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Observing time effect of SSRIs on suicide risk and suicide-related behaviour: a network meta-analysis protocol

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ABSTRACT

Introduction Suicide is a serious problem worldwide and 90% cases are associated with pre-existing or underlying mental illness. As a common treatment for depressive symptoms that suicidal people may receive, selective serotonin reuptake inhibitors (SSRIs) have been linked to a possible increase in suicide rates. Studies focusing on SSRIs and suicide have produced inconsistent results, suggesting that use of SSRIs decreases, increases, has no effect on suicide rates, or that the effect of SSRIs on suicide is age-dependent. This protocol of network meta-analysis aims to precisely evaluate the time effects of SSRIs by observing weekly changes of suicidality in the first 2 months of the treatment, and consequently, to explore whether the effect of the SSRIs on suicide varies depending on the stages of the treatment; if so, we will identify the turning point.

Methods and analysis We will search in the following databases: PubMed, Web of science, China National Knowledge Infrastructure and Wanfang Data, from dates of inception to 9 July 2021, with language restricted to English and Chinese. Studies focusing on the time effect of SSRIs on suicide will be retrieved. Then, the study selection process will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline, and the quality assessment will be conducted with Cochrane Collaboration's tool. Two researchers will work independently on data extraction using a standardised data extraction spreadsheet. Any disagreement between two researchers will be discussed and determined by a third researcher.

Ethics and dissemination This work does not require ethics approval as it will be based on published studies. This review will be published in peer-reviewed journals.

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Strengths and limitations of this study

- Rather than focusing solely on patients with depressive disorder, this meta-analysis includes all patients receiving selective serotonin reuptake inhibitors treatment, thus yielding a larger sample size.
- Various covariates such as dosage, age and sex will be included into the meta regression and subgroup analyses to produce accurate results.
- The limitation of this study may be connected to the high cross-study heterogeneity.
- Not all the suicidality assessment scales will be included in our analysis since some scales were designed for specific population, potentially leading to attenuated representativeness.
- Data may be insufficient after applying strict inclusion criteria.

INTRODUCTION

Suicide is defined as death caused by self-directed injurious behaviour with any intent to die as a result of the behaviour.[1] Suicide can occur throughout the lifespan and is considered as one of the most serious global health issues. Approximately 700 000 people die per year due to suicide, which is one person every 40 s.[2] Ninety per cent people who committed suicide suffered from underlying psychiatric disorders.[3] Reducing suicide, especially among people with mental illness, is therefore urgently important, as every suicide statistic represents 'real lives lost' and 'real families devastated'.[4] WHO takes reducing suicide as a public health priority and one of the primary tasks in the WHO Mental Health Gap Action Programme.

In the field of suicide research, several concepts are seriously considered and observed. To begin with, we quote the related definition in US Centers for Disease Control and Prevention and present as follows.[1] First, suicidal self-directed violence is distinguished from self-directed violence with undetermined or non-suicidal intent. Then suicidal self-directed violence is divided into two types: fatal (suicide) and non-fatal, among which suicide is defined as death caused by self-directed injurious behaviour with an intent to die as a result of the behaviour. Within the domain of non-fatal self-directed violence, suicide attempt is defined as a nonfatal, self-directed, potentially injurious behaviour with an intent to die as a result of the behaviour,

no matter whether the behaviour result in injury or not; and other suicidal behaviour is defined as acts or preparation towards making a suicide attempt, but before potential for harm has begun; suicidal ideation is defined as thinking about, considering or planning suicide.

Suicide risk (suicide and suicide attempt combined) was thought to be effective to assess the suicide-related roles of selective serotonin reuptake inhibitors (SSRIs) and other new-generation antidepressants in Hengartner *et al*'s study.[5] In Jakobsen *et al*'s study comparing SSRIs with placebo in MDD, suicides, suicide attempts and suicide ideation were used as their secondary outcome.[6] Also, Hetrick *et al* defined 'suicide-related behaviour' as a collection of suicide, suicide attempt and suicidal ideation when exploring new generation antidepressants for depression in children and adolescents, with suicidal ideation rated with standardised, validated and reliable rating scales.[7] Normally, suicide-related scales were used to detect suicidal ideation, suicide attempt and suicide behaviour in many previous studies. However, several recent studies cast doubts on the validity of these scales. Katz *et al* found that Neuropsychiatric Interview (MINI) Suicidality subscale only has a positive predictive value of 0.20 and a negative predictive value of 0.95 when being used to predict suicide attempt.[8] Columbia-Suicide Severity Rating Scale also failed to estimate suicide risk with suicide ideation in Simpson's study.[9]

