



Long-term efficacy of psychotherapy in major depression: protocol of a network meta-analysis

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Abstract

Background: Depression is currently considered the epidemic of the century. In recent decades, research has established that psychotherapy is globally effective for the treatment of depression; however, it remains open which psychotherapeutic treatment is most effective and, particularly, if its efficacy is maintained over the long term. Given the difficulty in performing randomized and controlled clinical trials (RCTs) that simultaneously compare several psychotherapeutic models, meta-analyses aim to provide answers by synthesizing the evidence generated through direct comparisons of treatments.

Goals: This protocol describes the meta-analysis study we will perform in order to assess the efficacy and acceptability of long-term results of psychotherapy (i.e., 18-month follow-up or higher) in the treatment of major depression in adults.

Methods: Through the use of a recent methodological approach - the network meta-analysis - we will integrate the direct and indirect analysis of evidence from randomized and controlled clinical trials in this domain. We will systematically search seven databases for RCTs of psychotherapy, published since 1994, with evaluation of the efficacy in terms of long-term results for the treatment of depression. All studies with adult participants (18 to 65 years of age) diagnosed with major depression (according to DSM-IV, IV-TR, V or ICD-9, 10) will be eligible and all studies that compare psychotherapy (individual and face-to-face treatment) with a control condition (waiting-list, placebo) will be considered. Data extraction, quality assessment and risk of bias will be carried out independently by three researchers. The primary outcome measure will be the long-term efficacy of treatments (follow-ups of 18 months or above) measured by changes in the overall clinical response and symptoms of depression since post-treatment and follow-ups. The secondary measure will be the acceptability of treatment as measured by the proportion of participants who drop out of follow-up or start another treatment (not psychotherapy). A direct comparison (pairwise meta-analysis) of all studies comparing different psychotherapies will be performed. We will compare relative efficacy and acceptability by indirect comparison, through a bayesian network meta-analysis of random effects to compare different psychological interventions. Further analyses will be conducted if inconsistency and heterogeneity values are found.

Discussion: The purpose of this review is to systematize and integrate evidence of long-term maintenance of the results of different psychotherapeutic treatments for major depression, administered individually and face-to-face in RCTs. For this reason, multiple direct and indirect comparisons of treatments (bayesian network) will be made, and the interrelationships between treatments will be estimated in terms of long-term efficacy and acceptability. Even though our scope will be focused on RCTs, we hope that the results obtained can contribute to summarize the present evidence available in terms of long-term results of psychotherapy (i.e., its effectiveness), optimizing the planning of future studies, providing public health guidelines and more informed clinical decisions on the treatment of depression.

Keywords: *Network meta-analysis, Systematic review, Psychotherapy, Effectiveness, Efficacy, Follow-up, Depression*

Introduction

Depression is currently considered a serious public health problem. It is the most frequent mental disorder, with a high relapse rate. About 50% of individuals relapse two years after the first occurrence of a major episode of depression (Emmelkamp, 2013; Vittengl, Clark, & Jarrett, 2009) and has a worse prognosis after each episode. According to Kessler, Petukhova, Sampson, Zaslavsky and Wittchen (2012), it is estimated that one in every 10 people, in the international scenario, suffers from major depression, pointing to a prevalence of 16.6%. Authors also estimate that 29.9% of healthy people so far will develop a major depression episode over the course of their life cycle (lifetime morbid risk – Kessler et al., 2005). With a global estimate of 350 million people directly affected worldwide (Marcus, Yasamy, Ommeren, Chisholm, & Saxena, 2012), depression is considered by the World Health Organization (WHO) as the world's fourth leading cause of disability and is expected to become the second leading cause of disability worldwide by 2020 and the first by 2030 (Christodoulou, 2012). For this reason, depression remains a challenging area of research of great concern and relevance, and the inquiry towards which are the most efficacious psychological treatments is still open, particularly with regard to the long-term evolution of this disorder. The lifetime morbid risk, high rates of recurrence and relapse throughout life are highlighted as major concerns regarding this disorder and seen as hallmarks of its long-term course (Vittengl, Clark, & Jarrett, 2009, 2010).

