•Original article•

Efficacy and safety of generic escitalopram versus Lexapro in the treatment of major depression: a multicenter double-blinded randomized controlled trial

Yimin YU[1], Huafang LI[1]*, Biao WANG[1]*, Keqing LI[2], Xiufeng XU[3], Jianguo SHI[4], Chengge GAO[5], Qingrong TAN[6]

Background: Depression is an increasingly important public health problem in China, but only a small minority of patients with this condition receive treatment. One of the reasons for low treatment rates is the relatively high cost of imported antidepressant medications.

Aim: Compare the efficacy and safety of the generic form of the selective serotonin re-uptake inhibitory (SSRI) antidepressant escitalopram to the proprietary form of escitalopram (Lexapro) in the treatment of major depression.

Methods: A multicenter double-blinded randomized controlled trial enrolled 260 patients with depression and randomly assigned them to receive eight weeks of treatment with either generic escitalopram (*n*=130) or Lexapro (*n*=130). Efficacy was assessed by the Hamilton rating scale for depression (HAMD-17). Safety was assessed by evaluating adverse events reported by patients, regularly recording vital signs, and conducting laboratory tests and electrocardiograms.

Results: There were 35 (27%) dropouts during the 8 weeks of treatment in the generic escitalopram group and 32 (25%) in the Lexapro group. In the intention-to-treat analysis (i.e., including all patients) the mean (s.d.) drop in the HAMD total score at the end of the 8th week of treatment was 13.9 (8.2) in the generic escitalopram group and 14.3 (8.1) in the Lexapro group (*t*=0.44, *p*=0.664). The proportions of patients responsive to treatment (i.e., >50% drop in total HAMD score) were 69% and 67% in the generic escitalopram group and Lexapro group, respectively (χ^2=0.16, *df*=1, *p*=0.690; and the proportions that achieved remission (i.e., final HAMD <7) were 51% and 49% (χ^2=0.06, *df*=1, *p*=0.804). The most frequently reported adverse events were dry mouth (12.3%), nausea (9.2 %) and dizziness (6.2%) in the generic escitalopram group and nausea (10.8%), fainting (7.7%) and drowsiness (6.9%) in the Lexapro group. During the first 35 days of treatment, one suicide and two suicide attempts occurred in the generic escitalopram group and one suicide occurred in the Lexapro group (Fisher exact test, *p*=0.314).

Conclusion: Generic escitalopram is as effective and safe as Lexapro in the initial treatment of patients with moderate to severe episodes of major depression who seek treatment in the outpatient departments of psychiatric hospitals in China. Careful monitoring of the risk of suicidal events is an essential component of the treatment of depressed patients.

Trial registration: NCT00866593 (clinical.trails.gov)

1. Introduction

Depression is characterized by high prevalence, frequent relapse, substantial disability, and increased mortality. In both high-income and low- and middle-income countries it is one of the two most important causes of disease burden.[1] The current combined prevalence of major depression and dysthymic disorder among adults in China is 4% -- representing more than 35 million individuals – but only about 8% of these individuals have ever received any type of treatment for their condition.[2] One of several reasons for the low treatment rates is the relatively high cost of

imported proprietary antidepressant medications, so the development of generic forms of antidepressants is an important step in increasing treatment rates for depressive conditions and, thus, reducing the huge health burden these conditions place on the country.

Selective Serotonin Reuptake Inhibitors (SSRIs) are one important category of antidepressants. Escitalopram is an SSRI antidepressant (the S-stereoisomer of citalopram) that has been shown to have good treatment effects with relatively few side effects.[3-5] The chemical structure and treatment mechanisms of generic escitalopram produced by Jiangsu Nhwa Pharmaceutical Corporation Limited are the same as those of the proprietary form of escitalopram (Lexapro) which is imported and supplied by Xi'an Janssen Pharmaceutica. The average monthly cost of treatment with the generic form of escitalpram is 223 Renminbi (36 US dollars) while that of the proprietary form is 501 Renminbi (81 US dollars). This study is a randomized controlled trial that aims to compare the clinical efficacy and safety of these two forms of escitalopram.

2. Methods

2.1 Sample

The Shanghai Mental Health Center served as the coordinating center for the study and five other psychiatric hospitals from different parts of China participated in the study. Inclusion criteria included: (a) outpatient psychiatric patient at the participating centers with a diagnosis of major depressive disorder based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)[6] (as determined by the treating clinician); (b) between 18 and 65 years of age; (c) not currently taking psychoactive medications other than sleeping medications (those previously taking medications had to be drug-free for at least 7 times the half-life of the medication); (d) Hamilton Depression Rating Scale (HAMD-17)[7] score $\geq$20 both at the time of screening and at the time of entry into the treatment phase of the study; (e) a score on the first HAMD item (about depressed affect) of $\geq$2; and (f) a score on the severity subscale of the Clinical Global Impression scale (CGI-S)[8] of $\geq$ 4.