Antidepressant has been used to alleviate depressive symptoms and prevent suicide in a wide spectrum of psychiatric disorders including depression, attention deficit hyperactivity disorder, bulimia, premenstrual dysphoric disorder, obsessive–compulsive disorder (OCD) and post-traumatic stress disorder.[10–13] It is thought to function by upregulating levels of different mood-related neurotransmitters, such as serotonin, dopamine and norepinephrine. Among all forms of antidepressant, SSRIs are well tolerated with less side effects, rendering it a first-line treatment for depression.[14] Yet there has been concern that antidepressants may increase suicide-related behaviour. Several studies found that antidepressant significantly elevates the rate of suicide (attempt) compared with placebo.[15–17] Some found no significant association between SSRIs and suicide risk in depression, but indicated that any new-generation antidepressant leads to a higher suicide risk.[5] On the contrary, Gunnell *et al* suggested that there was insufficient evidence supports that SSRIs promote the risk of suicide and that important protective or hazardous effects cannot be excluded.[18] A study about paediatric antidepressant treatment indicates no significant difference in suicidal ideation/suicide attempt between using antidepressant and placebo in OCD, and non-OCD anxiety disorders.[19] The same result was presented in a meta-analysis examining the effect of SSRIs among patients with major depression.[6] However, results of pharmacoepidemiologic studies opposed to that of the majority of randomised clinical trials and meta-analyses, associating the use of antidepressants with a lower rate of suicide.[20] So the same result was present in a former study.[21] Lastly, although studies focusing on the relationship between SSRIs and suicide yielded inconsistent results, as of today, there is no meta-analysis of clinical trials found that the use of antidepressants is negatively correlated with the risk of suicide.

It is also worth noting that the risk of suicidality associated with antidepressant use seems to be age-dependent. A study led by US Food and Drug Administration in 2009 found that antidepressant may increase risk of suicide in adolescents under aged 25 while acts as a protective factor for suicide among the elderly aged over 65.[22] Likewise, Näslund *et al* proposed that SSRIs play a protective role in people aged over 24 but the other way around in those aged 18–24.[23] However, in a large-scale study involving teenagers aged 12–19, no significant change in the prevalence of suicidal behaviour was detected following the significantly reduced prescription of antidepressants, as a regulatory action in 2003 restricted the use of SSRIs in under 18.[24]

In other words, question remains as to what role antidepressants play in suicidality. Patients suffering from depression or other mental illnesses and treated with antidepressants are very likely to experience suicidal thoughts or suicide attempt. It might be that the antidepressants also promote suicidality besides the mental illness itself: a popular theory is that antidepressants in the early stage of treatment provide patients with enough energy to suicide, but not enough for them to endure the mental suffering until noticeable symptom improvement. Thus, the onset time of antidepressants is pivotal to clarify whether they attenuate or aggravate suicidal ideation and behaviour. However, few meta-analyses probed into the time effect of antidepressants, and the effect of onset time in different drugs are less considered. Another problem is that most studies observed the effect of onset time of antidepressants on suicide either within a large class of antidepressants (eg, SSRI or TCA) or after a relatively long time (eg, 1 month after the beginning of treatment). For instance, a previous study found that the suicide rate rose in the first 28 days after starting and stopping antidepressant treatment in people aged 20–64,[25] whereas some reported that SSRIs caused a fivefold higher risk of suicide in the elderly compared with non-SSRIs in first month of treatment, and no difference was found in continued therapy, as SSRIs and non-SSRIs both led to an obvious decline.[26]

Understanding what role SSRIs play in suicide is necessary to help clinicians made the right decision and save lives. In this network meta-analysis, we attempt to accurately assess the onset of five SSRIs (fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram), respectively, by observing the weekly changes of suicide risk (suicide and suicide attempt combined) and suicide-related behaviour (suicidal ideation, suicide attempts and suicide) in the first 2 months of treatment. Here, 'onset' refers to the interval between the initiation of treatment and the exact time point at which the upward trend of suicidality goes into reverse. The reason we focus on the first 2 months is that the suicide rate tends to increase in

the first month of SSRIs treatment and decrease in the second month, according to earlier literature. Also, we will compare the effect of five SSRIs on suicide by calculating standardised mean differences (SMD). The result of our study may inform clinical practice and suicide prevention.

