Comprehensive database and individual patient data meta-analysis of randomised controlled trials on psychotherapies reducing suicidal thoughts and behaviour: study protocol

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ABSTRACT

Introduction Psychotherapy may reduce suicidal thoughts and behaviour, but its effectiveness is not well examined. Furthermore, conventional meta-analyses are unable to test possible effects of moderators affecting this relationship. This protocol outlines the building of a comprehensive database of the literature in this research field. In addition, we will conduct an individual patient data meta-analysis (IPD-MA) to establish the effectiveness of psychotherapy in reducing suicidality, and to examine which factors moderate the efficacy of these interventions.

Methods and analysis To build a comprehensive database, randomised controlled trials examining the effect of any psychotherapy targeting any psychiatric disorder on suicidal thoughts or behaviour will be identified by running a systematic search in PubMed, Embase, PsycINFO, Web of Science, Scopus and The Cochrane Central Register of Controlled Trials from data inception to 12 August 2019. For the IPD-MA, we will focus on adult outpatients with suicidal ideation or behaviour. In addition, as a comparison group we will focus on a control group (waiting-list, care as usual or placebo). A 1-stage IPD-MA will be used to determine the effectiveness of psychotherapy on suicidal ideation, suicide attempts and/or suicide deaths, and to investigate potential patient-related and intervention-related moderators. Subgroup and sensitivity analyses will be conducted to test the robustness of the findings. Additionally, a conventional MA will be conducted to determine the differences between studies that provided IPD and those that did not. IPD-MA may determine the effectiveness of psychotherapy in reducing suicidality and provide insights into the moderating factors influencing the efficacy of psychotherapy. Answering these questions will inform mental healthcare practitioners about optimal treatments for different groups of individuals with suicidal ideation and/or behaviour and consequently help to reduce suicide risk.

Ethics and dissemination An ethical approval is not required for this study. The results will be published in a peer-review journal.

Strengths and limitations of this study

► We will conduct an individual patient data meta-analysis to investigate the effectiveness of psychotherapy in reducing suicidal thoughts and behaviour.
► We will perform moderation analyses to examine which individuals benefit most from psychotherapy.
► We will perform moderation analyses to examine which kind of treatment is more effective in reducing suicidal thoughts and behaviour.
► This will be the first individual patient data meta-analysis investigating these research questions.
► We might not receive all primary datasets or variables of interest from eligible randomised controlled trials.

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BACKGROUND

Suicide is one of the most pressing and significant mental health issues worldwide. According to WHO,1 800 000 people globally die by suicide every year. Healthcare professionals have found treatment of individuals with suicidal ideation and behaviour to be difficult.2 Therefore, there is an urgent need to determine the effectiveness of treatments across the range of individuals who experience suicidality.

Several studies have demonstrated promising results regarding the effectiveness of psychotherapy (ie, the use of psychological methods to change behaviour or overcome problems) in reducing suicide ideation and preventing further suicide attempts.3–5 For instance, a meta-analyses by Calati and...
Given the ambiguity in these findings, not all studies show favourable results on suicidality after cognitive–behavioural therapy (CBT), dialectical behaviour therapy (DBT) and cognitive therapy (CT). However, not all studies show favourable results on suicidality after psychotherapy. Given the ambiguity in these findings, there is a need for studies to establish the effectiveness of psychotherapy on decreasing suicidal thoughts and behaviour. Furthermore, not all types of psychotherapy may be effective for the entire spectrum of individuals with suicidality. Few studies have attempted to answer questions about whether the efficacy of psychotherapy is affected by moderators related to participant (eg, psychiatric disorder, sociodemographic, clinical factors) or intervention characteristics (eg, type of psychotherapy, number of sessions). For instance, it has been suggested that female sex and a high number of treatment sessions per week may be associated with increased efficacy of psychotherapy in reducing suicidal thoughts and behaviour. In addition, there are many more factors associated with an increased risk of suicide (attempt) that may play a role in the effectiveness of psychotherapy on suicidality, such as age, ethnicity, education level, marital status, psychiatric diagnosis and history of prior attempt. However, most randomised controlled trials (RCTs) are underpowered to perform such moderator analyses, and seldom report such results. Therefore, it is impossible to investigate the aforementioned questions using a conventional meta-analysis (MA).

These questions may be appropriately answered by an individual patient data MA (IPD-MA). For IPD-MA, the raw data of predefined variables of every participant from RCTs are used. The obtained data are merged into a single dataset and standardised to analyse combined cases and/or subgroups. Analyses with IPD have greater statistical power to detect moderation than analyses on individual study level. In addition, IPD-MA allows for the investigation of variables not reported in primary trial outcome papers and improve the precision of the estimates.