Individuals with any of the following conditions were excluded: (a) serious suicidal ideation based on the clinician's evaluation; (b) any serious physical illness; (c) any history of epilepsy; (d) history of closed-angle glaucoma; (e) abuse of or dependence on alcohol or any psychoactive drug during the past year; (f) depressive episode induced by other mental or physical illnesses; (g) lactation, current pregnancy, or any possible preg-
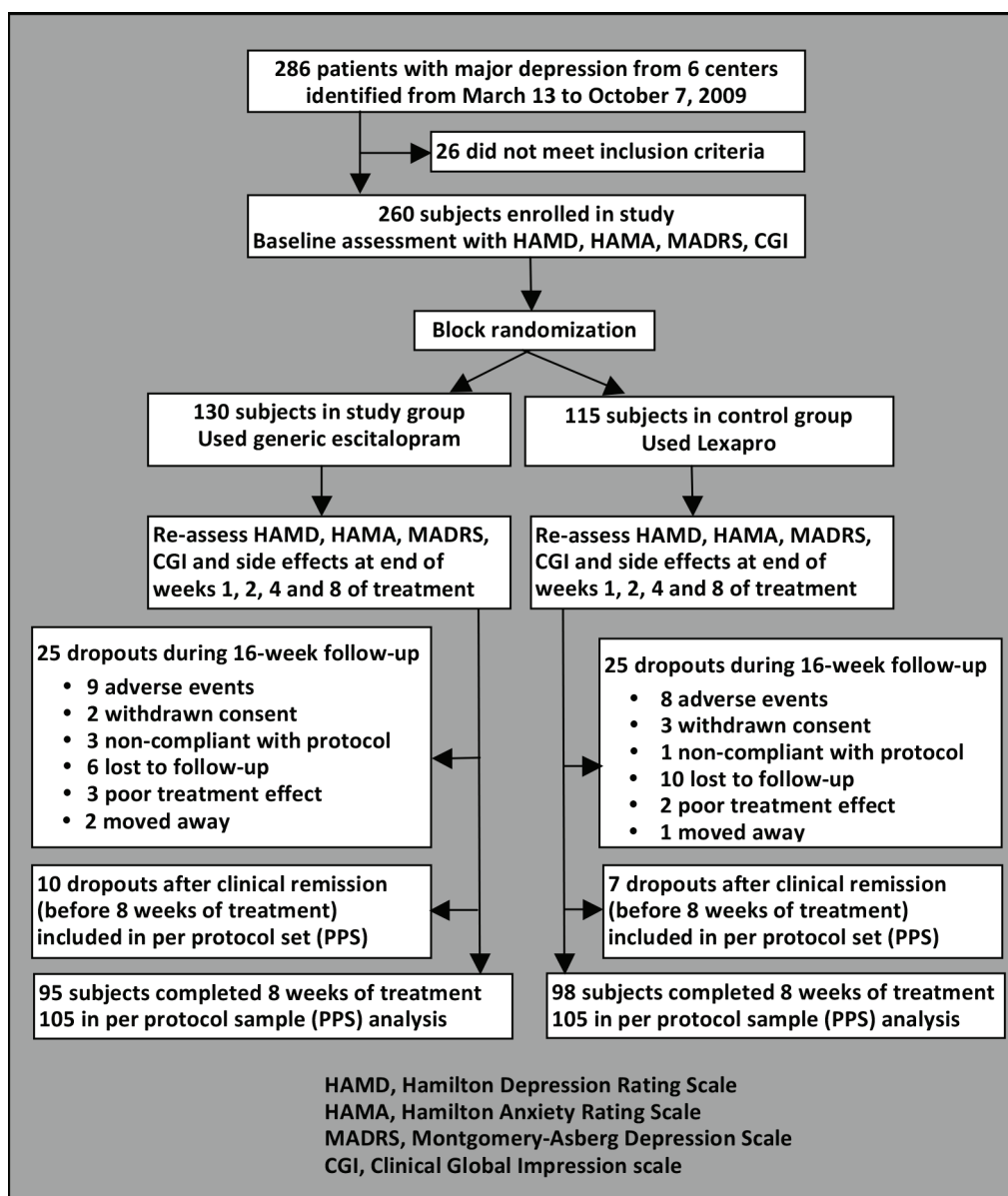
nancy during the trial; (h) history of severe drug allergy; or (i) a history of poor response to escitalopram.