The efficacy of psychotherapy in the treatment of mild to moderate depression has been well documented and supported through several randomized clinical trials (RCTs) and previous meta-analyses (see Barth et al., 2013; Cuijpers et al., 2013a; Cuijpers, van Straten, Warmerdam, & Andersson, 2008; Driessen et al., 2010). According to these studies, different psychological treatments are considered efficacious in the short-term treatment of depression, such as cognitive behavioral therapy (CBT) (Cristea et al., 2015; Cuijpers et al., 2013a; Cuijpers et al., 2013b; Tolin, 2010), brief psychodynamic therapy (Driessen et

al., 2015; Leichsenring & Rabung, 2011), interpersonal therapy (Barth et al., 2013; Weissman et al., 2014), problem-solving therapy (Cape, Whittington, Buszewicz, Wallace, & Underwood, 2010; Nieuwsma et al., 2012), mainly achieving equivalent results (classically known as the Dodo Bird Verdict – cf. Luborsky et al., 2002).

If there is *a priori* solid evidence and vast empirical support for the efficacy and equivalence of psychotherapies in the treatment of depression and its short-term outcomes (by comparing different psychotherapeutic approaches in the post-treatment and during the first months after therapy termination), the evidence regarding the maintenance of long-term outcomes is not yet clear (especially when considering therapeutic gains at a time distance superior than one year after the end of treatment). In fact, meta-analytical research that focuses on the comparison of the results of different psychotherapeutic modalities reveals inconsistencies regarding the most efficacious psychotherapeutic approach(es), taking into account the maintenance of gains in follow-up evaluations (FUP).

Focusing on CBT as an example, some meta-analyses (e.g. Tolin, 2010) indicate the superiority of this type of treatment (relative to others) in a short-term assessment of the evolution of depression (mean FUP of 6 months), while others find no differences in FUP between CBT and other treatments (e.g. Braun, Gregor & Tran, 2013; Driessen et al., 2015). Taking as an example the meta-analysis of Tolin (2010), this author concluded that CBT was more efficacious in FUPs when compared with other forms of psychotherapy. Marcus, Yasamy, Ommeren, Chisholm and Saxena (2014) also corroborated this result in favor of CBT, although only at the 6-month FUP. In contrast, in the study by Braun et al. (2013), when comparing FUP between one and 24 months (between psychodynamic therapy and interpersonal therapy), and in the study by Driessen et al. (2015), of short-term psychodynamic psychotherapy comparing other psychotherapies, including CBT, with FUP time points of four, eight and 33 weeks, no differences were found supporting superiority of CBT in short- and long-term.

This inconsistency of results has led some authors to point out criticisms to these previous meta-analyses and to highlight the need to adopt more appropriate methodological procedures. For example, Wampold et al. (2017) refer to the need of conducting additional tests that support the correct rejection or acceptance of the null hypothesis (i.e. that there are no differences between treatments) and to become more explicit regarding standardized treatments under comparison (i.e., there is some ambiguity between studies with regard to the definition, classification and characterization of CBT treatments being implemented given that they seem to be heterogeneous among studies). Wampold et al. (2017) also stress the need to mitigate methodological biases in the design of studies, given their possible impact on the conclusions that are drawn, particularly with regard to the comparative efficacy of treatments (see Comer & Kendall, 2013; Wampold et al, 2017, for a more complete critical reflection).

The long-term efficacy of psychotherapy in depression: why is this review important?

According to the evidence and criticisms pointed out to previous meta-analyses, this study aims to contribute for the answer to this crucial clinical question: What (or which) is the most effective and acceptable psychotherapeutic model to maintain long-term results (i.e., over 18 months) in the treatment of major depression? Answering this question would allow us to make more informed and substantiated clinical decisions at the level of public health guidelines and act with greater safety in the treatment of depression.

To this end, we will use a new meta-analytical approach, known as network meta-analysis, which integrates direct comparisons (primary study results, RCTs) with indirect comparisons of multiple treatments. In the absence of RCTs studies that directly compare all treatments of interest, this new approach will allow us to analyze whether treatment B is more efficacious than A, and how much treatment C is better than the same comparator A, (e.g.,

psychotherapeutic treatment Y or psychotherapeutic treatment X).