The aim of this study protocol is to describe the building of a comprehensive database of RCTs examining the effect of any psychotherapy targeting any psychiatric disorder on suicidal thoughts or behaviour. This database will provide an overview of the studies in this field and may be shared with interested researchers. In addition, we will conduct an IPD-MA focusing on adult outpatients with suicidal ideation or behaviour, as assessed by a suicidality scale or a previous suicide attempt. As a comparison group we will focus on a control group (waiting-list, care as usual or placebo). The following research questions will be investigated by means of the IPD-MA: (1) What is the overall effectiveness of any psychotherapy in reducing suicidal thoughts and behaviour? (2) Which participant characteristics moderate the overall effects of psychotherapy? (3) Which intervention characteristics moderate their effectiveness? In addition, the analyses will be performed in subgroups of interest: different types of psychotherapy and specific psychiatric patient groups.

METHODS/DESIGN

Study design

This protocol was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol guidelines (see online supplemental appendix A).

Literature search

Two researchers (CP and KS) will perform the systematic search from database inception to 12 August 2019, using the databases PubMed, Embase, PsycINFO, Web of Science, Scopus and The Cochrane Central Register of Controlled Trials. Index and free terms, such as ‘suicide’, ‘self-kill’, ‘self-poison’, ‘RCT’, ‘randomised’, ‘clinical trials’ and ‘psychotherapy’ will be used (see online supplemental appendix B) for the complete search string). Studies of interest will also be extracted from the reference lists of relevant articles. Unpublished studies (eg, trial registries, conference abstracts) will also be included. Study extraction and selection will be carried out in the Covidence software.

Eligibility criteria

Two researchers (CP and KS) will screen the articles for inclusion, first based on titles and abstracts and then on full text. In case of disagreement, consensus will be reached by discussion with a third researcher (MH).

Comprehensive database

To build a large comprehensive database on the effectiveness of psychotherapy on suicidality, we maintain broad inclusion criteria. Articles will be included if they meet the following criteria: (1) employ an RCT examining psychotherapy (ie, the use of psychological methods to change behaviour or overcome problems) targeting any psychiatric disorder and delivered in any setting (including distal intervention delivered via telephone or the internet), (2) compare the intervention to any comparison group (waiting list, care as usual, psychological placebo, pharmacological intervention, another psychotherapy or another intervention), (3) include as primary or secondary outcome (A) suicidal ideation, (B) suicide attempts, (3) death by suicide or (4) self-harm leading to hospitalisation, measured at baseline and immediately post-treatment, (4) are written in English, Dutch, German or Greek according to the languages spoken by the authors. Studies will be excluded if they: (1) employ an intervention, such as a postcard or community intervention, that do not involve any psychotherapeutic technique, (2) measure suicide with less than three items from a scale developed for a different construct, such as depression and (3) only report on suicide as an adverse event.

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Individual patient data meta-analysis

For the IPD-MA to be conducted, we will largely follow the above inclusion criteria, with the exception of a few added stringencies. We will focus on (1) adults (18+ years), (2) outpatients, (3) with suicidal ideation or behaviour at baseline, as assessed by a suicidality scale or a previous suicide attempt (if suicidal intent is unclear, we will only consider self-harm as suicide attempt when resulting in hospitalisation), (4) a control group as comparison condition (waiting-list, care as usual or placebo). For studies where only a subsample of participants is eligible, we will include the data of this subsample in the IPD-MA.

Risk of bias assessment

Two researchers (CP and MH) will independently assess the risk of bias for the included studies, in both the aggregate MA and IPD-MA, using the Revised Cochrane risk-of-bias tool for randomised trials, published on 15 March 2019,17 which assesses bias related to selection, performance, detection, attrition and outcome reporting. Disagreement will be resolved through discussion and referral to the original manuscript in consultation with a third researcher (WvB). In case of unclear risk of bias for one or more key domains, we will contact the first authors of the included studies for clarifications.

Data extraction

This study will be conducted in collaboration with the Australian National Health and Medical Research Council Centre for Research Excellence in Suicide Prevention at the Black Dog Institute, and the Australian National University. Researchers from these institutions have compiled a database for articles on psychosocial interventions for suicidal thoughts and behaviours published up to 1 January 2018.18 As there will be substantial overlap between the articles in this existing database and the articles included in the current database and IPD-MA, we will use the previously extracted data from the overlapping articles and extract additional data of interest from these articles. Complete data will be extracted from new articles found by the IPD-MA. The following characteristics of all included studies will be extracted by two researchers (CP and MH): first author, year of publication, number of randomised participants, mean age of participants, percentage of females, setting, recruitment strategy, main diagnosis of participants, inclusion criteria, exclusion criteria, type of psychotherapy, type of control condition, type of outcome (scale for suicidal ideation and/or (number of) suicide attempts and/or death by suicide), effect size and other important clinical information (see online supplemental appendix C).