The enrollment of subjects is shown in Figure 1. A total of 260 individuals were recruited from March 13 to October 7, 2009 and 130 individuals were randomly assigned to the study group (those using generic escitalopram) or the control group (those using Lexapro). The study group included 46 males and 84 females; their mean (s.d.) age was 37.2 (12.9) years; 37 (28.5%) had a college education; 53 (40.8%) were in their first episode of illness, 58 (44.6%) had had multiple depressive episodes, and 19 (14.6%) had chronic depression; the median (intraquartile range) duration of the current episode of depression and the total duration of depressive episodes were 3 (1 to 4) months and 15 (4 to 48) months, respectively; and 80 (61.5%) reported that 'psychological pressure' was the main precipitant of their current depressive symptoms. The control group included 49 males and 81 females; their mean age was 39.4 (12.8) years; 43 (33.1%) had a college education; 59 (45.4%) were in their first episode of illness, 51 (39.2%) had had multiple depressive episodes, and 20 (15.4%) had chronic depression; the median duration of the current episode of depression and the total duration of depressive episodes were 3 (1 to 6) months and 16 (6 to 55) months, respectively; and 69 (53.1%) reported that psychological pressure was the main precipitant of their current depressive symptoms. No statistically significant differences were found between the groups for sex, age, level of education, duration of current episode, total duration of depressive episodes, type of depressive episode, or reported triggers of the depressive episode. Before treatment, the mean scores on the HAMD-17 were 24.7 (3.2) and 24.7 (3.3) for the study group and control group, respectively (t=0.04; p=0.970).

2.2 Study design

This is a multicenter double-blind randomized controlled trial comparing the efficacy and safety of generic escitalopram and its commercial counterpart, Lexapro, in the treatment of major depressive disorder. At each of the six centers two or three research clinicians were trained in the protocol and in the administration of the evaluative instruments employed in the study. Standard methods were employed to ensure maintenance of blinding; only the study coordinator at each site (who was not involved in the evaluation or treatment of subjects) was able to break the blind during the course of the study. Stratified randomization (stratified by institution) was used to assign participants to the study or the control group using the 'Drug and

Figure 1. Flowchart of the study

```
┌─────────────────────────────────────────────┐
│  286 patients with major depression from 6   │
│  centers identified from March 13 to         │
│  October 7, 2009                             │
└─────────────────────────────────────────────┘
          │────────► 26 did not meet inclusion criteria
          ▼
┌─────────────────────────────────────────────┐
│  260 subjects enrolled in study             │
│  Baseline assessment with HAMD, HAMA,       │
│  MADRS, CGI                                  │
└─────────────────────────────────────────────┘
          ▼
      Block randomization
       ╱          ╲
┌──────────────────┐   ┌──────────────────┐
│ 130 subjects in  │   │ 115 subjects in  │
│ study group      │   │ control group    │
│ Used generic     │   │ Used Lexapro     │
│ escitalopram     │   │                  │
└──────────────────┘   └──────────────────┘
```

130 subjects in study group — Used generic escitalopram

115 subjects in control group — Used Lexapro

Re-assess HAMD, HAMA, MADRS, CGI and side effects at end of weeks 1, 2, 4 and 8 of treatment

Re-assess HAMD, HAMA, MADRS, CGI and side effects at end of weeks 1, 2, 4 and 8 of treatment

25 dropouts during 16-week follow-up
- 9 adverse events
- 2 withdrawn consent
- 3 non-compliant with protocol
- 6 lost to follow-up
- 3 poor treatment effect
- 2 moved away

25 dropouts during 16-week follow-up
- 8 adverse events
- 3 withdrawn consent
- 1 non-compliant with protocol
- 10 lost to follow-up
- 2 poor treatment effect
- 1 moved away

10 dropouts after clinical remission (before 8 weeks of treatment) included in per protocol set (PPS)

7 dropouts after clinical remission (before 8 weeks of treatment) included in per protocol set (PPS)

95 subjects completed 8 weeks of treatment 105 in per protocol sample (PPS) analysis

98 subjects completed 8 weeks of treatment 105 in per protocol sample (PPS) analysis

HAMD, Hamilton Depression Rating Scale
HAMA, Hamilton Anxiety Rating Scale
MADRS, Montgomery-Asberg Depression Scale
CGI, Clinical Global Impression scale

Statistics' (DAS) software version 2.1.1 (a Chinese statistical package). The total duration of observation was eight weeks. Both generic escitalopram (10 mg/tablet, batch number, 20071001) and Lexapro (10 mg/tablet, batch number, 2163474) were taken orally once a day. (These medications were all provided by the Jiangsu Nhwa Pharmaceutical Corporation Limited.) The initial dosage for both groups was 10 mg/d. At the end of the second week the dosage was increased to 20 mg/d if the patient tolerated the medication well but the treatment effect was considered poor (i.e., a score of ≥ 3 on the improvement subscale of the Clinical Global Impression scale [CGI-I][8]) or if the treating clinician thought it necessary to increase the dosage.

