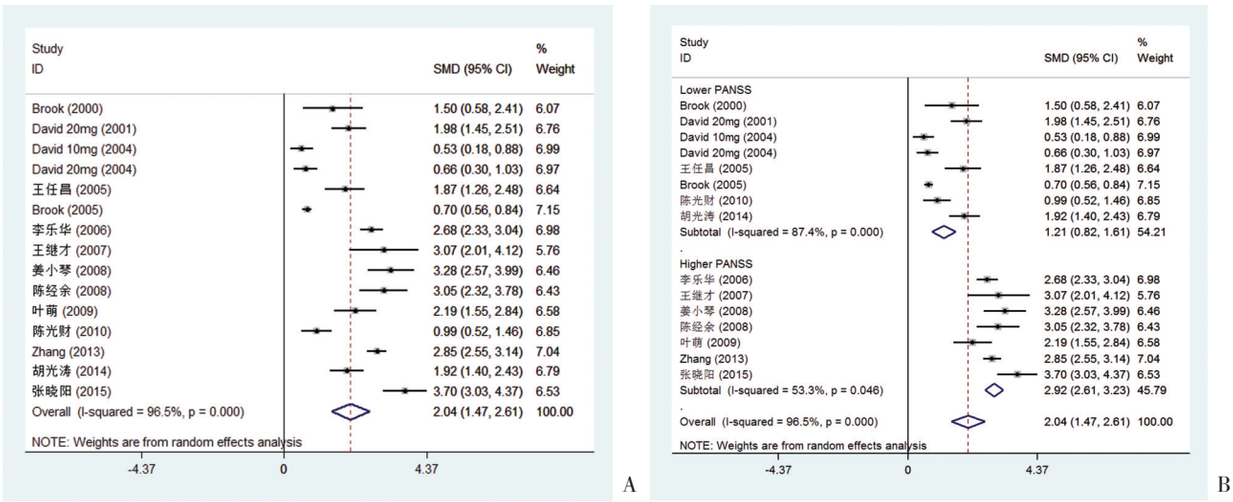
Meta回归是基于文献的二次数据分析，其优点是可充分利用以前发表研究的数据、使用统计学模型整合现有信息，给临床实践提供循证医学证据[25]。本研究结果显示齐拉西酮针剂治疗精神分裂症患者激越症状疗效显著，其疗效与治疗前病情严重度有关，Meta回归的结果也显示合并使用口服抗精神病药物者疗效更好，疗效可能存在

表1 纳入Meta分析和Meta回归的14个研究概括,续上

Table 1 Summaries of included studies in Meta Analysis and Meta Regression

Studies	Details of studies design, treatment of ziprasidone
1	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 3 days, dose of the first day was 10 mg bid, dose of day 2 and day 3 was10 mg bid or 20 mg bid according to symptoms, not combined oral antipsychotics, maximum dose was 40 mg/d.
2	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 3 days, dose of the first injection was 10 mg, repeated treatment after 4-6 h according to symptoms, not combined oral antipsychotics, maximum dose was 40 mg/d.
3	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 3 days, the original dose was 10 mg or 20 mg, repeated treatment after 4-6 h, not combined oral antipsychotics, maximum dose was 40 mg/d and maximum treatment less than 3 times.
4	Randomized double blind, schizophrenia diagnostic criteria was DSM-IV, patients treated by ziprasidone injection for 3 days, the original dose was 10 mg or 20 mg, repeated treatment after 4-6 h, not combined oral antipsychotics, maximum dose was 40 mg/d and maximum treatment less than 3 times.
5	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 3 days, the original dose was 10 mg or 20 mg, repeated treatment after 4-6 h, not combined oral antipsychotics, maximum dose was 40 mg/d and maximum treatment less than 3 times.
6	Randomized double blind, schizophrenia diagnostic criteria was ICD-10, patients treated by ziprasidone injection for 3 days, the dose was 10 mg or 20 mg, repeated treatment after 4-6 h, not combined oral antipsychotics, maximum dose was 40 mg/d.
7	Randomized double blind, schizophrenia diagnostic criteria was ICD-10, patients treated by ziprasidone injection for 3 days, the original dose was 10 mg or 20 mg, repeated treatment after 4-6 h according to symptoms, not combined oral antipsychotics, maximum dose was 40 mg/d and mean dose was 34 mg.
8	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 3 days, the original dose was 10 mg, repeated treatment after 6-8 h, not combined oral antipsychotics, mean dose was 21mg and maximum dose was 30 mg/d and maximum treatment less than 3 times/d.
9	Randomized double blind, schizophrenia diagnostic criteria was CCMD-3, patients treated by ziprasidone injection for 7 days, the original dose was 10-20 mg, not combined oral antipsychotics, bid or tid and maximum dose was 40 mg/d.
10	Randomized double blind, schizophrenia diagnostic criteria was ICD-10, patients treated by ziprasidone injection for 3 days (72 h), the original dose was 10 mg or 20 mg, combined oral antipsychotics, maximum dose was 40 mg/d.
11	Randomized double blind, schizophrenia diagnostic criteria was DSM-IV, patients treated by ziprasidone injection for 1 days, the original dose was 20 mg, repeated treatment after 4 h according to symptoms, not combined oral antipsychotics, maximum dose was 80 mg/d a and maximum treatment less than 3 times/d.
12	Randomized open study, schizophrenia diagnostic criteria was DSM-III-R, patients treated by ziprasidone injection for 7 days, dose of two groups were 10 mg qid or 20 mg qid, not combined oral antipsychotics, and maximum dose was 40mg/d and 80 mg/d respectively.
13	Randomized open study, schizophrenia diagnostic criteria was DSM-III-R, patients treated by ziprasidone injection for 3 days, first dose was 10 mg or 20 mg, not combined oral antipsychotics, maximum dose was 40 mg/d.
14	Randomized double blind, schizophrenia diagnostic criteria was DSM-IV, patients treated by ziprasidone injection for 3 days, first dose was 10 mg or 20 mg, combined oral antipsychotics, maximum dose was 40 mg/d.