Thus, this article aims to outline the steps of a systematic literature review protocol and its empirical evaluation, through the methodology of network meta-analysis in order to systematize and synthesize the evidence from different studies carried out in this area and to compare the efficacy and acceptability of different psychotherapeutic treatments. Acceptability is defined here by the proportion of participants who abandon follow-up or initiate another type of treatment (see Kazdin, 1981, for a broader understanding of the construct of treatment acceptability). We are interested in comparing the efficacy of “pure” psychotherapies (i.e., psychotherapy treatments without combination with pharmacology or other non-psychotherapeutic interventions) in the maintenance of long-term results (FUP of 18 months or more) for the treatment of major depression in adults.

In addition to the innovative potential of this systematic review and meta-analysis due to the adoption of statistical procedures that are currently more recommended, up until now there are no meta-analytical studies whose primary objective is to systematize and compare the long-term effects of psychotherapy treatments for major depression in adults (using moderator analyses in relation to treatment FUP time and considering FUP times equal to or superior than 18 months). Thus, the results of this meta-analysis will contribute to a better grounding of decisions regarding the treatment and management of the course and long-term evolution of depression, with the aim of ultimately reducing its negative impact at individual, societal and economic levels (Christodoulou, 2012; Kessler et al., 2012; Marcus et al., 2012).

Methods

This systematic review of the literature and network meta-analysis will be conducted in accordance with Cochrane's recommendations (guidelines), as outlined

in the *Handbook for Systematic Reviews of Interventions* (Higgins, & Green, 2011). Results will be reported following the verification items of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA-NMA – Moher et al, 2015).

Eligibility criteria for studies in this review

Type of studies

Inclusion criteria: We will include in this network meta-analysis, randomized controlled clinical trials (RCTs) of psychotherapeutic treatments for major depression with evaluation of therapeutic efficacy in the maintenance of long-term results (FUP \geq 18 months), using the Beck Depression Inventory (BDI) or other similar standardized measures to evaluate the results at the level of symptomatology of depression. All RCTs with a control condition (e.g., waiting list or placebo) or other psychotherapeutic treatment will be included. We will also include relevant follow-up studies (prospective) provided that participants derive from controlled RCTs, with detailed reporting of the results of the primary study (RCT) in which those participants were involved.

Exclusion criteria: We will exclude clinical trials of treatment efficacy for major depression (such as, for example, routine practice studies), non-randomized and uncontrolled trials, cross-sectional studies or case series.

Type of participants

Inclusion criteria: All studies with adult participants between 18 and 65 years of age who meet the criteria for diagnosis of major depression will be eligible. Diagnostic criteria should be in accordance with the Diagnostic Manual of Mental Disorders (DSM-IV, IV-TR, V; American Psychiatric Association (APA), 1994, 2000, 2013) or International Classification of Diseases and Health Related Problems (ICD-9 – World Health Organization, 1978 or ICD-10 – World Health Organization, 1992) for major depression. In order to reduce clinical heterogeneity, this meta-analysis will only include studies whose participants have been evaluated by self-reporting instruments of depression,

namely, the Beck Depression Inventory (BDI), or other similar standardized measures to evaluate outcome at the level of symptomatology of depression (standardized instruments measure).

Exclusion criteria: In demographic terms, studies with children, adolescents and the senior population over 65 years of age will be excluded. In clinical terms, studies with participants who come from specific populations, such as patients with chronic diseases (e.g. myocardial infarction, multiple sclerosis, stroke, cancer, arterial disease, etc.) or with major depression related to pregnancy, childbirth or puerperium (e.g. postpartum major depression) will be excluded. Studies involving participants with comorbidity of psychiatric disorders related to substance use or addiction will also be excluded.

We assume that any participant who meets the inclusion criteria is equally likely to be randomized for any of the eligible interventions.

Type of interventions

We will include RCT studies that directly compare the efficacy of long-term psychotherapy with a control condition (waiting list or placebo) and another psychotherapeutic intervention, administered in individual and face-to-face formats. We will include clinical trials with different dose (dose-effect) of treatment, in particular, the number of sessions involved in the initial RCT treatment (i.e. whether 12 sessions is better or worse than 16 sessions, with respect to the maintenance of post-treatment results over the course of FUP times). Interventions will be stratified according to the treatment and dose of treatment to detect inequalities that may affect comparative efficacy. Due to the fact that different psychotherapies have different therapeutic approaches and differ in dose (Zhou et al., 2019; Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013), we will classify level of dose in: low (six sessions or less); medium (six to 12 sessions) and high (12 sessions or more). Based on the expert authors (e.g. Barth et al, 2013; Cuijpers et al, 2008) and the guidelines of the Society of Clinical Psychology, interventions will be included as follows: *Cognitive-behavior therapy, Behavior Therapy/Behavioral Activation, Cognitive*