Alternatively, the dosage was maintained at 10 mg/d after two weeks of treatment if the treatment was considered effective (e.g., CGI-I <3), if the treating clinician did not think it necessary to increase the dosage, or if the patient did not tolerate the medication well.

During the trial, sleep medications (e.g., zolpidem, zopiclone, midazolam, alprazolam, clonazepam, and estazolam) at usual dosages were allowed before the patient went to sleep. The maximum duration of consecutive treatment with sleep medication was one week. No other forms of treatment that could potentially interfere with the treatment outcome were

allowed, including antipsychotics, antidepressants, anti-anxiety medications, mood stabilizers, systematic psychological therapy, or electroconvulsive therapy.

Patients were withdrawn from the study if any of the following occurred: (a) patient or family request to withdrawal (usually due to poor treatment effect or severe side effect); (b) discontinuation of medication for at least three consecutive days; (c) loss to follow-up; (d) treating clinician recommends withdrawal from study (usually due to poor compliance or the occurrence adverse events); (e) break of blinding (i.e., treating clinician or patient knows which type of medication is being administered); (f) the occurrence of manic or psychotic symptoms for at least two weeks; (g) the occurrence of a suicide attempt; (h) poor treatment effect or exacerbated symptoms after four weeks of treatment; or (i) pregnancy during the trial.

This study was approved by the institutional review board of the Shanghai Mental Health Center.

2.3 Evaluation of treatment effect and safety

The main index for treatment effect was the change in the HAMD total score at the end of eight weeks of treatment. Clinical remission was considered when the total HAMD score was equal to or less than seven. Treatment was considered effective when there was a 50% or greater reduction in the baseline HAMD total score; treatment was considered ineffective if the HAMD reduction was less than 50%. Secondary outcome measures included the Montgomery-Asberg Depression Scale (MADRS),[9] the Hamilton Anxiety Scale (HAMA),[10] and changes in the CGI score. The validity and reliability of Chinese versions of HAMD, MADRS, and HAMA are satisfactory.[11] These outcomes were assessed by the treating clinician at baseline, and at the end of the 1st, 2nd, 4th, and 8th weeks of treatment (or at the time of termination from the study).

Evaluations of safety included assessment of vital signs and identification of adverse events by asking patients about the occurrence of any physical or psychological changes (whether or not they are related to medication use) at the end of the 1st, 2nd, 4th, 6th and 8th weeks of treatment. Laboratory tests of blood and urine and electrocardiograms were conducted at baseline and at the end of the 8th week of treatment.

2.4 Statistical analysis

The required sample sizes were estimated using standard methods for tests of non-inferiority (equivalence trial). Based on data reported from the company that developed escitalopram, the total HAMD score dropped 12.3 points after eight weeks of treatment. Using 12 as the average required drop in HAMD scores, a δ (non-inferiority index) of 2.5, a type I error of 0.025, a type II error of 0.2, and an overall standard deviation in the mean before versus after HAMD change score of 6, the calculated sample size for each group was 90. Considering the requirement of the national Law about the registration of new drugs and potential loss of follow-up, the final sample size was set at 260, 130 in each group.

SAS 9.1.3 was used for all data analysis. Two-sample and one-sample t-tests were used to compare continuous variables and chi-square tests were used to compare categorical variables. Analysis of covariance was used to analyze changes in the main outcome measure (the HAMD-17 total score) after treatment with the center and group assignment as covariates. Repeated measures analysis of variance was used to compare the change in outcome measures between the groups over the five evaluation points (baseline and at the end of the 1st, 2nd, 4th, and 8th weeks of treatment). The Full Analysis Set (FAS) and Safety Set (SS for safety analysis) included all 260 individuals enrolled in the treatment phase of the study; that is, they were 'Intention-to-Treat' (ITT) analyses in which the Last Observation Carried Forward (LOCF) imputation method was used. The Per Protocol Set (PPS) included 210 individuals, including 193 individuals who completed all eight weeks of treatment and 17 individuals who dropped out before completion of eight weeks of treatment but had achieved remision criteria prior to dropping out (their final assessment results were used to impute values at subsequent evaluation periods).

3. Results

3.1 Recruitment and completion

A total of 260 individuals were enrolled in the study with 130 in either arm. There were 35 (26.9%) dropouts in the study group and 32 (24.6%) in the control group (χ^2=0.18, *p=0.671*). Figure 1 provides a list of the reasons for dropout in both groups.