The authors of the eligible studies will be contacted in order to obtain the data of baseline and all available follow-up measurements. The full list of requested moderator variables is given in online supplemental appendix C. These variables are based on expert knowledge of the authors of this protocol on important factors that have been associated to suicidality in the literature.13 An email requesting the raw data will be sent to the corresponding authors of the articles. If no answer is received, a reminder will be sent to both the corresponding author and the first/last author after 3 weeks. If necessary, a second reminder will be sent after 6 weeks. If no author has responded 9 weeks after the first email request or if the contacted authors indicate that they do not have access to the data, the study data will be considered unavailable.

We are planning to adopt a collaborative approach by inviting the authors of eligible trials to share the raw data of their eligible trial, by encouraging them to give advice and input throughout the whole process, and by sharing authorship of the final publication of the study with them. When requested, we will also draft a written agreement on data sharing, management and use. The data will be stored at the server of the VU University and is owned by SURE-NET (WvB, ME and RG). The server will be managed by WvB and MH and will be available to all team members.

Patient and public involvement

There was no patient or public involvement in the development of the research question, outcome measures, planning, design or conduct of this research. As we will be using individual patient data gathered by previous studies, dissemination of the results to study participants will be determined by these original studies.

Statistical analyses

Conventional MA

Because it is unlikely to obtain IPD of all included studies, we will first conduct a conventional MA on study level data with a random effects model in R with the packages ‘meta’ and ‘metaphor’. The analyses will focus on outcomes obtained at post-treatment (i.e., the first timepoint of measurement following end of treatment). For suicidal ideation, we will first standardise the different scales used in the studies by transformation into z-scores across the pool of the studies, and then calculate Hedges’ g as a measure of the effect size indicating the difference between the comparison conditions post-treatment. A Hedges’ g of 0.2 is considered to be small, 0.5 as moderate and 0.8 as large.19 For suicide attempt and death by suicide, we will calculate the relative risks (RRs). The I² statistic will be calculated as an indicator of heterogeneity in percentages (with 0% indicating no observed heterogeneity, and with values of 25%, 50% and 75% indicating low, moderate and high heterogeneity, respectively).20 Publication bias will be tested by visually inspecting the funnel plot and by the Egger’s test, which quantifies the bias captured by the funnel plot.21 The results of the IPD-MA will be compared with the conventional MA with a mixed-effects model and the differences will be determined between studies that provided IPD and those that did not.

Individual patient data meta-analysis

The IPD-MA will be performed in R package ipdmeta in one stage. A one-stage MA is preferred over a two-stage IPD
approach, as it allows for more sophisticated modelling of the moderators.\(^2\) In addition, a one-stage approach is recommended for dichotomous outcomes with rare events and when most studies are small. Indeed, we expect the prevalence rates for suicide attempt and death by suicide to be small in the included studies.\(^3\) \(^2\)\(^3\)\(^4\)\(^5\) The IPD-MA will focus on outcomes obtained at post-treatment (ie, the first timepoint of measurement following end of treatment). Analyses will be performed according to the intention-to-treat principle. In case of studies with a Zelen design, we will include all randomised participants in the analyses. The participants who withdrew from participation after randomisation will be considered drop-outs and any missing values will be imputed. Multiple imputations will be conducted within studies under the missing at random assumption. This method will generate 100 imputed datasets using data available across studies (if available, predictors for imputation will be at least baseline suicidality scores, age, sex and psychiatric disorder). In addition, we will run analyses with complete cases only to examine the differences in results between imputed and complete cases.

**Suicide ideation**
A multilevel linear regression analysis will be used to assess the effect of the intervention on standardised suicidal ideation scores post-treatment, while controlling for baseline suicidal ideation. Patient-level data will be treated as level 1, and study-level data as level 2. In case of trials with multiple arms we will randomly split the ‘shared’ control group in two groups with smaller sample size. In case of a cluster RCT design, we will add the cluster as a third level. We will use a random-effects model to estimate summary intervention effects and to capture unobserved heterogeneity between study populations and study efficacy, respectively. Hedges’ g will be calculated as an effect size measure.

**Suicide attempt and death by suicide**
A multilevel logistic regression analysis will be used to assess the efficacy of the intervention on dichotomous variables (suicide attempt and death by suicide) post-treatment. RRs and the corresponding 95% CIs will be calculated using the Kenward-Roger variance estimator. Again, a random-effects model will be used.