OBJECTIVE

This network meta-analysis aims to evaluate the time effect of onset in five SSRIs on suicide risk and suicide-related behaviour mainly by analysing the mean score of assessment scales and suicide risk.

METHODS AND ANALYSIS

This meta-analysis will be conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[27] This work will be based on published studies; therefore, patient or public involvement will be not required. Relevant results will be published in peer-reviewed journals.

Eligibility criteria

Any studies not meeting following inclusion criteria will be excluded.

In the studies, patients should be diagnosed with psychiatric disorder (eg, anxiety disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, depression, OCD, post-traumatic stress disorder) according to ICD-9 or ICD-10, or DSM-4 or DSM-5 criteria. Participants should be treated with SSRIs including fluvoxamine, fluoxetine, paroxetine, sertraline or citalopram, without receiving non-pharmacological therapies at the same time. Race and age will not be restricted.

Interventions should be SSRIs, or a combination of SSRIs and non-SSRIs, for the experimental group, and placebo or active placebo (eg, other antidepressants) for the controlled group. Studies involving non-pharmacological therapies (eg, transcranial magnetic stimulation, psychotherapy) are excluded. Sedatives are allowed to use.

Studies with a placebo or active placebo arm will be included.

Our primary outcome is the mean value and/or the mean changes of the following suicidality assessment scores of every week in the first 2 months of the SSRIs treatment: Columbia Suicide Severity Rating Scale (C-SSRS), Beck Scale for Suicide ideation (BSS), Item 3 on the 17-item Hamilton Depression Rating Scale (HAM-D). The weekly suicide risk indexed by relative risk or ORs will also be evaluated as primary outcome. The secondary outcome will be the SMD of the following suicidality assessment scales or items involving specific SSRIs, which will be showed with forest plots: C-SSRS, BSS, Adult Suicidal Ideation Questionnaires, Suicidal Possibility Scale, Multi-attitude Suicide Tendency (MAST), SEmantic Differential scale Attitude towards Suicidal Behaviour, Suicidal Behaviour Seriousness Scale, Suicide Status Form, Item 10 on the Montgomery-Åsberg Depression Rating Scale (MADRS), Item 3 on the 17-item (HAM-D) Item 12 on the Quick Inventory of Depressive Symptomatology-Self Report Scale (MAST), Item 9 on the Beck Depression Inventory.

This study will include randomised, controlled studies with a single- or double- blind design, while meta-analyses, reviews, systematic reviews or other secondhand studies will be excluded. Articles published in English or Chinese from inception to 15 June 2021 will be retrieved.

Searching strategy

Relevant articles in Chinese or English will be searched in the following database: PubMed, Web of Science, Wanfang Database, China National Knowledge Infrastructure. Our searching strategy is presented in tables 1 and 2.

Selection process

The selection process will conform to the PRISMA statement. We will use Endnote V.X9 (Thomson Reuters, New York, USA) to manage the retrieved articles. After deleting the reduplicative article, two reviewers will independently screen the titles, abstracts and full texts based on the selection criteria defined in this protocol. Articles sharing a same dataset with other articles will be removed. Any disagreement will be discussed, and the final decision made by a third reviewer who will examine all articles after the selection process.

Quality assessment

Two independent reviewers will assess the selected articles based on the sample size, methods of randomisation and blinding, the completeness of outcome data, selective reporting and other bias, using the Cochrane Collaboration's tool. The GRADE will be used to assess the quality of the available evidence provided by studies we collected.[28] The assessment will be done at study level. If disputes arise, resolution will be made by discussion, after working with a third reviewers. We will employ the following checklist to screen the selected studies, as shown in box 1.

Data collection

The following data will be extracted independently by two reviewers from the selected studies based on standardised pilot-tested data forms. A third reviewer will check and decide the final extraction in case of any disagreement.

Study characteristics: article title, first author(s), publishing time, unit, country or region, funding support.

Study design: medication, sample size, diagnostic criteria, clinical assessment, times of follow-up.

Study population: demographic characteristics (including age, sex, illnesses), clinical variables (eg, duration of illnesses, severity, mode of suicidality), dosage.

Study results: scores of suicidality assessment scales at baseline and follow-up, and/or mean changes of the these

Table 1 PubMed searching strategy

ID	Searching term
#1	Selective serotonin reuptake inhibitors (MeSH terms)
#2	SSRI (MeSH terms)
#3	Selective serotonin reuptake inhibitors (All fields)
#4	SSRI (All fields)
#5	Fluvoxamine (All fields)
#6	Fluoxetine (All fields)
#7	Paroxetine (All fields)
#8	Sertraline (All fields)
#9	Citalopram (All fields)
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	Suicide (MeSH terms)
#12	Suicidality (MeSH terms)
#13	Suicidal (MeSH terms)
#14	Suicide (All fields)
#15	Suicidality (All fields)
#16	Suicidal (All fields)
#17	#11 OR #12 OR #13 OR #14 #15 #16
#18	Randomized controlled trial [pt]
#19	Randomized(Title/Abstract)
#20	#18 OR #19
#21	Randomized(Title/Abstract)
#22	Placebo(Title/Abstract)]
#23	#21 OR #22
#24	Case-control study(pt)
#25	Case-Comparison Studies (All fields)
#26	Case-Referent Study (All fields)
#27	Nested Case-Control Study (All fields)
#28	Matched Case-Control Studies (All fields)
#29	#24 OR #25 OR #26 OR #27 OR #28
#30	Cohort study [pt]
#31	Cohort*(Title/Abstract)
#32	Cohort effect [MeSH Terms)
#33	Cohort studies(MeSH:noexp)
#34	#30 OR #31 OR #32 OR #33
#35	#20 OR #23 OR #29 OR #34
#36	Systematic review publication Type)
#37	Review [Publication Type)
#38	Meta-analysis [Publication Type)
#39	Final search terms: #10 AND #17 AND #35 NOT #36 NOT #37 NOT #38
ID	Searching term

scales, mean differences, standardise error, standardise differences, CIs, suicide rates at baseline and follow-up.

Any missing information or questions about the above data will be settled by contacting the authors. If no clarification is provided in 4 weeks, the study will be included in the final analysis with the missing information marked.

Table 2 CNKI searching strategy

ID	Searching term
#1	5-羟色胺再摄取抑制剂 (主题词)
#2	SSRI (主题词)
#3	西酞普兰 (主题词)
#4	氟西汀 (主题词)
#5	帕罗西汀 (主题词)
#6	舍曲林 (主题词)
#7	氟伏沙明 (主题词)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	自杀 (主题词)
#10	Final search terms: #8 AND #9

CNKI, China National Knowledge Infrastructure.

Data synthesis

Treatment to the missing data and data presentation

Before the network meta-analysis, variability measures (ie, mean changes from baseline, mean scores at baseline and follow-ups) expressed as SEs or CIs will be converted to SD through algebraic manipulation, while the formulas proposed in the Cochrane Handbook will be adopted to recalculate the SD.[29]

When calculating SDs, two imputation methods will be used when the incomplete variability measures are unavailable from the authors. The first method applies to articles without any variability measures reported; in this case, the SD of this study will be substituted with the highest SD among included articles that used the same suicidality assessment. The other method is for papers reported baseline and follow-up data; here, to calculate the SD of the changes, the correlation between baseline and follow-up scores will be estimated based on another article included.[29–31] If computing a correlation from any

Box 1 Quality assessment of individual studies

Category 1: Sample characteristics

1. Patients were diagnosed with standardised diagnostic criteria.
2. Important demographic data (age and gender) were reported with mean (or median) and SDs (or range).
3. A patient in experimental group had only one type of mental illness and was treated with a specific selective serotonin reuptake inhibitor (SSRI) we involved, but not non-SSRIs. Sedatives are allowed to use.
4. Medications used before the trial did not affect subsequent outcomes.
5. Sample size per group was >10.

Category 2: Methodology and reporting

1. The specified suicidality assessments were applied.
2. Using a randomised, controlled, blinded or non-blinded design.
3. Scores of suicidality assessments at baseline and follow-up, and/or the mean changes from the baseline, and/or the number of suicide, suicide attempts were reported.
4. Conclusions were consistent with the results obtained and the limitations discussed.

of the included studies is impossible, we use an approximate value of 0.5.

Also, we will create three line-graphs to show the changes of mean scores of three suicide-related scales including C-SSRS, BSS and HAM-D (item 3) at different time points. The change of suicide risk also will be put into the same line-graphs mentioned above.

Finally, all extracted data will be presented in a table.

Network meta-analysis

Next, to determine and compare the effect of different SSRIs on suicide, we will perform a Bayesian network meta-analysis with random effect and non-informative priors using R software, with which all analyses in this protocol will be performed.[32] The SMD of each drug, as expressed by the Hedges' g or Glass's delta in this study, will be calculated because different suicidal scales were adopted in different studies. The Glass's delta is applicable when experimental manipulation might affect the SD.[33 34] All SMDs will be reported in a table.

Assumption of transitivity and consistency

Transitivity is a basic premise of a network meta-analysis. We will cautiously assume and evaluate the transitivity based on methodologies,[35] as drug combination, different types of placebo and their effects on patients, as well as different kinds of psychiatric disorders potentially affect the transitivity. The assumption of consistency is the extension of the assumption of transitivity. The consistency assumption will reduce to transitivity if there's no direct comparations between drug A and B.[36] If there is, the node-split models will be implemented through Markov chain Monte Carlo (MCMC) method. Gelman-Rubin diagnostic will be used to access the convergence.[31] The MCMC simulation will be implemented using the R software (gemtc and pcnetmeta packages) (V.4.1.0) (http://cran.r-project.org/) with interfacing to OpenBUGS (V.3.2.3, MRC Biostatistics Unit, Cambridge, UK) (http://www.openbugs.net/w/Downloads).[37–39]

Subgroup analyses and sensitivity analyses

Heterogeneity across studies will be assessed through the I^2 statistics.[40] The value of I^2 ranges from 0% to 100%, with null value indicating absolute homogeneity and higher values indicating greater heterogeneity. When modest heterogeneity is detected, we will discuss the source of the heterogeneity and whether it is methodological, clinical or statistical. In case of high heterogeneity, meta regression analysis will be conducted using random effects models to adjust covariates like gender, age, suicidality, illnesses, duration and severity of the illness, and dosage. Next, we will perform subgroup analyses based on the outcome we derived. Additional subgroup analysis regarding suicidal ideation, suicide attempts and suicide will be attempted if related data is sufficient.

Since handling missing data may bias the results, sensitivity analyses will be conducted with two methods. One is excluding papers using the maximum SD imputation, the other is excluding papers using the maximum SD imputation as well as papers applying the correlation imputation. Additionally, considering that some studies may exist pharmaceutical marketing bias and conflict of interests, a sensitivity analyses will be conducted to exclude studies with financial conflict of interest (fCOI). fCOI was defined as present when lead authors accepted industry-sponsored professorship, received industry payments, or when the study was industry-sponsored.[5]

Small-study effects and publication bias

We will assess the small-study effect using funnel plots. The publication bias will be evaluated with funnel plots and the Egger's test and adjusted using the trim-and-fill method.[41 42]

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination.

Data synthesis and analysis are expected to be completed by 29 October 2021.

Patient and public involvement

This study is a network meta-analysis based on published articles, therefore, does not involve any patient or the public.

ETHICS AND DISSEMINATION

Ethical approve is not required as primary data will not be collected. This review will be published in peer-reviewed journal.

Contributors BZ was responsible for this study. BZ, Q-HC and Y-LL conceived and designed the study. Y-LL, Y-RH, W-YL and Q-HC participated in drafting the protocol and preparing the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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