3.2 Treatment effect

3.2.1 Changes in the HAMD total score and test of the null hypothesis

As shown in Tables 1 and 2, FAS analysis and PPS analysis found no statistically significant differences in the reduction from baseline of the HAMD scores at any of the four follow-up time periods used in the study.

Table 1. Comparison of mean (sd) HAMD-17 total scores between the groups based on an the Full Analysis Set (FAS) analysis

Time point	Study group (generic escitalopram) (*n* =130)	Control group (Lexapro) (*n* =130)	*t*	*p*	reduction from baseline in study group	reduction from baseline in control group	*t*	*p*
Baseline	24.7 (3.2)	24.7 (3.3)	0.04	0.970	----	----		
1 week	21.2 (5.2)	20.6 (5.3)	1.00	0.318	-3.5 (4.0)	-4.1 (4.6)	1.25	0.214
2 week	17.5 (6.6)	17.8 (6.3)	0.37	0.716	-7.2 (5.9)	-6.9 (5.8)	0.38	0.701
4 week	14.3 (7.3)	14.5 (7.0)	0.19	0.849	-10.4 (6.8)	-10.2 (6.6)	0.19	0.853
6 week	12.0 (7.9)	11.9 (7.6)	0.13	0.898	-12.7 (7.7)	-12.8 (7.4)	0.15	0.883
8 week	10.8 (8.4)	10.4 (8.1)	0.41	0.680	-13.9 (8.2)	-14.3 (8.1)	0.44	0.664

Table 2. Comparison of mean (sd) HAMD-17 total scores between the groups based on patients who completed the study according to the protocol, the Per Protocol Set (PPS)

Time point	Study group (generic escitalopram) (*n* =105)	Control group (Lexapro) (*n* =105)	*t*	*p*	reduction from baseline in study group	reduction from baseline in control group	*t*	*p*
Baseline	24.6 (3.2)	24.6 (3.2)	0.02	0.983	----	----		
1 week	20.7 (5.0)	19.8 (5.3)	1.17	0.242	-4.0 (3.9)	-4.8 (4.7)	1.42	0.158
2 week	16.3 (6.0)	16.6 (6.0)	0.31	0.755	-8.3 (5.4)	-8.1 (5.6)	0.33	0.744
4 week	12.1 (5.5)	12.4 (5.6)	0.38	0.702	-12.5 (5.1)	-12.2 (5.5)	0.39	0.697
6 week	9.3 (5.3)	9.2 (5.2)	0.09	0.926	-15.4 (5.2)	-15.4 (5.5)	0.10	0.918
8 week	7.8 (5.4)	7.3 (5.2)	0.60	0.548	-16.8 (5.5)	-17.3 (5.6)	0.59	0.559

The overall time trend analysis also showed no statistically significant difference between the two groups either in the FAS analysis (*F*=0.44, *p*=0.664) or in the PPS analysis (*F*=0.59, *p*=0.559). The mean difference in the HAMD total scores between the two groups (study group – control group) at week 8 was 0.43 (95% confidence interval [*CI*]=-1.55, 2.41) for the FAS analysis and 0.43 (95% *CI*= -0.96, 1.81) for the PPS analysis. As shown in Table 3, after adjusting for baseline HAMD scores and for the six treatment centers using an analysis of covariance, the difference between groups in the HAMD total score at the end of 8 weeks of treatment remained statistically insignificant for both the FAS and PPS analyses. Moreover, the proportion of subjects who reached remission criteria (total HAMD score ≤7) and the proportion in which the treatment was considered effective (≥50% reduction from baseline HAMD score) after 8 weeks of treatment were not significantly differ-

ent between the two groups: in the FAS analysis, 50.8% (66/130) and 49.2% (64/130) achieved remission in the study and control groups, respectively (χ^2=0.06, *df*=1, *p*=0.804); and in 69.2% (90/130) and 66.9% (87/130) of the study and control group subjects, respectively, the treatment was considered effective (χ^2=0.16, *df*=1, *p*=0.690).

3.2.2 Comparisons of MADRS, HAMA, and CGI-I scores

Analysis of the FAS showed that eight weeks after the beginning of the treatment, the MADRS total score decreased from 30.2 (6.1) at baseline to 8.0 (5.9) in the study group and from 30.9 (6.3) to 8.1 (6.8) in the control group (*t*=1.12, *p*=0.902). Similarly, the HAMA score decreased from 21.0 (5.2) at baseline to 6.2 (3.9) in the study group and from 20.4 (5.8) to 6.0 (4.6) in the control group (*t*=0.43, *p*=0.669). After 8 weeks of treatment the proportions of 'substantially improved'

Table 3. Analysis of covariance of changes in mean Hamilton Depression Rating Scale (HAMD-17) total scores after 8 weeks of treatment using both a Full Analysis Set (FAS) analysis and a Per Protocol Set (PPS) analysis

Variable	FAS analysis (n=130 in each group)				PPS analysis (n=105 in each group)		
	df	F	p		df	F	p
Group assignment	1	0.185	0.667		1	0.365	0.546
Research center	5	0.279	0.924		5	2.075	0.070
Baseline	1	7.089	0.008		1	29.873	<0.001

and 'improved' on the CGI-I were 64.2% and 27.4% in the study group and 66.3% and 24.5% in the control group (t=0.14, p=0.886).