Therapy, Cognitive Behavioral Analysis System of Psychotherapy, Interpersonal Therapy, Problem-Solving Therapy, Self-Management/Self-Control Therapy, Acceptance and Commitment Therapy, Emotion-Focused Therapy, Rational Emotive Behavioral Therapy, Reminiscence/Life Review Therapy, Self-System Therapy, Short-Term Psychodynamic Therapy. All other forms of administration of psychotherapeutic treatments will be excluded (e.g., group intervention, using the telephone or internet, such as blended treatments). In addition, psychotherapeutic treatments combined with pharmacotherapy or other forms of non-psychological treatments will also be excluded. In order to reduce outcome bias, studies with a “usual care” or “treatment as usual” control group will also be excluded, since this intervention may have combined treatments (Barth et al, 2013), including a psychological intervention. If another type of psychological intervention not listed here is identified, its comparability will be assessed based on the assumptions defined *a priori* and, if considered eligible, it will be included in the network analysis. Studies with follow-up inferior to 18 months after the end of treatment will be excluded.

Type of outcome measures

Primary outcome (follow-up measures). The outcome measures obtained in the post-treatment period will be compared with the outcome measures related to long-term FUP results (considering FUP at multiple moments and final FUP, equal to or superior than 18 months) (Shinohara et al., 2013; Zhou et al., 2015). Studies whose participants initiated another type of treatment in the follow-up period (pharmacotherapy or other psychological treatment/psychotherapy) will be excluded.

Overall efficacy. We will obtain the primary results based on the changes (scores) obtained in depression inventories (e.g., BDI; Beck, Steer, & Garbin, 1988), adopting the cut-off points defined by the authors (standardized instruments measuring). Two analytical approaches will be used for evaluating efficacy:

1. Comparing the efficacy of treatments in maintaining long-term results, from post-treatment, across follow-ups (time points) and end of follow-up. The efficacy of long-term outcomes in the different psychotherapeutic interventions will be defined here as the general change in the mean of the depression severity scales.

2. Comparing the efficacy of treatments in maintaining long-term results, measured by the follow-up time in which it remained stable (without relapse).

Acceptability. We will compare the acceptability of different interventions, defined by the proportion of participants who dropout the follow-up for any reason (namely, because they start another type of treatment: psychotherapeutic treatment, pharmacology).

Secondary outcomes. In all eligible studies, and where available, we will analyze the perception of improvement (in general), quality of life, improved functioning, and/or overall well-being measure.

Search methods for identification of studies

The systematic literature search strategy will involve electronic databases (through pre-defined key words) and manual literature search. In addition, a literature review will be carried out specifically for unpublished studies that are already in the process of preparing/submitted publications. For this purpose, direct contact with researchers in psychotherapy will be initiated through an e-mail that will be sent to the mailing list of members of a research society in psychotherapy (i.e. Society of Psychotherapy Research – SPR).

The references listed in the articles accepted for full reading will also be consulted and used (this strategy will allow us to find other studies that have not been accessed by the previous research).

For the electronic search, and to “guarantee adequate and efficient coverage” (Bramer, Rethlefsen, Kleijnen, & Franco, 2017) for our topic of interest, we will select the following seven databases: *Academic Search Complete, ERIC, PsycARTICLES, PsycINFO, Medline, B-*

on, and *NCBI Resources (PubMed)*. The keywords used in the search will be: *Major depression, Randomized control trial, Psychotherapy, Follow up*, used in different combinations with the terms ((major depression) OR (major depressive) OR (depression)) AND ((random* control* trial*) OR (random* trial*) OR (random* clinical trial*)) AND ((therap*) OR (psychotherap*) OR (psychological treatment*) OR (counsel*)) AND ((follow up) OR (followup) OR (follow-up) OR (long term) OR (longterm) OR (relapse) OR (maintenance) OR (maintenance "of" gains)). In order to ensure that the included studies are of an acceptable quality, only literature published (or submitted for publication) in peer-reviewed scientific journals will be included; dissertations and books will be excluded from the review. Taking into account the innovative nature of this meta-analysis (focusing exclusively on long-term results, with follow-ups of 18 months or more), and to ensure that as many articles are retrieved as possible, we will consider the DSM-IV, DSM-IV TR and DSM-V versions (APA, 1994, 2000, 2013) of the diagnostic criteria for major depression. Literature published from 1994 to December 2016 will be eligible for consideration.