**Moderator analyses**
We will investigate the moderating effects of patient characteristics (eg, sex, age, psychiatric disorder), and intervention characteristics (eg, type of psychotherapy, type of delivery (face to face vs distal), number of sessions, duration). We will test whether these factors will moderate suicidal outcome at post-treatment assessment. To examine this, we will add the selected moderators as well as the moderator*intervention interaction terms to the multilevel (logistic) regression analyses, separating within-study and across-study interaction effects to avoid ecological bias by centring the patient-level moderator about its mean. Each potential moderator will be added separately to the model. The moderators that show a statistically significant effect will then be tested simultaneously in one model to investigate which moderators have an independent effect on treatment outcome. We will perform moderator analyses only within the studies for which these moderators are available.

**Subgroup analyses**
The above analyses will additionally be performed in subgroups of psychiatric disorder and type of psychotherapy. For types of psychotherapy, subgroup analyses will likely be performed for CBT, DBT, problem-solving therapy, CT, mindfulness-based therapy and collaborative assessment and management of suicidality, as these are the mostly used psychotherapies for suicidality. Regarding psychiatric patient groups, the following subgroups will likely be analysed: (borderline) personality disorder, depression, substance abuse, post-traumatic stress disorder, psychosis and sleep disorder. Subgroup analyses will also be performed for different suicidality scales and comparison groups to investigate whether effect sizes differ substantially when using a different scale or control condition. Other subgroup analyses may be performed depending on which factors reach statistical significance in the moderator analyses.

**Sensitivity analyses**
Sensitivity analyses will be conducted that exclude trials with high risk of bias and those with a deviating RCT design (eg, Zelen design). After data collection, the need for other sensitivity analyses may become apparent. Additionally, we will verify the effect sizes found by the included studies by replicating their original analyses. The robustness of the findings of the one-stage IPD-MA will be tested by replicating the main outcomes using a two-stage IPD approach in which the effects are calculated per individual trial and then pooled together using a random-effects model.

**DISCUSSION**
Psychotherapy has shown promising results in reducing suicidal thoughts and behaviour.\(^3\)\(^1\) However, the overall effectiveness of psychotherapy on suicidality is yet to be established. In addition, many questions remain unanswered regarding moderating factors (eg, which individuals—with different psychiatric disorders—respond better to different types of psychotherapies). To the best of our knowledge, this will be the first IPD-MA conducted in this field of research.

Strengths of this study include its more precise estimation of the effectivity of psychotherapy on suicidality and its higher power to detect small effects compared with a conventional MA. Moreover, IPD-MA has increased power to conduct moderation analyses, compared with most individual studies. There are limitations regarding the search strategy, as we will only include articles written in the languages spoken by
the authors. We might miss relevant articles written in other languages. Also, relevant papers might be missed as some key search terms might not have been included in their title or abstract. In addition, although we include trial registries and conference abstracts, some influence of publication bias is inevitable. Another limitation may be our definition of suicide attempt. When intent to die is unclear, we will only include cases of self-harm resulting in hospitalisation and exclude cases of self-harm not severe enough to lead to hospitalisation. We are aware that this is a somewhat arbitrary definition of suicide attempt that may result in the exclusion of possibly relevant studies. Other limitations of the study are the inherent disadvantages of IPD studies, such as the combining of heterogeneous variables from heterogeneous studies and the loss of important variable characteristics in the process of reaching homogeneity to facilitate the analysis. The pooling of different types of psychotherapies may also add to heterogeneity between the studies. These possible sources of heterogeneity will be investigated and discussed. In addition, many relevant moderators associated with suicidality may not be included in many studies. Moreover, we may not be able to obtain raw data for some studies at all, as there may be obstacles in reaching the authors and accessing their data. The latter limitation will be addressed by comparing the IPD-MA results with those of the traditional MA. If the overall patterns are consistent, we may assume that the results of the IPD-MA are representative for all studies. Lastly, many of the limitations for a conventional MA also hold for IPD-MA, such as the pooling of interventions and control conditions that may be very heterogeneous, and risk of bias in the included studies (eg, allocation concealment and reporting bias and (self-)selection bias). Although the impact of these biases will be assessed in sensitivity analyses, they cannot be entirely accounted for.

Despite these limitations, IPD-MA provides the best up to date method to answer the questions at hand. This study may be paramount for clinical practice as it aims to improve personalised treatment options for patients with suicidality. Knowledge about which type of psychotherapy is best for which type of individual will help mental healthcare practitioners in their choice of treatment and, hopefully, help to reduce suicide risk.

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