3.3 Safety

3.3.1 Occurrence of adverse events

During the trial 59 (45.4%) individuals in the study group and 74 (56.9%) in the control group experienced one or more adverse events (x^2=3.46, p=0.063). Most of these adverse events were mild to moderate in severity and of relatively short duration but in 9 (6.9%) individuals in the study group and 8 (6.2%) individuals in the control group these adverse events were severe enough, persistent enough or distressing enough to require withdrawal from the study (x^2=0.06, p=0.802). Four severe adverse events occurred in the study group during the trial (one case of lung cancer, two suicide attempts, and one suicide death) and one severe adverse event occurred in the control group (a suicide death) (Fisher Exact Test p=0.176). In the study group the suicide occurred on the 35th day of treatment and the two suicide attempts occurred on the 2nd day and 20th day of treatment; in the control group the suicide occurred on the 6th day of treatment. Only one of these severe adverse events (the suicide death in the study group) was considered by the treating clinician as possibly related to the use of study medication.

The adverse events with an occurrence of greater than 1% in the study group (i.e., that occurred in at least two different individuals) included dry mouth (12.3 %), nausea (9.2%), dizziness (6.2%), decreased appetite (5.4%), drowsiness (5.4%), fatigue (3.8%), insomnia (3.1%), headache (3.1%), diarrhea (2.3%), heartburn (2.3%), constipation (2.3%), excessive sweating (2.3%), irregular heartbeat (2.3%), pressure in the chest (2.3%), stomach bloating (1.5%), stomach discomfort (1.5%), upper respiratory infection (1.5%), feeling of distention in the head (1.5%), excessive yawning (1.5%), palpitation (1.5%), overall physical discomfort (1.5%), and suicide

attempt (1.5%). The majority of adverse events were in the digestive system (37.7%) or the neurological system (27.7%).

In the control group adverse events with an occurrence of greater than 1% included nausea (10.8%), fatigue (7.7%), drowsiness (6.9%), dizziness (5.4%), dry mouth (4.6%), decreased appetite (4.6%), diarrhea (3.8%), constipation (3.8%), headache (3.8%), palpitation (3.8%), discomfort in the stomach (3.1%), upper respiratory infection (2.3%), fainting (2.3%), sleepiness (2.3%), urine track infection (2.3%), abdominal pain (1.5%), insomnia (1.5%), sprain in the right leg (1.5%), delayed urination (1.5%), and formication (1.5%). The majority were events in the digestive (36.2%) or the neurological system (34.6%).

3.3.2 Lab tests, vital signs and physical examinations related to safety

Clinically significant changes in blood and urine tests were identified at the end of the 8th week of treatment in 8 (6.2%) individuals from the study group and 12 (9.2%) from the control group (x^2=0.87, p=0.351). In the study group one individual had an elevated white blood count, one had elevated neutrophils, one had urinary leucocytes, two had elevated alanine aminotransferase (ALT), and three had elevated aspartate aminotransferase (AST). In the control group two individuals had and elevated white blood cell count, one had a decreased white blood count, one had elevated neutrophils, one had a low hemoglobin, one had urinary protein, one had white blood cells in the urine, one had elevated ALT, one had elevated AST, and two had elevated fasting blood glucose. No serious physical consequences were observed among study participants who had these changes.

No statistically significant changes or abnormalities in heart rate, in the systolic and diastolic blood pressure, or in the electrocardiogram results were observed during the treatment in either of the groups.

4. Discussion

4.1 Main findings

In this study, the baseline HAMD-17 score was 24, indicating that the majority of patients were moderately to severely depressed. The magnitude of the mean drop in the total HAMD score after 8 weeks of treatment of 13.9 (8.2) in the study group was similar to that found in other studies of escitalopram.[12] The proportions of subjects in whom the treatment was effective (69% in the study group and 67% in the control group) and the proportions who achieved clinical remission (51% in the study group and 49% in the control group) were also in line with the findings of other studies.[13] Our results indicate that both the generic and trade name forms of escitalopram are efficacious antidepressants and that there are no significant differences in the efficacy of the two forms of the medication.

Some studies from other countries have found that escitalopram has a good treatment effect on anxiety symptoms.[14,15] This is supported by findings from the current study. After 8 weeks of treatment, the HAMA score decreased significantly in both groups. The magnitude of the reduction in anxiety symptoms was not significantly different between the two forms of escitalopram.

Common adverse events in both groups were dry mouth, nausea, dizziness, drowsiness and decreased appetite; this pattern of adverse effects is similar to that reported in other studies of escitalopram.[12,16]

The occurrence of four suicidal events (two fatalities and two attempts) in the 260 enrolled subjects (1.5%, 95% CI=0.4, 3.9%) during 8 weeks of treatment despite excluding patients considered at high risk of suicide from the study was concerning. Three of the four suicidal events occurred in the first month of treatment and two of them occurred in the first week of treatment. Suicidal behaviors are rare, but depressed persons are certainly at elevated risk of suicide and there is some evidence that suicidal risk is highest during the first month of antidepressant treatment, so this relatively high rate could be a statistical outlier.[17] Nevertheless, larger studies in which subjects are followed over longer periods are needed to determine whether the rates of suicidal events are higher in those treated with escitalopram than in those treated with other antidepressants. And further efforts are needed to better identify and effectively intervene with the minority of depressed patients who are at high risk of suicide.

A meta-analysis comparing effectiveness and safety of 12 commonly used antidepressants found that generic escitalopram was one of the antidepressants with the best treatment effects and one of the highest rates of treatment adherence.[18] Results from this study confirm this finding in Chinese patients with moderate to severe episodes of major depression who seek treatment in psychiatric outpatient services.

4.2 Limitations

The current study is a multi-center study that enrolled outpatients with depression from six psychiatric hospitals in China. It is unclear how many patients were screened at the centers to identify the 286 potential participants so it is not possible to be certain of the extent to which recruited patients were representative of all depressed individuals in China who receive psychiatric treatment. Moreover, the results could be different in a sample of patients treated at non-specialty hospitals, who typically have less severe forms of depression than those treated at psychiatric hospitals. The sample size, though sufficiently large to assess the main hypothesis about the similarity of the two forms of the medication, was not large enough to conduct stratified analysis (e.g., by gender, age group, number of previous depressive episodes, etc.) so there may be some differences in the outcomes of the two forms of the medication in subgroups of subjects that were not identified. The follow-up period was only 8 weeks, so it is not possible to say anything about the comparability of the two forms of medications during prolonged usage or during the maintenance phase of the treatment of depression. The dropout rate of 27% in the study group and 25% in the control group was relatively high but not out of line with what is seen in similar studies. Additional work is needed to identify biological markers that can identify which patients will respond best to which antidepressants.

4.3 Significance

This study compared the efficacy and safety of generic and brand name escitalopram. In summary, the efficacy and safety of the generic form of escitalopram (produced by Jiangsu Nhwa Pharmaceutical Corporation Limited) during the first 8 weeks of treatment of a depressive episode are not significantly different from the efficacy and safety of the brand name form of escitalopram (Lexapro, produced by Xi'an Janssen Pharmaceutica) when used at a dosage of 10 to 20 mg per day in moderate to severely depressed patients treated in the outpatient departments of psychiatric hospitals in China. Both forms of the medication are effective and safe and they are also both relatively

effective in alleviating the anxiety symptoms that commonly co-occur with depression. The occurrence of 4 suicidal events (2 deaths and 2 attempts) in the 260 patients (1.5%) treated with escitalopram during the first 35 days of treatment may be a statistical outlier, but the rates of suicidal events should be re-assessed in larger studies with longer follow-up times.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

Funding

References

1. Murray CJL, Vos T, Lozano R, Naghavi M, Abraham D. Flaxman AD, et. al Global Burden of Disease Study Diseases and Injuries Group. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2197-2223.

2. Phillips MR, Zhang JX, Shi QC, Song ZQ, Ding ZJ, Pang ST et. al. Prevalence, associated disability and treatment of mental disorders in four provinces in China, 2001-2005: an epidemiological survey. *Lancet* 2009, **373**:2041-2053.

3. Feighner JP, Overo K. Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression *J Clin Psychiatry* 1999; **60**(12):824-830.

4. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescent. *Am J Psychiatry* 2004; **161**(6):1079-1083.

5. Kasckow JW, Welge J, Carroll BT, Thalassinos A, Mohamed S. Citalopram treatment of minor depression in elderly men: an open pilot study. *Am J Geriatr Psychiatry* 2002; **10**(3): 344-347.

6. American Psychiatric Association. *DSM IV Sourcebook*. Virginia: Am Psychiatric Press Inc; *1994.*

7. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; **6**(4): 278-296.

8. Guy W. *ECDEU Assessment Manual for Psychopathology*. Rockville, MD: U.S National Institute of Health, Psychopharmacology Research Branch; 1976: 534-537.

9. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Brit J Psychiatry* 1979; **134** (4): 382-389.

10. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959; **32**(1): 50-55.

11. Zhang MY. *Handbook of Rating Scales in Psychiatry*. 2nd ed. Changsha: Hunan Science and Technology Press; 1998. (in Chinese)

12. Ou JJ, Xun GL, Wu RR, Li LH, Fang MS, Zhang HG. Efficacy and safety of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, randomized, double-blind, flexible-dose study. *Psychopharmacology (Berl)*2011; **213**(2-3): 639-646.

13. Schmitt L, Tonnoir B, Arbus C. Safety and efficacy of oral escitalopram as continuation treatment of intravenous citalopram in patients with major depressive disorder. *Neuropsychobiology* 2006; **54**(4): 201-207.

14. Davidson JR, Bose A, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 2005; **66**(11): 1441-1446.

15. Waugh J, Goa KL. Escitalopram: a review of its use in the management of major depressive and anxiety disorders. *CNS Drugs* 2003; **17**(5): 343-362.

16. Chen HY, Li HF, Kuang WH, Zhao JP, Xie SP, Tao M. Randomized double-blind controlled trial of escitalopram versus citalopram in the treatment of depression. *Shanghai Archives of Psychiat*ry 2010; **22**(5): 301-303. (in Chinese)

17. Jick H, Kaye JA, Jick SS. Antidepressants and the Risk of Suicidal Behaviors. *JAMA* 2004; **292**(3): 338–43.

18. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; **373**(9665): 746-758.

Dr. Yimin Yu graduated from the Shanghai Second Medical University in 2001 and received a Master's of Medicine degree from the Shanghai Jiao Tong University School of Medicine in 2009. She has worked at the Shanghai Mental Health Center since 2001 and is currently an attending psychiatrist in the Medical Institute for Clinical Trails (MICT) responsible for conducting clinical trials of psychopharmacological agents.

国产草酸依地普仑片与来士普治疗抑郁症有效性和安全性: 随机双盲、对照、多中心临床研究

余一旻[1] 李华芳[1]* 王飚[1]* 栗克清[2] 许秀峰[3] 师建国[4] 高成阁[5] 谭庆荣[6]

[1]上海交通大学医学院附属精神卫生中心 上海
[2]河北省精神卫生中心 河北保定
[3]昆明医学院第一附属医院 云南昆明
[4]西安市精神卫生中心 陕西西安
[5]西安交通大学附属第一医院 陕西西安
[6]第四军医大学西京医院 陕西西安

通信作者: 李华芳: lhlh5@yahoo.com.cn; 王飚: wangbaio@yahoo.com.cn

摘要

背景 抑郁症已日益成为影响国人健康的公共卫生问题,但只有少部分抑郁症患者获得治疗。治疗率低的原因之一在于进口抗抑郁药治疗花费高昂。

目的 比较选择性5-羟色胺再摄取抑制剂(Selective Serotonin Reuptake Inhibitors, SSRIs) 艾司西酞普兰国产药草酸依地普仑片与专利药来士普治疗抑郁症的有效性和安全性。

方法 采用随机双盲、阳性药平行对照、多中心临床研究,入组抑郁症病例260例,其中研究组(草酸依地普仑治疗组)和对照组(来士普组)各130例,治疗8周。主要疗效指标为17项汉密尔顿抑郁量表(Hamilton rating scale for depression, HAMD-17)评分。安全性评估包括不良事件、定期体检、实验室检查和心电图检查等。

结果 为期8周的治疗中研究组有35名(27%) 受试者脱落,对照组为32名(25%)。意向治疗分析(intention-to-treat analysis, ITT) 发现治疗8周后,研究组的HAMD量表评分减分(标准差)为13.9(8.2)分,对照组为14.3(8.1)分(t=0.44, p=0.664)。研究组和对照组的有效率(HAMD减分率≥50%)分别为69%和67%(χ^2=0.16, df=1, p=0.690);临床痊愈率(研究终点HAMD总分≤7分)分别为51%和49%(χ^2=0.06, df=1, p=0.804)。研究组常见的不良反应为口干(12.3%)、恶心(9.2%)和头晕(6.2%),对照组为恶心(10.8%)、乏力(7.7%)和嗜睡(6.9%)。 在研究的前35天中,治疗组出现1例自杀和2例自杀未遂,对照组出现1例自杀(Fisher精确检验,p=0.314)。

结论 对在精神卫生中心门诊就诊的中、重度抑郁症患者,采用国产草酸依地普仑片与来士普初步治疗的疗效与安全性相当。治疗过程中需要严密关注自杀风险。

试验注册号: NCT00866593 (clinical.trails.gov)