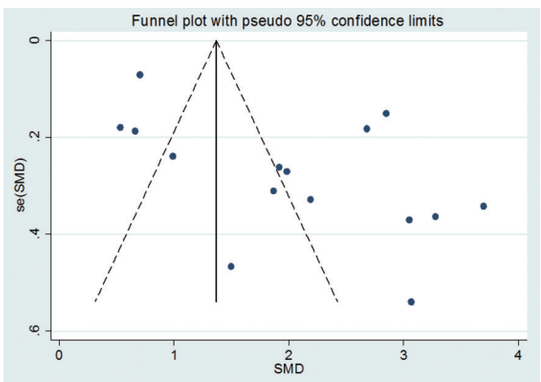
CCMD-3: Chinese Classification and Diagnostic Criteria of Mental Disease (3rd version); ICD-10: The International Statistical Classification of Diseases and Related Health Problems 10th Revision, DSM: Diagnostic and Statistical Manual of Mental Disorders; bid: twice a day (bis in die); 1) Duration of agitation symptoms



A：Ziprasidone injection for agitation，SMD = 2.04，P = 0.000；B：subgroup analysis，SMD = 1.21，P = 0.000（Lower PANSS group）and SMD = 2.92，P = 0.000（Higher PANSS group），respectively.

图2　齐拉西酮针剂肌注治疗激越症状的疗效的森林图

Fig.2　Forest plot of efficacy on ziprasidone injection for agitation



Begg′s Test，n = 15，Z = 1.29，P = 0.198

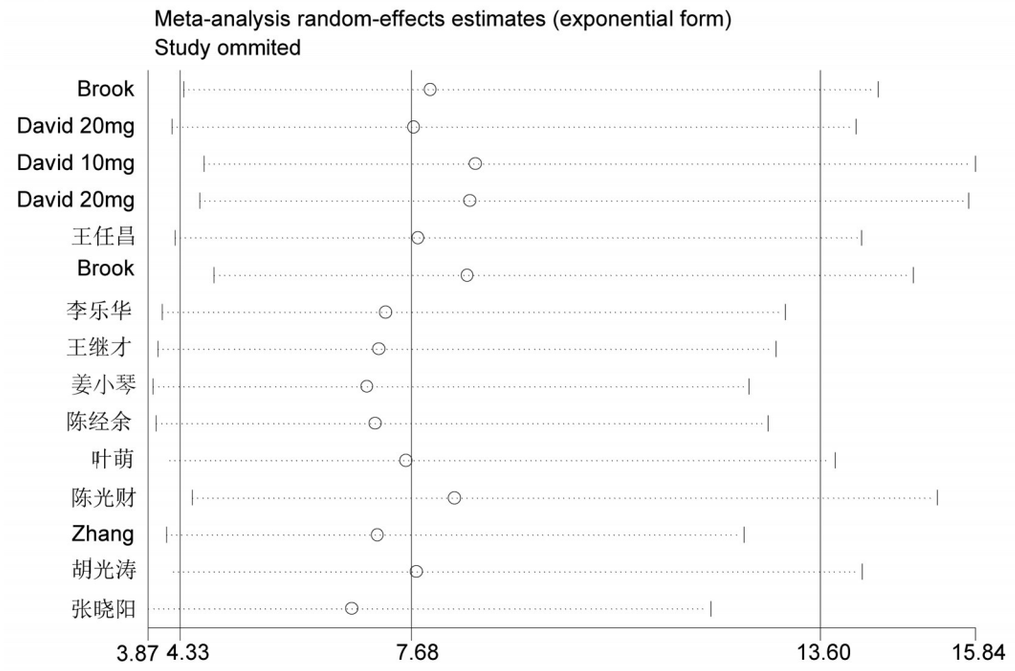
图3　发表性偏倚分析的倒漏斗图

Fig.3　Funnel plot of publication bias

抗精神病药物已成为精神分裂症患者治疗的首选[25]。虽然非典型抗精神病药物针剂在激越症状的治疗中越来越重要，但相关的研究结果并不多，其疗效的影响因素也并不明确。我们既往曾通过网络Meta分析，比较中国人群精神分裂症患者激越症状肌注药物治疗，综合排序结果显示齐拉西酮疗效和可接受度优于氟哌啶醇和氯硝西泮，可以作为精神分裂症患者激越症状的一线治疗[3]。本研究的结果同样显示齐拉西酮针剂治疗精神分裂症患者的激越症状疗效显著，且Meta回归的结果显示基线激越症状较重者治疗效果更好，同时齐拉西酮针剂的不良反应较传统抗精神病药物明显降低。

本次研究的对象不再局限于中国人群患者，Meta回归的结果显示文献发表的语种亦无统计学差异，提示中国人群患者齐拉西酮针剂治疗的效果可能与其他人群一致，齐拉西酮针剂的疗效可能无种族差异[26]。我们的研究结果与Kishi等[27]在日本人群精神分裂症患者中的研究结果一致，即抗精神病药物对于精神分裂症的疗效可能无明显的种族差异。尽管统计指标上Meta回归结果未达到显著性统计学意义，但本研究提示齐拉西酮针剂的疗效可能存在性别差异的趋势（P = 0.060，接近统计学差异），与Haddad等[28]的报道一致，均提示女性患者可能对抗精神药物治疗的反应更佳。

虽然精神分裂症患者急性期往往依从性差，特别是急性期激越症状明显时，我国《激越患者精神科处置专家共识》仍推荐非药物干预是精神病性激越精神科处置第一步，当非药物控制激越效果不佳时，考虑采取通过口服给药或者肌肉注射药物干预[2]。而肌肉注射治疗起效快，有助于快速缓解激越相关症状，降低伴有攻击暴力行为或倾向患者的风险[18]。本研究显示合并口服药物者



n = 15, random-effects, combined Z = 7.68

图4 齐拉西酮针剂治疗激越症状的敏感性分析

Fig.4 Sensitivity analysis plot of ziprasidone injection for agitation

疗效更佳,故可考虑针剂肌肉注射控制激越症状的同时予以口服给药。但有学者认为,齐拉西酮针剂肌肉注射时,不应合并使用其他口服抗精神病药物[3]。故临床实践中,仍应根据患者的情况个体化制定治疗方案。

3.2 研究局限

本研究存在以下不足之处:首先,Meta回归要求纳入Meta分析的研究数不能太少,推荐10篇以上,本研究纳入14项研究15个比较,数量相对偏少,且其中部分研究的样本量也较小,可能会导致统计学偏倚;其次,由于Meta分析结果存在异质性,尽管我们采用了随机效应模型进行统计,但对研究结果的解释仍需要谨慎;最后,由于临床实践中齐拉西酮针剂肌肉注射时合并口服抗精神病药物存在争议,故以上的研究结论还有待进一步证实,以期得出更加全面的结论,从而更有利于精神分裂症患者激越症状治疗的临床实践。

3.3 研究意义

本研究的结果可以为临床决策提供有价值的信息,齐拉西酮针剂肌肉注射治疗精神分裂症患者激越症状的疗效显著,不良反应较少;治疗前激越症状严重者、口服给药者疗效更好,年龄、人种等不影响齐拉西酮针剂的疗效,女性可能疗效更好。

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