Principal Investigator

First Name: Florian
Last Name: NAUDET
Degree: MD, PhD
Primary Affiliation: Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France; Univ Rennes, CHU Rennes, Inserm, Irset (Institut de recherche en sante?, environnement et travail) - UMR_S 1085, F-35000 Rennes, France
E-mail: claude.pellen@chu-rennes.fr
Phone number:
Address:
2 rue Henri Le Guilloux
City: Rennes
State or Province: France
Zip or Postal Code: 35000
Country: France

General Information

Key Personnel (in addition to PI):
First Name: Claude
Last name: PELLEN
Degree: PharmD, PhD student
Primary Affiliation: Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France
SCOPUS ID: NA

First Name: Florian
Last name: NAUDET
Degree: MD, PhD
Primary Affiliation: Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France
SCOPUS ID: NA

First Name: Estelle
Last name: Le Pabic
Degree: MA / MS / MSc
Primary Affiliation: CHU Rennes
SCOPUS ID:

First Name:
Last name:
Degree:
Primary Affiliation:
SCOPUS ID:

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Programme Hospitalier de Recherche Clinique, French Ministry of Health [Esketamine for "treatment resistant depression": an Individual Patient Data Meta-analysis: ESK-T-Dep]
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_fn.pdf
https://yoda.yale.edu/system/files/coi_cp.pdf
https://yoda.yale.edu/system/files/coi_form_elp.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT02417064 - ESKETINTRD3001 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
2. NCT02418585 - ESKETINTRD3002 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
3. NCT02422186 - ESKETINTRD3005 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects With Treatment-resistant Depression
4. NCT02497287 - ESKETINTRD3004 - An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression
5. NCT02493868 - ESKETINTRD3003 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression
6. NCT01998958 - ESKETINTRD2003 - A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression (SYNAPSE)
7. NCT02133001 - ESKETINSUI2001 - A Double-blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Subjects Who Are Assessed to be at Imminent Risk for Suicide
8. NCT03039192 - 54135419SUI3001 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide
9. NCT03097133 - 54135419SUI3002 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide
10. NCT02918318 - 54135419TRD2005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Doses of Intranasal Esketamine in Japanese Subjects With Treatment Resistant Depression
11. NCT01627782 - KETIVTRD2002 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression
12. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression
13. NCT03434041 - ESKETINTRD3006 - A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

Research Proposal

Project Title

Efficacy of esketamine for "treatment resistant depression" assessed by MADRS score after at least 4 weeks, an IPD meta-analysis

Narrative Summary:

In 2019, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a nasal spray formulation of esketamine for “treatment resistant depression” (TRD). However, the evidence base for its use proved to be controversial.

This study aims to independently reappraise the efficacy and safety of esketamine in TRD and to explore the effect of resistance stage and age as treatment effect modifiers with a meta-analysis of individual patient data.

The results will be of direct interest to national, European and American health authorities to help them assess whether the efficacy of esketamine adequately balances its safety concerns.

Scientific Abstract:

Background:
In 2019, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a nasal spray formulation of esketamine for “treatment resistant depression” (TRD). However, the evidence base for its use proved to be controversial.

Objective:
This registered report aims to independently reappraise the efficacy of esketamine in TRD, by i) exploring the possibility of data integrity issues, ii) re-analyzing and iii) pooling the trial data. Main secondary objectives are to reappraise the safety of esketamine in the treatment of TRD and to explore whether esketamine’s efficacy and safety vary with level of treatment resistance and patient age.

Study Design:
Systematic review and meta-analysis of individual patient data derived from double-blind, randomised, placebo-controlled [placebo or active placebo] trials for the indication of TRD.

Participants:
All doubleblind, randomised, placebo-controlled trials of intranasal esketamine (with the following approved doses: 56 mg or 84 mg or “flexible” doses) for the indication of TRD.

Main Outcome Measure(s):
The primary outcome will be the MADRS score (continuous outcome) assessed after at least 4 weeks (the end of treatment in the pivotal initiation trials / it is expected to be 4 weeks but may be longer depending on the studies selected for the meta-analysis). To take into account the possible rapid effect of esketamine, we will also study the MADRS score at week 1 as a secondary outcome.