Studies that meet the quality and eligibility criteria described above but are not included in the databases because they have not yet been published will involve direct contact with researchers in psychotherapy, established through an email explaining the objectives and scope of this study which will be sent to the mailing list of members of psychotherapy research societies, specifically, the *Psychotherapy Research listserv*.

Data selection

Selection of studies. The analysis and selection of the studies, at all stages, will meet the defined eligibility criteria. The group will consist of five researchers (authors and three more researchers to be recruited). One researcher (first author) will do the bibliographic research. Two researchers (first author and another judge) will independently analyze titles and abstracts. Secondly, a team of four researchers (first author and three judges) will analyze the full texts and determine the inclusion and eligibility of the studies. The inter-

judge agreement will be assessed using the Cohen's kappa (Cohen, 1960). In case of disagreement, this will be resolved by consensus or arbitration/audit with a fifth researcher (second author).

Data extraction and management

Data will be independently extracted by the above-mentioned researchers. The audit researcher will resolve any disagreement. From the studies under analysis, the scores of the standardized scales (e.g., BDI), population studied, sample size, interventions in focus (treatment, dose-response, follow-up time, time points), comparators, potential risks of bias, results and statistical analysis methods used will be extracted into an Excel sheet.

In case of high variability in the follow-up time and the time points of the studies under analysis, the intermediate measures will be converted into means and compared to the means of the last follow-up.

Risk assessment of bias. The Cochrane's data extraction form 'Risk of bias' tool (Higgins, 2011) will be used to assess the methodological quality and determination of the risk of "low risk", "unclear risk" and "high risk" bias, according to six domains: 1. Random sequence generation; 2. Allocation concealment; 3. Blinding the evaluation of results; 4. Incomplete results data; 5. Selective reports and 6. Other sources of bias. The risk of bias "Concealment of participants and therapists, domains of data extraction" will not be assessed, since psychological treatments are differentiated not only by theoretical assumptions, but also by the set of interventional techniques imposing mastery of the therapeutic model on the therapist (cf. Barth et al, 2013).

Statistical analysis

Measures of treatment effect

Relative treatment effects. We will extract the relative estimates of effects by comparison between pairs of treatments (pairwise) of the different psychotherapeutic interventions and control conditions in the post-treatment and throughout the

follow-up. The results with dichotomous outcomes (clinical response) will be analyzed by calculation of odds ratio (OR) and respective 95% confidence intervals. When different measures are used to evaluate the same outcome in continuous variables (change in severity scales of symptoms of depression, change in the scale of functioning, quality of life or well-being), these will be grouped by the difference of the standardized mean and respective 95% confidence intervals, using Hedges' adjusted g . In studies where the means or standard deviation are not available, they will be calculated using standard errors, 95% confidence intervals and/or p -values (Follmann, Elliott, Suh & Cutler, 1992).

Ranking treatments. We will obtain a hierarchy (the best treatment, the second best and so on) of the competing treatments using the surface under the cumulative ranking curve (SUCRA) and odds ratio (OR). We will also estimate the probability of each treatment being ranked first by the percentage efficacy and acceptability, according to the surface under the cumulative classification curve (SUCRA) as described by Salanti, Ades, and Ioannidis (2011).