Statistical Analysis:
For efficacy and safety outcomes a two-step approach will be adopted. First, we will perform a reanalysis of each study. Then, a fixed effect meta-analysis, or a random effect meta-analysis (in case of heterogeneity), will be used to employed the different efficacy indexes derived from these re-analyses. Initiation and continuation design will be analysed separately. In order to explore the impact of resistance stage and age, a one stage IPD meta-analysis using a mixed model will be performed. If applicable (> 10 studies), we will use a funnel plot to look at small study effects. We will use GRADE to rate the overall certainty of evidence.

Brief Project Background and Statement of Project Significance:

In 2019, the Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for “treatment

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

resistant depression" (TRD). Esketamine's licensing application was granted "breakthrough designation", an expedited review process for drugs "intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)" [1]. The European Medicines Agency EMA promptly followed and approved esketamine [2]. However, the evidence base for its use proved to be controversial, as outlined by Schatzberg [3], Gastaldon and colleagues [4] and in various comments by our group in the Lancet Psychiatry [5-8].

The randomised controlled trials (RCTs) barely demonstrate short-term benefits and did not investigate long-term efficacy of esketamine. Two [9, 10] out of the 3 pivotal initiation RCTs [9-11] failed to demonstrate that esketamine was superior to placebo [5]. For the first time for the FDA's Division of Psychiatry Products, a continuation RCT was counted as a second positive pivotal trial. The FDA described in its assessment some possible data integrity issues for two trials [5]. For the continuation study, the FDA reported that "one site in Poland drives the overall study result due to a 100% rate of placebo arm relapses" [12]. After our pieces drew attention to this issue, the sponsor reported a sensitivity analysis [13]: the P-value changed from highly significant to "barely significant". However, the sponsor did not explain why the FDA used the word "drives", implying that its result was nonsignificant when this center was removed, nor why the FDA reported slightly different numbers of relapsed patients [8].

In August 2020, the FDA approved a supplemental New Drug Application for esketamine nasal spray (SPRAVATO). However, even the sponsor's press release admits that "effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated" [14]. In contrast, a pharmacovigilance analysis showed that suicide ideation might be increased in people taking esketamine [15].

In UK, the National Institute for Health and Care Excellence (NICE), did not recommend its use [16]. In France, the "Commission de la transparence" expressed a favorable opinion for reimbursement for a subgroup of patients; an unfavorable opinion regarding reimbursement in the other indications and stressed that there was no clinical added value in the therapeutic strategy [17].

Based on these divergent viewpoints, concerns surrounding data integrity, and doubts about esketamine's efficacy in TRD patients, an independent re-appraisal of the evidence is urgently warranted. An independent reanalysis and IPD meta-analysis will help resolve these uncertainties. These data will be of direct interest to national, European and American health authorities such as EMA and FDA. The exploration of efficacy/safety modifiers may help to better delineate the clinical indications of esketamine.

Specific Aims of the Project:

The main objective is to independently reappraise the efficacy of esketamine in TRD using an individual participant data meta-analysis methodology. The secondary objectives are to reappraise the safety of esketamine in the treatment of TRD and to explore moderating factors of esketamine efficacy and safety, including level of treatment resistance, patient age, site-specific effects, among others.

For the primary outcome, mean differences in MADRS scores observed will be calculated. Point estimates and confidence intervals will be compared with 0 (absence of difference) and 6.5 points (the threshold defined a priori in initiation studies).

Please find attached the protocol for more details. It is also registered on the Open Science Framework (https://osf.io/xetvn); and on Prospero (ID CRD42021290721, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=290721).

The protocol has been reviewed and accepted for publication (in-principal acceptance) at BMC Medicine as a registered report.

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data source:
Systematic searches will be conducted by two independent researchers using PubMed, the Cochrane library, Embase, ClinicalTrials.gov, Clinicaltrialsregister.eu, FDA, EMA and the manufacturer website. Selection, coding and risk of bias assessment of the different study characteristics will be performed by two independent researchers in a blinded manner.

Inclusion/Exclusion Criteria:
We will consider studies that include all patients with TRD meeting the inclusion criteria of esketamine's development program for this indication: depressive episode with inadequate response to at least two antidepressant trials of adequate doses and duration. There will be no age limit. In terms of strategy the systematic review search criteria will include all studies of esketamine for the primary treatment of depression. The IPD analysis will then be restricted to patients with TRD within the included studies. Included studies will be studies that compare the use of intranasal esketamine (56 mg or 84 mg or "flexible" doses) to a placebo. All randomised controlled trials (initiation and continuation trials) will be considered.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome will be the MADRS score (continuous outcome) assessed after at least 4 weeks (end of treatment in pivotal initiation trials). The possible rapid effect of esketamine will be assessed by the MADRS score at week 1 as a secondary outcome.