Statistical procedure

First, we will conduct a meta-analysis (pairwise, direct comparison) with a random effects model using Review Manager (V.5.2). Second, we will conduct a Bayesian network random effects meta-analysis (indirect comparison), allowing the estimation of the effects of all psychotherapies (intervention vs. control) in the post-treatment and follow-ups analysis by combining direct and indirect evidence. We will perform the network meta-analysis using the WinBUGS version 1.4.3 (MRC Biostatistics Unit 2007) and we will estimate the parameters based on 100 000 interactions by the Markov chain Monte Carlo methods (MCMC; Barth, 2013, Zhou, 2015). From the results of the network meta-analysis, a summary of the relative effect sizes (standardized mean difference or odds ratio) will be presented. We will evaluate the presence of heterogeneity in each pairwise comparison using the I^2 squared statistic and 95% confidence interval. The evaluation of statistical

heterogeneity throughout the network will be based on the magnitude of the parameter of variance between studies (τ^2) (Turner, Davey, Clarke, Thompson, & Higgins, 2012). We will compare the distribution of comparator effects (e.g., psychotherapeutic treatment vs. psychotherapeutic treatment or waiting list or placebo) from the studies in the different pairwise comparisons to assess assumption of transitivity. Inconsistency will be evaluated between direct estimates (all intra-study comparisons) and indirect estimates (e.g., psychotherapies, treatment time, dose response, type of analysis, outcome assessment and study sample size) (Higgins, Jackson, Barrett, Lu, Ades, & White, 2012; White, Barrett, Jackson & Higgins, 2012). The presence of inconsistency will be inferred by the magnitude of the inconsistency factors and 95% confidence interval for each loop (Song, Altman, Glenny, & Deeks, 2003). The forest plot chart will present the results graphically.

Subgroup analysis

We will carry out, whenever possible, analyzes by sex of the participants (men or women), age of the participants, dose response and time of follow-up.

Additional analysis

In the presence of high inconsistency values or high heterogeneity, we will perform a meta-regression or subgroup analysis (precision of the study, results in terms of severity of symptoms of depression in the post-treatment, studies with a high bias) to analyze the estimated effect size. If there is a significant change estimated effect size, studies related to the increase of the variance effect size will be removed from further analysis.

Ethics and dissemination

A systematic review and network meta-analysis will be subsequently submitted for publication in peer-

reviewed journal. Since the study that will be performed is based on data already collected by the authors of the primary studies and the consent of the participants was already obtained, we will not need a new formal submission to the ethics committee.

This systematic review/meta-analysis protocol was registered in the International prospective register of systematic reviews (Vieira & Cunha, 2017) with number: PROSPERO 2017 CRD42017080305 Available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080305

Discussion

Our review will analyze the efficacy of psychotherapy for treating major depression through multiple direct and indirect comparisons of evidence regarding different psychotherapeutic treatments tested in randomized controlled clinical trials (RCTs), taking into account the maintenance of gains evidenced in follow-up evaluations (FUPs) equal to and greater than 18 months, after the completion of treatments for major depression in adults. We will prioritize the treatments administered individually and face-to-face, given that the largest volume of reviews focuses on the results of interventions in blended treatments (mixed formats), such as comparing the results of different treatments administered in group *versus* individual formats (Tolin, 2010), group *versus* individual *versus* face-to-face *versus* self-help formats (Cuijpers et al., 2013a), psychotherapeutic *versus* pharmacological treatments (Cuijpers et al., 2013b), or treatments for different diagnoses (Marcus et al., 2014; Tolin, 2010).

We aspire to be able to provide insights for the protocol definition of future RCTs, specifically with regards to the designs of clinical research, based on the analysis of the evidence provided by previous trials (Salanti et al., 2018), as well as to support the definition of clearer and more informed public health guidelines that may help to make adequate clinical decisions for the treatment of major depression, supported by more sustained evidence. Although our review does not analyze the mechanisms of therapeutic change, or as Wampold et al. (2017) puts it, "*What makes psychotherapy work?*", we consider that an innovative and relevant aspect of this work is

to address the long-term effectiveness of currently evidence-based and empirically supported treatments (according to the understanding of entities such as the Society of Clinical Psychology – division 12 of the APA, 2016).

Furthermore, considering that the rates of relapse of depression are high (50% after two years of the first occurrence; Vittengl, Clark, & Jarrett, 2009), it is essential to grasp which are psychotherapeutic treatments that may be more promising in the long-term. This study aims to contribute for the answer to this essential question, with relevant implications for the definition of public health guidelines that can prevent the recurrence of major depression and minimize the socioeconomic impact of this disorder.

Declaration of Conflicting Interests

We declare that there is no conflict of interest. This manuscript is an integral part of the doctoral thesis of the first author, supervised by the second author.

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