All of the following secondary outcomes will be assessed at end of treatment and at the last follow-up visit post-treatment in initiation trials; at the end of the study in continuation trial.
Efficacy: suicide/suicide attempt (binary outcome); suicidal ideations, e.g. Beck Scale for Suicidal Ideation (BSS, continuous outcome); MADRS (continuous outcome, similar to the primary outcome but, here using the last follow-up visit post-treatment); remission (binary outcome); Sheehan Disability Scale (continuous outcome); PHQ-9 (continuous outcome); relapse (censored outcome) for continuation trials.
Safety: serious adverse events (count outcome, events per patient); dropout for any cause (binary outcome); dropout due to adverse events (binary outcome); Adverse events (count outcome events per patient); Blood pressure (continuous repeatedly measured outcome); Dissociation (binary outcome); Sedation (binary outcome).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Reanalysis:
Same predictors as in the initial studies, at least the group (esketamine versus placebo).

Moderators of response to esketamine:
In order to study the impact of resistance stage and age, a one-step meta-analysis approach will be used: each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. This classification, as well as age of the patient will be explored as treatment effect modifiers in a one stage IPD meta-analysis using a mixed model.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Reanalysis:
For each RCT, we will explore a center effect by performing sensitivity analyses removing a center at a time.

Moderators of response to esketamine:

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

Sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.

Statistical Analysis Plan:

Analysis strategy:
For efficacy and safety outcomes a two-step approach will be adopted, the a one-stage approach will be used to explore moderators of esketamine efficacy. All the analyses will be performed with R (R core Team, 2021).

Reanalysis:
First, we will perform a reanalysis of each study following the initial protocol of each study and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This first approach will allow for indepth description of any deviations from the protocol and for documentation of the data integrity issues mentioned in the FDA appraisal. For each RCT, we will explore a center effect by performing sensitivity analyses removing a center at a time.

Meta-analysis:
Then, a fixed effect meta-analysis, or a random effect meta-analysis (in case of heterogeneity defined as an I2 index > 25 % and/or detection of significant heterogeneity ($p<0.10$) detected using Cochran's Q test statistic), will be used to pool the different efficacy indexes (mean differences or relative risks or odds ratio or hazard ratios) that will be derived from these reanalyses. Initiation and continuation designs will be analyzed separately. For the primary outcome, mean differences in MADRS scores observed (point estimates and confidence intervals will be compared with 0 (absence of difference) and 6.5 points (the threshold defined a priori in initiation studies). A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis. If applicable (> 10 studies), we will use a funnel plot to look at small study effects. We will use GRADE to rate the overall certainty of evidence.

Moderators of response to esketamine:
In order to study the impact of resistance stage and age, a one-step approach will be used: each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. This classification, as well as age of the patient will be explored as treatment effect modifiers in a one stage IPD meta-analysis using a mixed model. Another sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.
Software Used:
RStudio

Project Timeline:

January 2022: Systematic review and request of the data
March 2022: Access to the individual patient data
April to November 2022: Analysis of the data
December 2022: Writing of the article
January to March 2023: Submission of the article and responses to reviwers
June 2023: End of data sharing (15 months after the beginning of the data sharing of all required trials)

Dissemination Plan:

We will make sure that our protocol is peer reviewed. For this reason, we have chosen to publish the study as a registered report. This approach eliminates many questionable research practices, including low statistical power, selective reporting of results, and publication bias, while still allowing flexibility to report serendipitous findings. In addition, the protocol will be registered on PROSPERO prior starting our research. All prespecified analysis plans and the code to reproduce our analyses will shared on the Open Science Framework. We will indicate how to retrieve and access all the datasets as we did in a previous project [26]. Before submission of the final manuscript, results will be shared using a pre-print server (e.g. medRxiv) and will encourage peer review at this step. We will detail each step of the project in dedicated blogpost, on the ReiTheR website (https://www.reither.org/blog) and will invite comments.

Bibliography:

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

1. Breakthrough Therapy [https://www.fda.gov/patients/fast-track-breakthroughtherapy- accelerated-approval-priority-review/breakthrough-therapy]
2. Spravato : EPAR - Public assessment report https://www.ema.europa.eu/en/documents/assessment-report/spravato-eparpu... assessment-report_en.pdf]
3. Schatzberg AF: A Word to the Wise About Intranasal Esketamine. The American journal of psychiatry 2019, 176(6):422-424.
4. Gastaldon C, Papola D, Ostuzzi G, Barbui C: Esketamine for treatment resistant depression: a trick of smoke and mirrors? Epidemiology and psychiatric sciences 2019, 29:e79.
5. Cristea IA, Naudet F: US Food and Drug Administration approval of esketamine and brexanolone. The lancet Psychiatry 2019, 6(12):975-977.
6. Naudet F, Cristea IA: Approval of esketamine for treatment-resistant depression - Authors' reply. The lancet Psychiatry 2020, 7(3):235-236.
7. Turner EH: Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. The lancet Psychiatry 2019, 6(12):977-979.
8. Turner EH: Approval of esketamine for treatment-resistant depression - Author's reply. The lancet Psychiatry 2020, 7(3):236.
9. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, Vitagliano D, Blier P, Fava M, Liebowitz M et al: Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). The international journal of neuropsychopharmacology 2019, 22(10):616-630.
10. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, Hough D, Manji H, Drevets WC, Sanacora G et al: Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression- TRANSFORM-3. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2020, 28(2):121-141.
11. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, Mazzucco C, Hough D, Thase ME, Shelton RC et al: Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. The American journal of psychiatry 2019, 176(6):428-438.
12. Briefing Information for the February 12, 2019 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). [https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM630970.pdf]
13. Singh JB, Daly EJ, Mathews M, Fedgchin M, Popova V, Hough D, Drevets WC: Approval of esketamine for treatment-resistant depression. The lancet Psychiatry 2020, 7(3):232-235.
14. Janssen Announces U.S. FDA Approval of SPRAVATO® (esketamine) CIII Nasal Spray to Treat Depressive Symptoms in Adults with Major Depressive Disorder with Acute Suicidal Ideation or Behavior [https://www.janssen.com/janssen-announces-us-fdaapproval- spravator-esketamine-ciii-nasal-spray-treat-depressive-symptoms]
15. Gastaldon C, Raschi E, Kane JM, Barbui C, Schoretsanitis G: Post-Marketing Safety Concerns with Esketamine: A Disproportionality Analysis of Spontaneous Reports Submitted to the FDA Adverse Event Reporting System. Psychotherapy and psychosomatics 2021, 90(1):41-48.
16. Mahase E: Esketamine for treatment resistant depression is not recommended by NICE. BMJ (Clinical research ed) 2020, 368:m329.
17. Avis de la commission de la transparence [https://www.hassante. fr/jcms/p_3192924/en/spravato]
18. Warren E: Strengthening Research through Data Sharing. The New England journal of medicine 2016, 375(5):401-403.
19. Krumholz HM, Waldstreicher J: The Yale Open Data Access (YODA) Project—A Mechanism for Data Sharing. The New England journal of medicine 2016, 375(5):403-405.
20. Thase ME, Rush AJ: When at first you don't succeed: sequential strategies for antidepressant nonresponders. The Journal of clinical psychiatry 1997, 58 Suppl 13:23-29.
21. Sterne JAC, Savovi? J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM et al: RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2019, 366:l4898.
22. ICH E9 statistical principles for clinical trials [https://www.ema.europa.eu/en/iche9- statistical-principles-clinical-trials#current-version-section]
23. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. 2008, 336(7650):924-926.
24. Kontopantelis E: A comparison of one-stage vs two-stage individual patient data meta-analysis methods: A

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

simulation study. Research synthesis methods 2018, 9(3):417-430.
25. Klein T, Weinmann S, Becker T, Koesters M: Antidepressant treatment effects and country income: meta-regression analysis of individual participant data from duloxetine trials. Acta psychiatrica Scandinavica 2021, 144(3):277-287.
26. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, Ioannidis JPA: Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in The BMJ and PLOS Medicine. BMJ (Clinical research ed) 2018, 360:k400.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/registered_report_stage_1_acceptance.pdf

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }