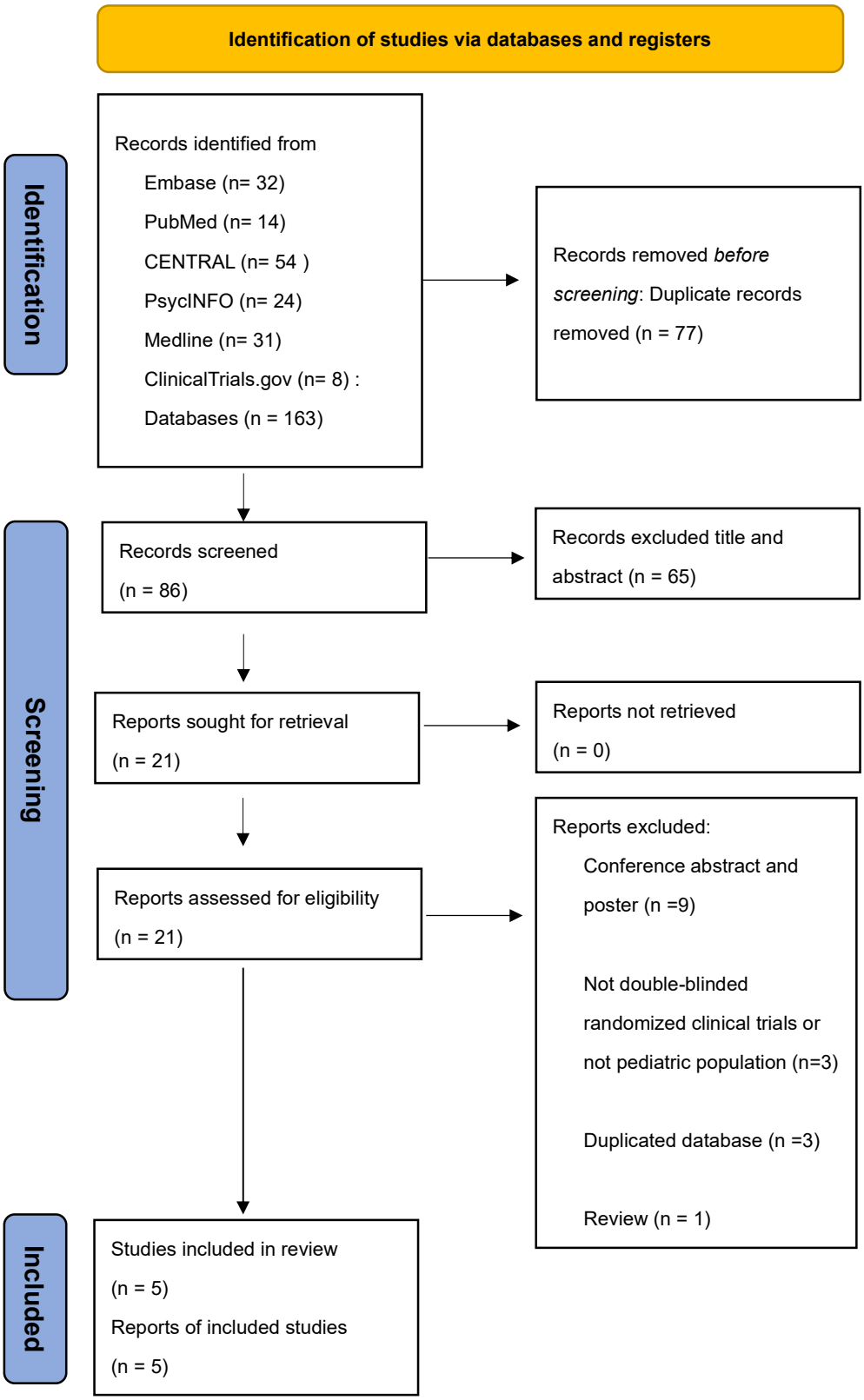
# Supplemental Online Content

Yu C, Kao Y, Thompson T, et al. Response trajectories and temporal trends of viloxazine treatment for young people with ADHD: a meta-analysis. *JAMA Netw Open.* 2024;7(11):e2445885. doi:10.1001/jamanetworkopen.2024.45885

**eFigure 17.** Dose Response Meta-Analysis for Risk Ratio of Somnolence

This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Study Flowchart




*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

**eAppendix 1.** Search Strategy

| Database |
|---|
| **PubMed search strategy** |
| #1 "viloxazin"[All Fields] OR "viloxazine"[MeSH Terms] OR "viloxazine"[All Fields] (408) |
| #2 "attention deficit disorder with hyperactivity"[MeSH Terms] OR ("attention"[All Fields] AND "deficit"[All Fields] AND "disorder"[All Fields] AND "hyperactivity"[All Fields]) OR "attention deficit disorder with hyperactivity"[All Fields] OR "adhd"[All Fields] (51,100) |
| #3 #1 AND #2 (68) |
| #4 #3 AND (randomizedcontrolledtrial[Filter]) (14) |
| **Cochrane Central Register of Controlled Trials (CENTRAL) search strategy** |
| #1 MeSH descriptor: [Viloxazine] explode all trees (69) |
| #2 (viloxazine):ti,ab,kw (Word variations have been searched) (158) |
| #3 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees (3,836) |
| #4 ADHD (6,146) |
| #5 ("Attention Deficit Disorder with Hyperactivity"):ti,ab,kw (3,868) |
| #6 #1 OR #2 (158) |
| #7 #3 OR #4 OR #5 (6,890) |
| #8 #6 AND #7 (54) |
| **Embase search strategy** |
| #1. 'viloxazine'/exp OR viloxazine (1,646) |
| #2. 'attention deficit hyperactivity disorder'/exp OR 'attention deficit hyperactivity disorder' OR 'adhd'/exp OR adhd (89,423) |
| #3. #1 AND #2 (147) |
| #4. #3 AND 'randomized controlled trial'/de (32) |
| **PsycInfo search strategy** |
| S1 Viloxazine AND ( (attention deficit disorder with hyperactivity or adhd) ) (24) |
| **Medline search strategy** |
| 1 Viloxazine/ or Viloxazine.mp. (395) |
| 2 Attention Deficit Disorder with Hyperactivity/ or Attention Deficit Disorder with Hyperactivity.mp. or ADHD.mp. (44,956) |
| 3 randomized controlled trial.pt. (613,775) |
| 4 controlled clinical trial.pt. (95,538) |
| 5 randomized.ab. (638,049) |
| 6 placebo.ab. (246,320) |
| 7 clinical trials as topic.sh. (202,458) |

| |
|---|
| 8 randomly.ab. (429,890) |
| 9 trial.ti. (305,586) |
| 10 3 or 4 or 5 or 6 or 7 or 8 or 9 (1,586,859) |
| 11 exp animals/ not humans.sh. (5,225,418) |
| 12 10 not 11 (1,460,560) |
| 13 1 and 2 and 12 (31) |
| **ClinicalTrials.gov (https://clinicaltrials.gov/)** |
| Attention Deficit Disorder With Hyperactivity \| Viloxazine (8) |

CENTRAL: Cochrane Central Register of Controlled Trials

**eAppendix 2**. Reasons for Exclusion

**Not DBRCT, not pediatric population (n=3)**

1. A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered With Psychostimulants in Children and Adolescents (6 to 17 Years of Age) With Attention-Deficit/Hyperactivity Disorder (ADHD) [Internet]. 2021. Available from: https://clinicaltrials.gov/study/NCT04786990.
2. Nasser A, Hull JT, Chaturvedi SA, Liranso T, Odebo O, Kosheleff AR, et al. A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder. CNS drugs. 2022;36(8):897-915.
3. Nct. Evaluation of SPN-812 (Viloxazine Extended-release Capsule) in Adults With ADHD. https://clinicaltrialsgov/show/NCT04016779. 2019.

**Duplicated data (n=3)**

1. Nasser A, Hull JT, Chowdhry FA, Adewole T, Liranso T, Marcus R. Phase 3, randomized, double-blind, placebo-controlled studies evaluating efficacy and safety of extended-release viloxazine (SPN-812) for pediatric ADHD: update on the second adolescent study (p304). Neurotherapeutics. 2019;16(3):915.
2. Nct. Efficacy and Safety of SPN-812 (Viloxazine Extended-release Capsule) in Children With ADHD. https://clinicaltrialsgov/show/NCT02633527. 2015.
3. Nasser A, Hull JT, Liranso T, Busse GD, Melyan Z, Childress AC, et al. The effect of viloxazine extended-release capsules on functional impairments associated with attention-deficit/hyperactivity disorder (ADHD) in children and adolescents in four phase 3 placebo-controlled trials. Neuropsychiatric disease and treatment. 2021;17:1751-62.

**Conference abstract or Poster (n=9)**

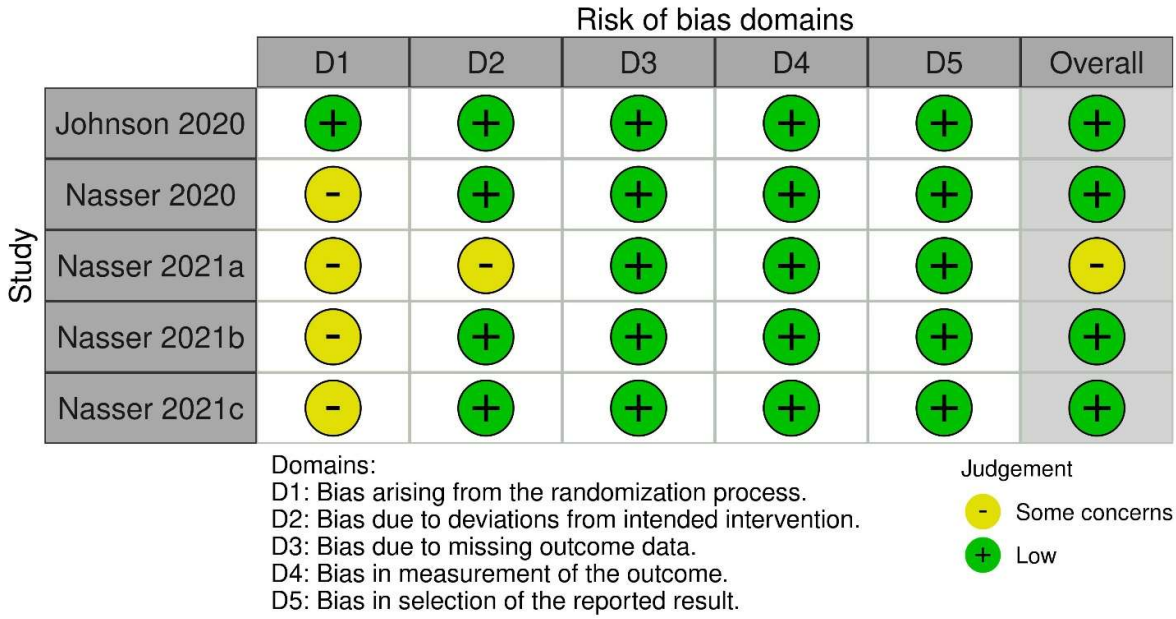
1. Findling RL, Newcorn JH, Cutler AJ, Childress AC, Hull JT, Qin P, et al. 5.13 Evaluation of the Efficacy of Viloxazine ER in ADHD Inattentive and Combined Presentations. Journal of the American Academy of Child and Adolescent Psychiatry. 2023;62(10):S262-S3.
2. Johnson JK, Saylor K, Brittain ST, Tulloch G, Liranso T. A double-blind, placebo-controlled, dose-ranging study of extended-release viloxazine (SPN-812 ER) in children with attention-deficit/hyperactivity disorder (ADHD). Journal of the American Academy of Child and Adolescent Psychiatry. 2017;56(10):S283-S4.
3. Nasser A, Busse GD, Hull J, Chowdhry F, Adewole T, Liranso T, et al. 1.70 A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (P301) ASSESSING THE EFFICACY AND SAFETY OF SPN-812 (EXTENDED-RELEASE VILOXAZINE) 100 AND 200MG FOR THE TREATMENT OF ADHD IN CHILDREN. Journal of the American Academy of Child and Adolescent Psychiatry. 2019;58(10):S169-S70.
4. Nasser A, Hull JT, Chaturvedi S, Adewole T, Liranso T, Busse G, et al. 5.31 THE EFFICACY AND SAFETY OF SPN-812 (VILOXAZINE EXTENDED-RELEASE) FOR THE TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS. Journal of the American Academy of Child and Adolescent Psychiatry. 2020;59(10):S159.
5. Nasser A, Hull JT, Chowdhry FA, Adewole T, Liranso T, Marcus R. Extended-release viloxazine (SPN-812) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adolescents: topline results of a phase 3, randomized, double-blind, placebo-controlled study (p302). Neurotherapeutics. 2019;16(3):914-5.

6. Nasser A, Hull JT, Chowdhry FA, Adewole T, Liranso T, Schwabe S. 112 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study (P302): efficacy and Safety of Extended-Release Viloxazine in Adolescents with ADHD. CNS spectrums. 2020;25(2):272-3.
7. Nasser A, Hull JT, Chowdhry FA, Adewole T, Liranso T, Schwabe S. 113 Phase 3, Randomized, Double-Blind, Placebo-Controlled Study (P303) Assessing Efficacy and Safety of Extended-Release Viloxazine in Children with ADHD. CNS spectrums. 2020;25(2):273-4.
8. Nasser A, Johnson JK, Adewole T, Liranso T, Marcus R. Phase 3 randomized, double-blind, placebo-controlled studies evaluating efficacy and safety of extended-release viloxazine for pediatric ADHD. CNS spectrums. 2019;24(1):177-8.
9. Nasser A, Kosheleff AR, Hull JT, Liranso T, Qin P, Busse GD, et al. Evaluating the likelihood to be helped or harmed after treatment with viloxazine extended-release in children and adolescents with attention-deficit/hyperactivity disorder. International Journal of Clinical Practice. 2021;75(8).

**Review (n=1)**

1. Raible H, D'Souza MS. Extended-Release Viloxazine for the Treatment of Attention-Deficit Hyperactivity Disorder in School-Age Children and Adolescents. Annals of pharmacotherapy. 2023;57(12):1436-48.

**eFigure 2**. Risk of Bias Plot of the Included Studies



**eTable 1.** Model Fitting for the Dose-Response Association Between the Dose of Viloxazine and the Outcome

| Outcome | Dose-response association | Best model fitting (linear vs quadratic vs spline)[a] | $R^2$ (Goodness-of-fit) |
|---|---|---|---|
| All ADHD symptoms* | p<0.001 | Spline, p<0.001 | 0.948 |
| Inattention symptoms* | p<0.001 | Spline, p<0.001 | 0.924 |
| Hyperactivity symptoms* | p<0.001 | Spline, p<0.001 | 0.923 |
| Response rate* | p<0.001 | Spline, p<0.001 | 0.923 |
| Response trajectory of 100 mg/d* | p<0.001 | Spline, p<0.001 | 0.978 |
| Response trajectory of 200 mg/d* | p<0.001 | Spline, p<0.001 | 0.945 |
| Response trajectory of 400 mg/d* | p<0.001 | Spline, p<0.001 | 0.927 |
| Dropout | p=0.05 | Linear, p=0.05 | 0.194 |
| Dropout due to adverse effect | p=0.182 | Linear, p=0.18 | 0.156 |
| Nausea* | p<0.001 | Spline, p=0.01 | 0.642 |
| Headache* | p=0.040 | Linear, p=0.04 | 0.269 |
| Somnolence* | p=0.029 | Spline, p=0.03 | 0.709 |
| Poor appetite* | p=0.037 | Linear, p=0.04 | 0.662 |
| Abdominal pain | p=0.916 | Linear, p=0.92 | 0.110 |
| Fatigue | p=0.050 | Linear, p=0.05 | 0.585 |

[a] spline is restricted cubic spline with three knots (0.1, 0.5, 0.9)

*: statistically significant dose-response association between the dose of viloxazine and the outcome

Abbreviations: ADHD=attention deficit/hyperactivity

**eTable 2.** Model Fitting for the Dose-Response (mg/kg) Association Between the Dose of Viloxazine and the Outcome

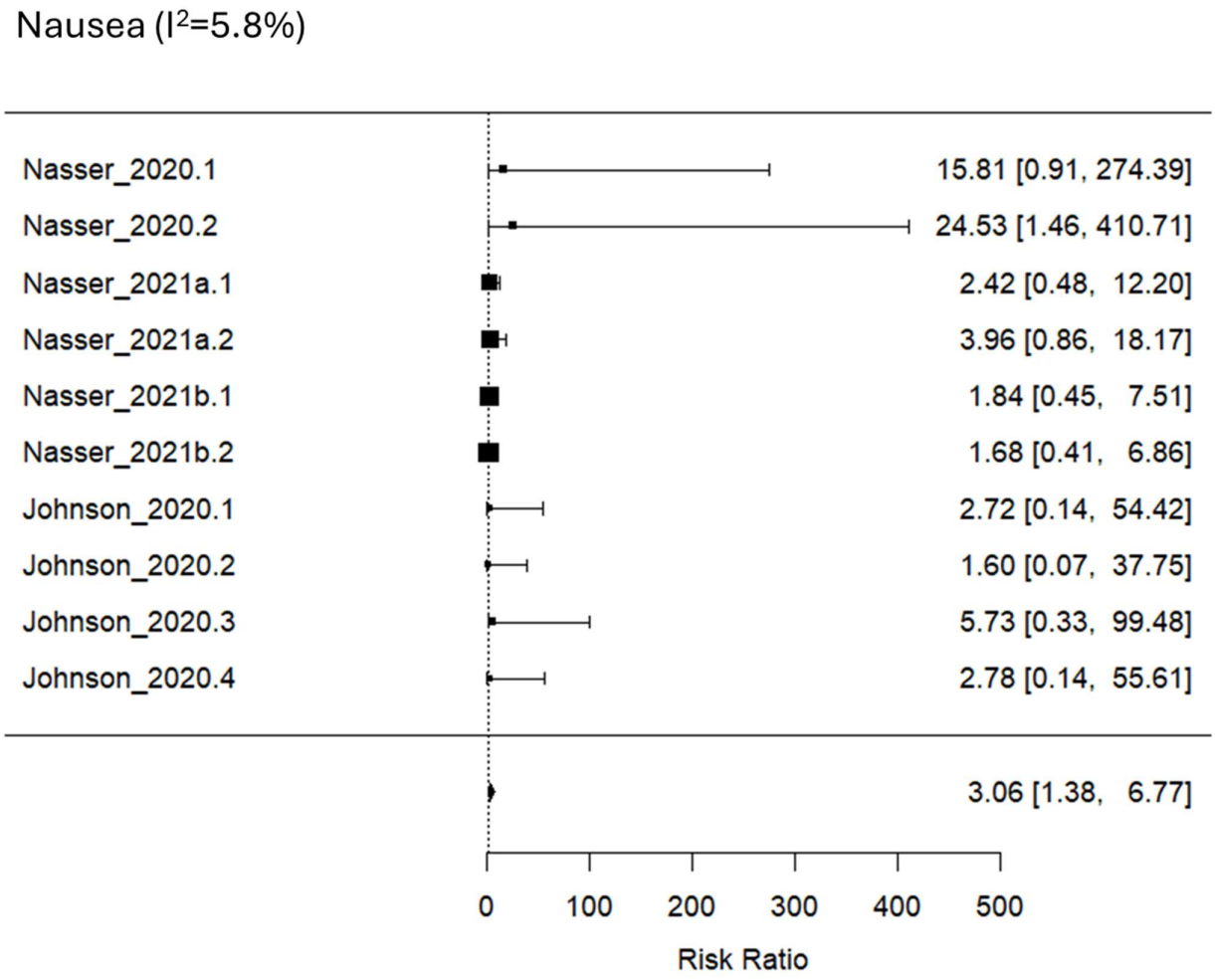
| Outcome | Dose-response association | Best model fitting (linear vs quadratic vs spline)[a] | $R^2$ (Goodness-of-fit) |
|---|---|---|---|
| All ADHD symptoms* | p<0.001 | Spline, p<0.001 | 0.930 |
| Inattention symptoms* | p<0.001 | Spline, p<0.001 | 0.901 |
| Hyperactivity symptoms* | p<0.001 | Spline, p<0.001 | 0.893 |
| Response rate* | p<0.001 | Spline, p=0.004 | 0.846 |

[a] spline is restricted cubic spline with three knots (0.1, 0.5, 0.9)

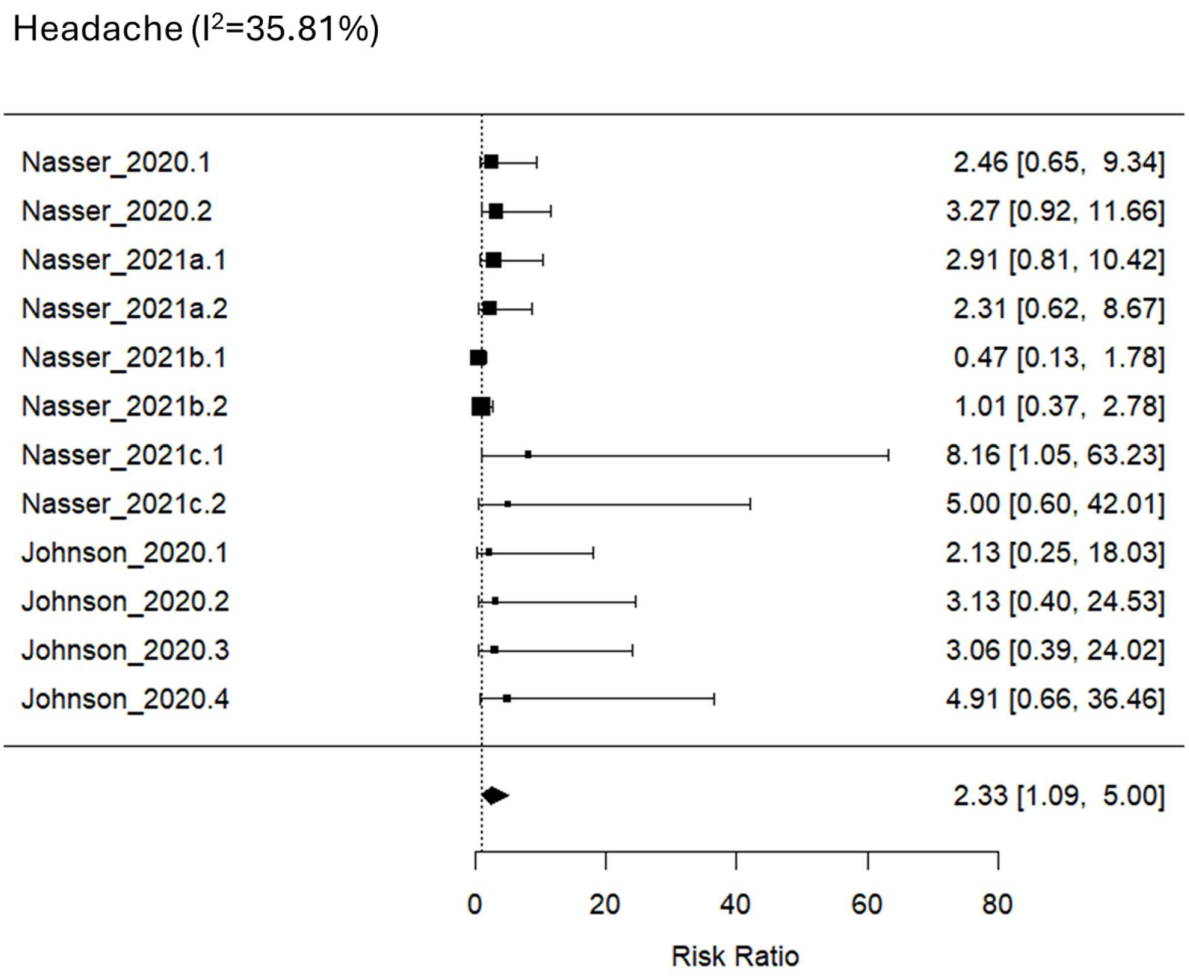
*: statistically significant dose-response association between the dose of viloxazine and the outcome

Abbreviations: ADHD=attention deficit/hyperactivity

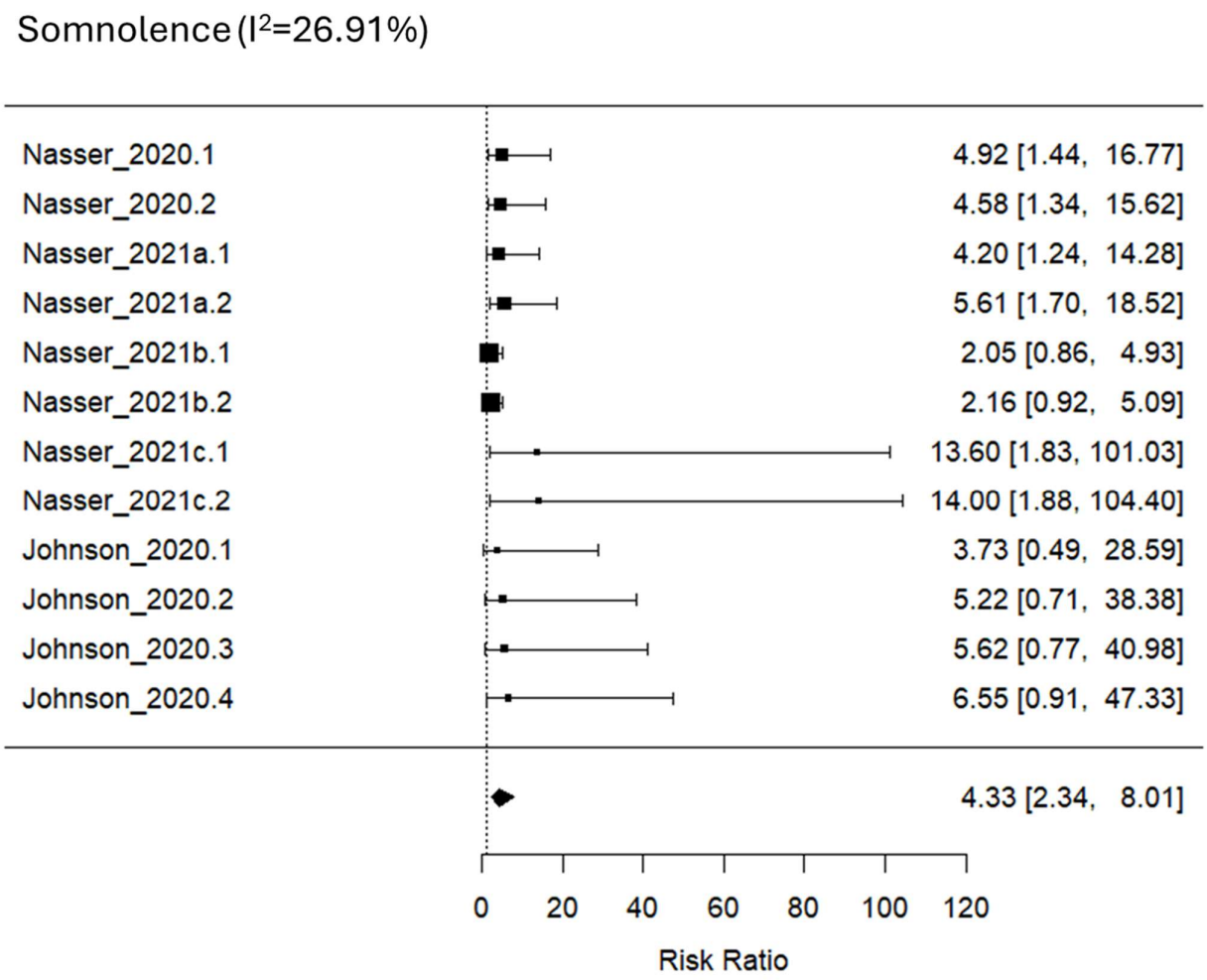
**eFigure 3.** Pairwise Meta-Analysis for Risk Ratio of Nausea



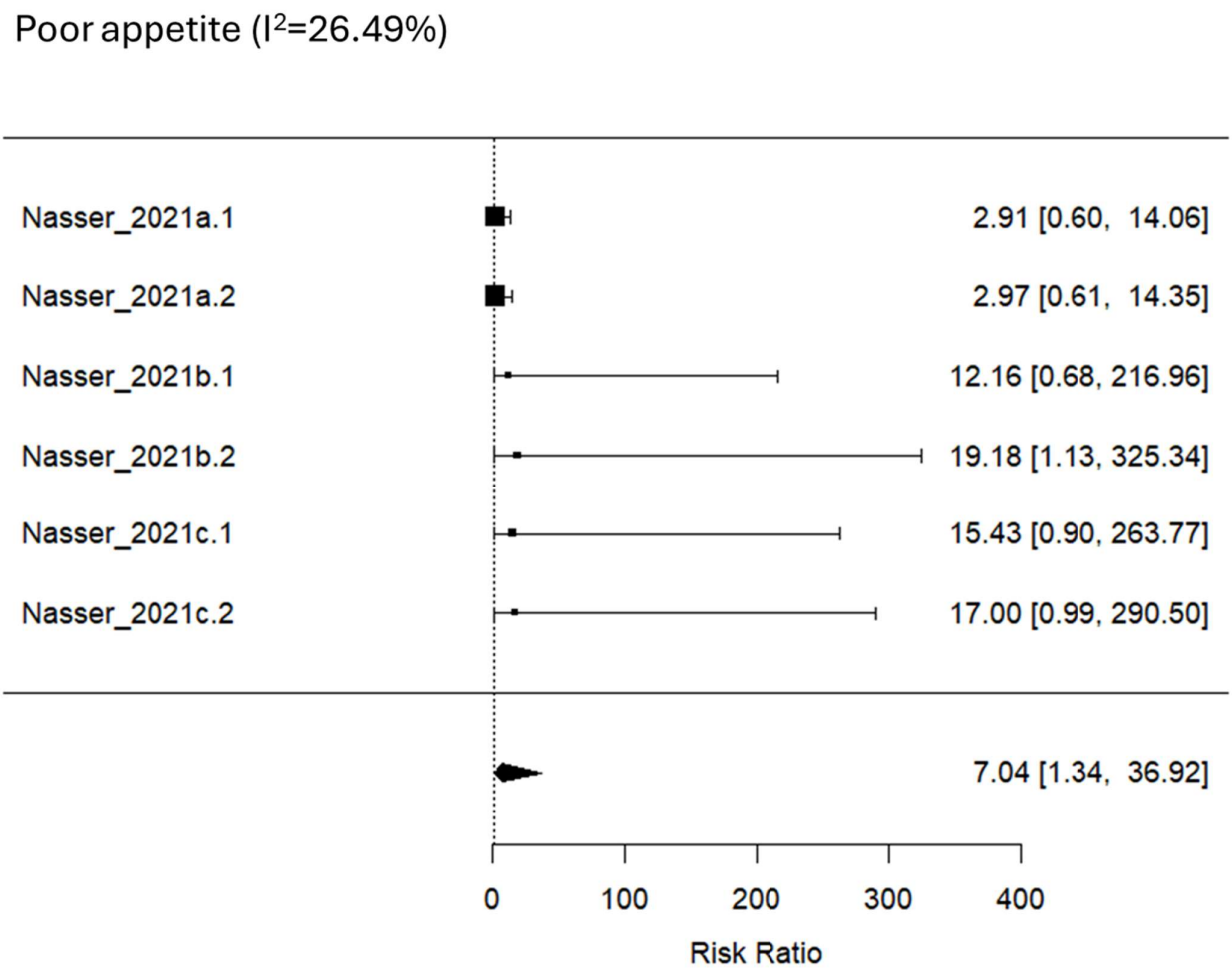
**eFigure 4.** Pairwise Meta-Analysis for Risk Ratio of Headache



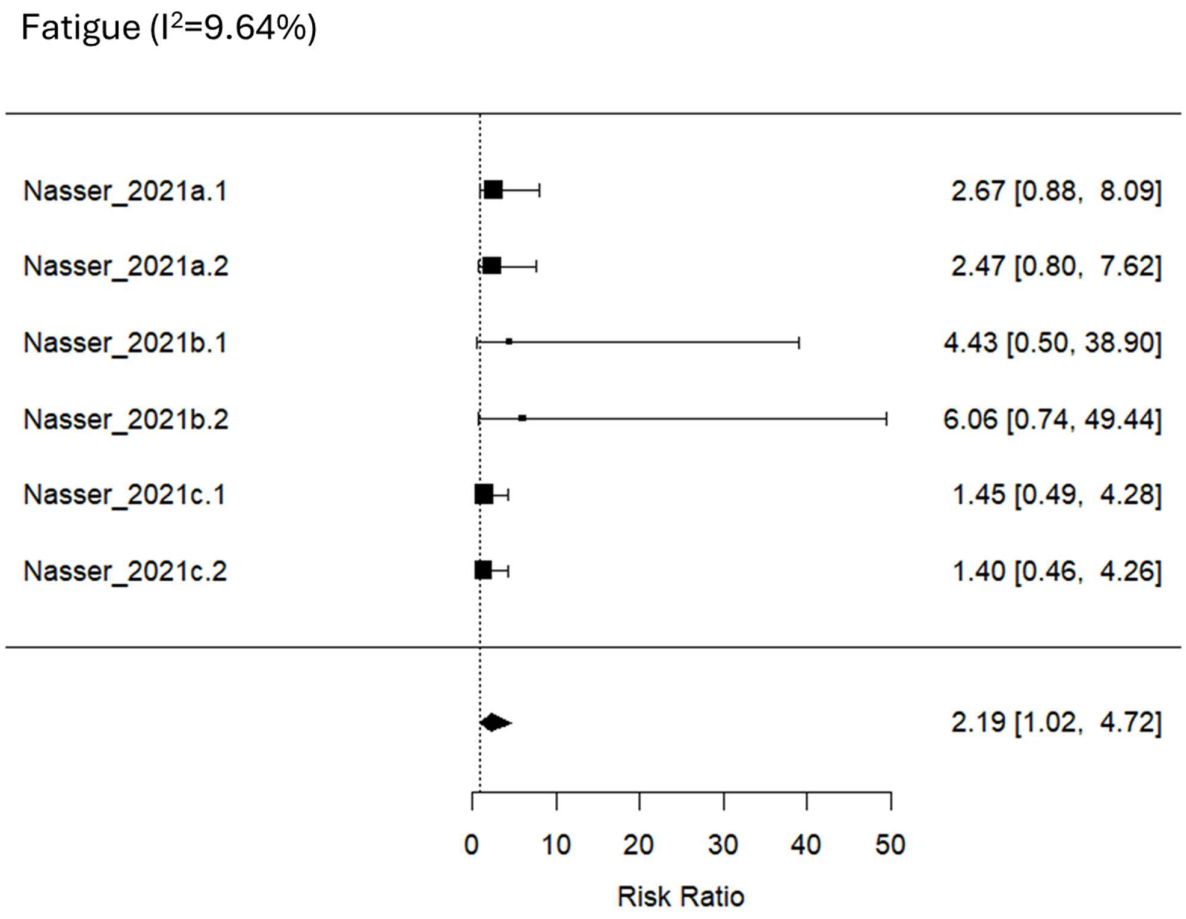
**eFigure 5.** Pairwise Meta-Analysis for Risk Ratio of Somnolence



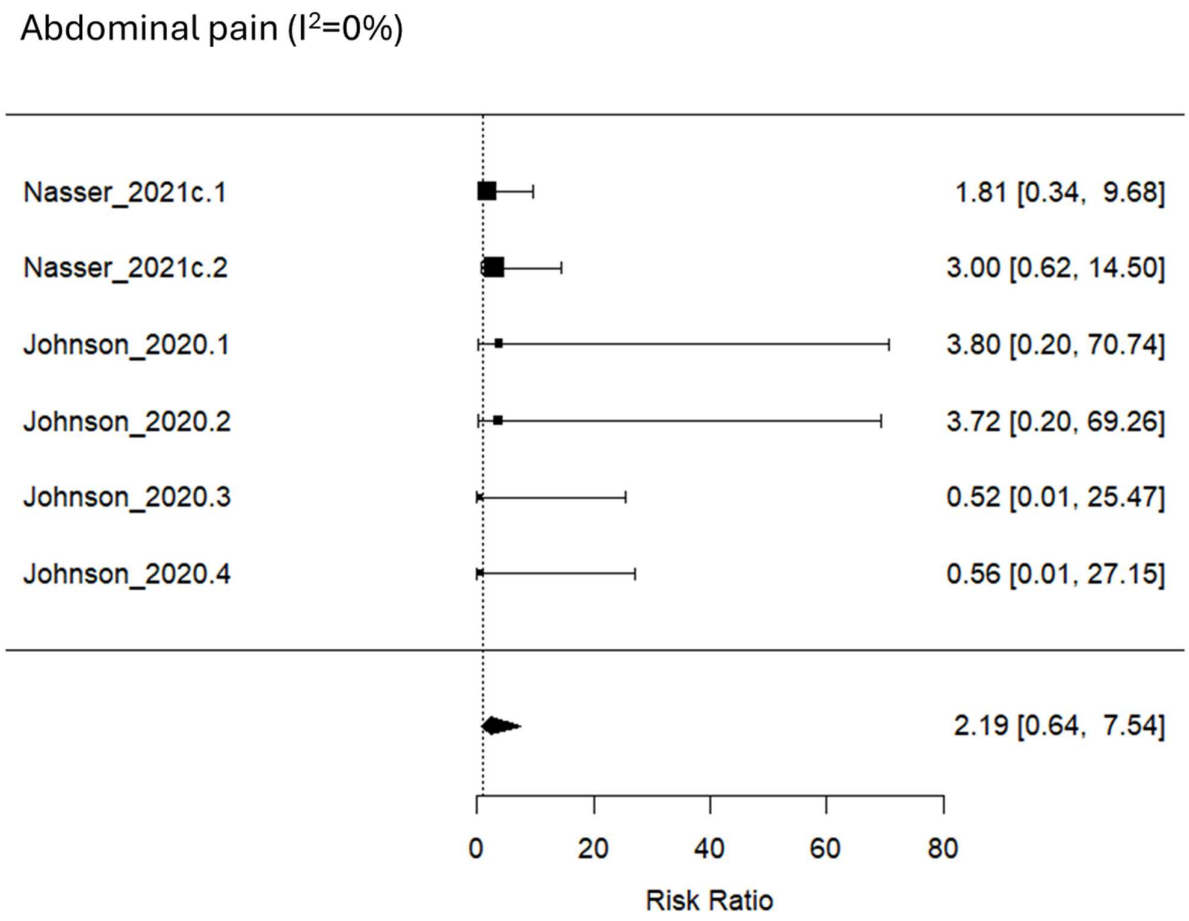
**eFigure 6.** Pairwise Meta-Analysis for Risk Ratio of Poor Appetite



**eFigure 7.** Pairwise Meta-Analysis for Risk Ratio of Fatigue



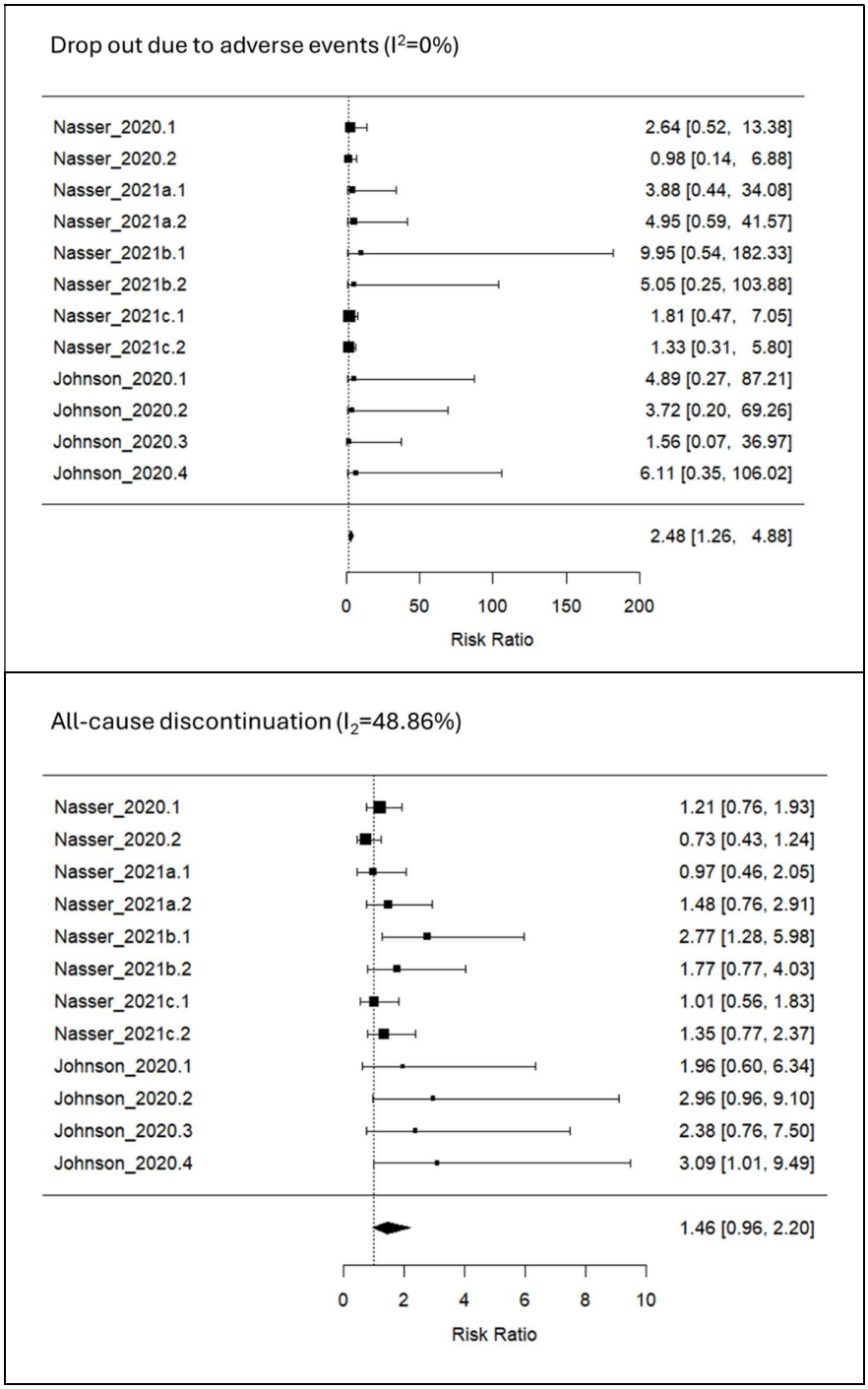
**eFigure 8**. Pairwise Meta-Analysis for Risk Ratio of Abdominal Pain



**eTable 3**. Raw Incidence of Adverse Effects

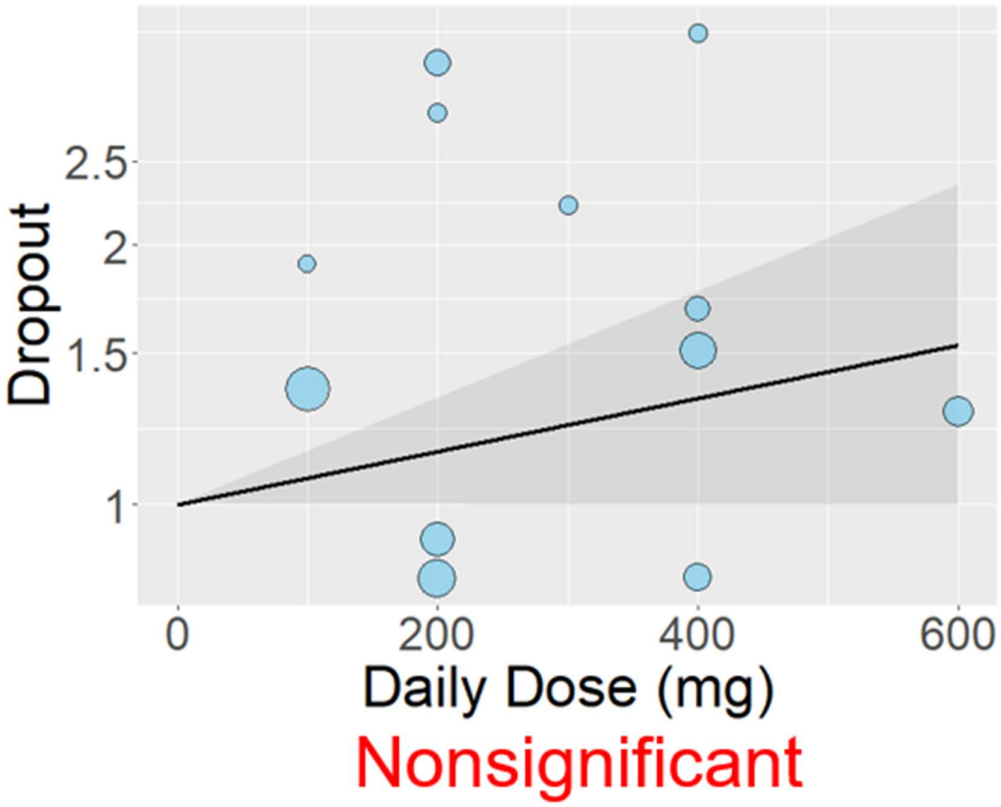
| Study | Intervention arms | sample size | Drop out | Drop out due to AE | Decreased appetite | Abdominal pain | Nausea | Headache | Somnolence | Fatigue |
|---|---|---|---|---|---|---|---|---|---|---|
| Nasser 2020 | Viloxazine 100mg | 147 | 31 | 5 | | | 7 | 7 | 14 | |
| | Viloxazine 200mg | 158 | 20 | 2 | | | 12 | 10 | 14 | |
| | Placebo | 155 | 27 | 2 | | | 0 | 3 | 3 | |
| Nasser 2021a | Viloxazine 400mg | 99 | 12 | 4 | 6 | | 5 | 9 | 13 | 11 |
| | Viloxazine 600mg | 97 | 18 | 5 | 6 | | 8 | 7 | 17 | 10 |
| | Placebo | 96 | 12 | 1 | 2 | | 2 | 3 | 3 | 4 |
| Nasser 2021b | Viloxazine 200mg | 94 | 20 | 4 | 5 | | 5 | 3 | 13 | 4 |
| | Viloxazine 400mg | 103 | 14 | 2 | 9 | | 5 | 7 | 15 | 6 |
| | Placebo | 104 | 8 | 0 | 0 | | 3 | 7 | 7 | 1 |
| Nasser 2021c | Viloxazine 200mg | 107 | 19 | 6 | 8 | 4 | | 9 | 15 | 8 |
| | Viloxazine 400mg | 97 | 23 | 4 | 8 | 6 | | 5 | 14 | 7 |
| | Placebo | 97 | 17 | 3 | 0 | 2 | | 1 | 1 | 5 |
| Johnson 2020 | Viloxazine 100mg | 45 | 11 | 4 | | 3 | 2 | 4 | 7 | 2 |
| | Viloxazine 200mg | 46 | 17 | 3 | | 3 | 1 | 6 | 10 | 2 |
| | Viloxazine 300mg | 47 | 14 | 1 | | 0 | 5 | 6 | 11 | 1 |
| | Viloxazine 400mg | 44 | 17 | 5 | | 0 | 2 | 9 | 12 | 5 |
| | Placebo | 24 | 3 | 0 | | 0 | 0 | 1 | 1 | 0 |

**eFigure 9**. Pairwise Meta-Analysis for Risk Ratio of Dropout Due to Adverse Events and All-Cause Discontinuation

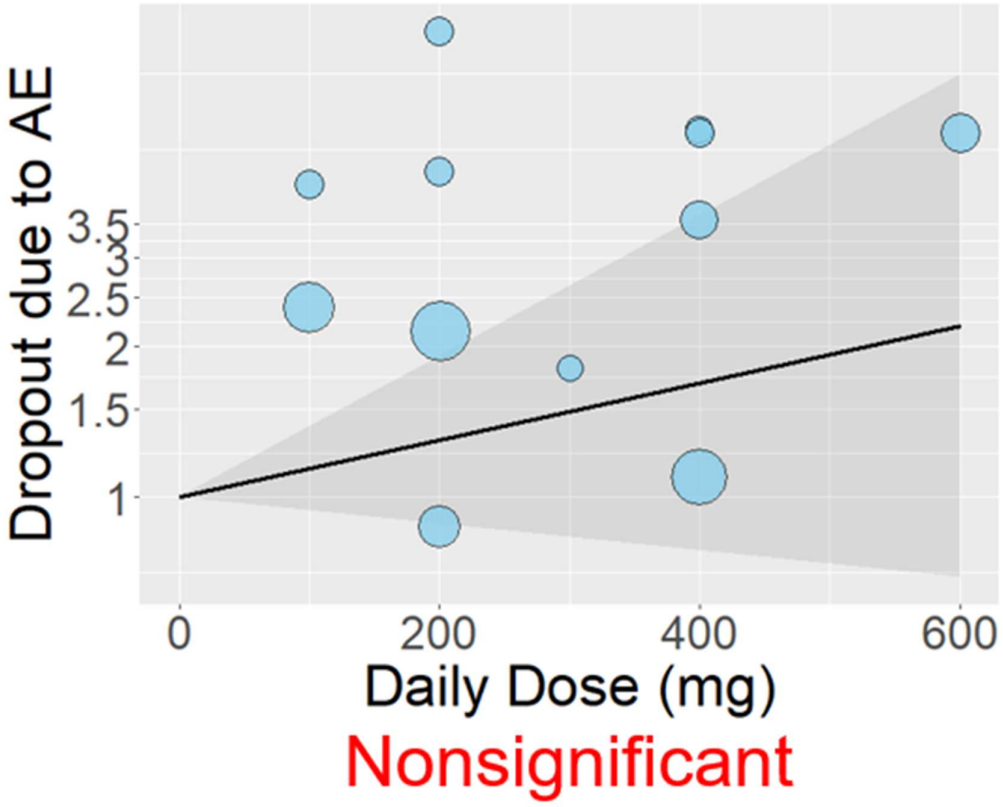



Nasser_2020.1/2 = 100/200mg; Nasser_2021a.1/2 =400/600mg; Nasser_2021b. 1/2= 200/400mg; Nasser_2021c. 1/2= 200/400mg; Johnson_2020.1/2/3/4= 100/200/300/400mg.

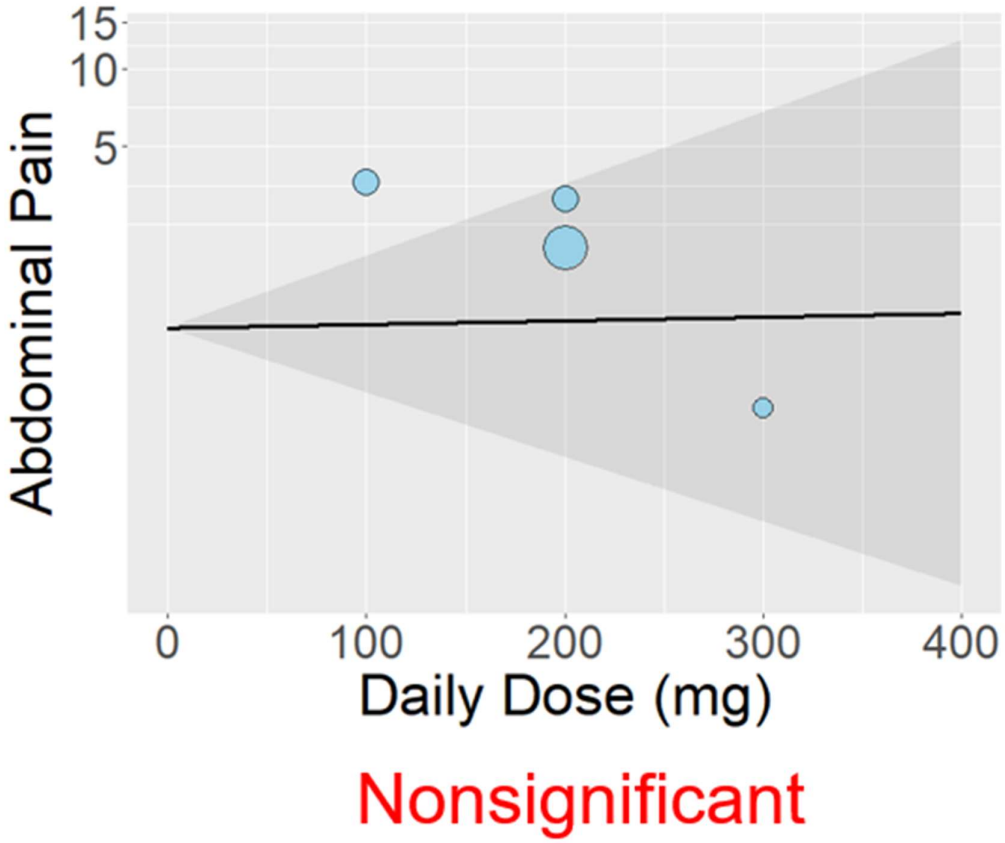
**eFigure 10.** Dose Response Meta-Analysis for Risk Ratio of All-Cause Discontinuation



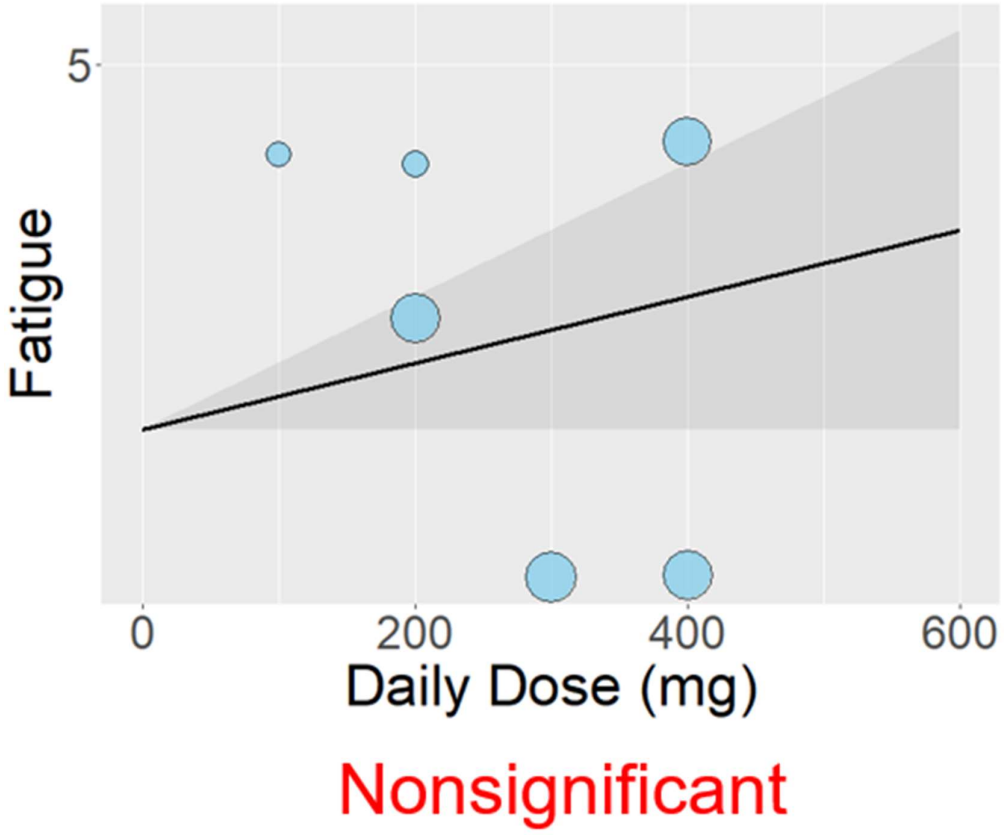
**eFigure 11.** Dose Response Meta-Analysis for Risk Ratio of Dropout Due to Adverse Events



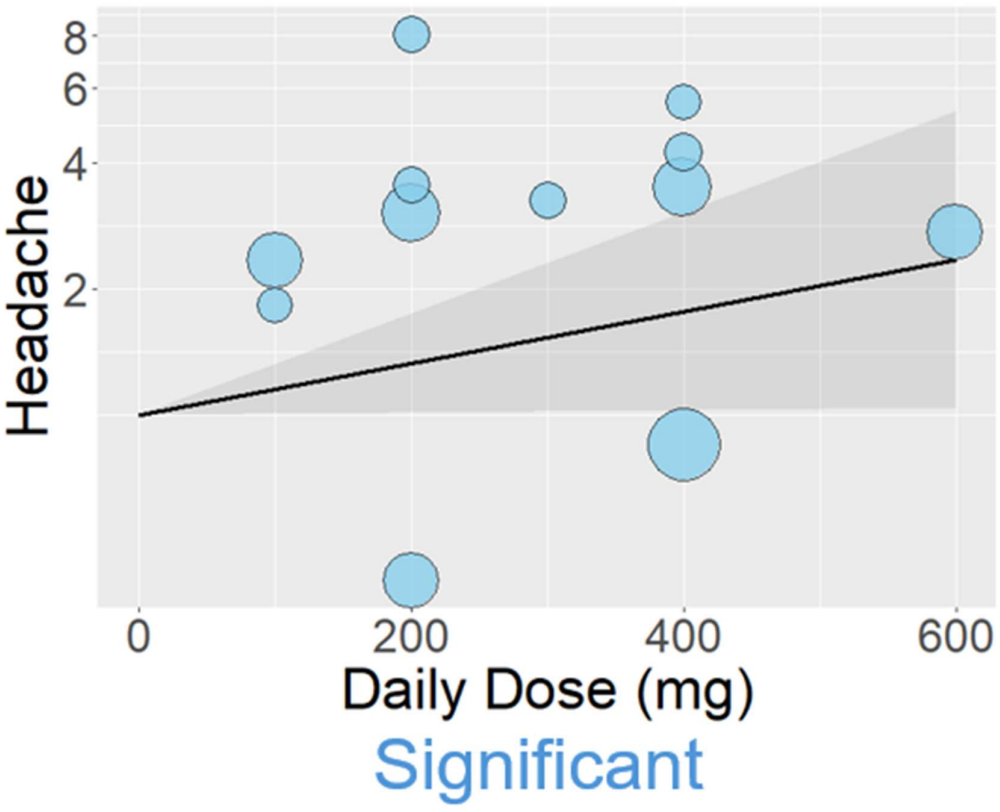
**eFigure 12.** Dose Response Meta-Analysis for Risk Ratio of Abdominal Pain



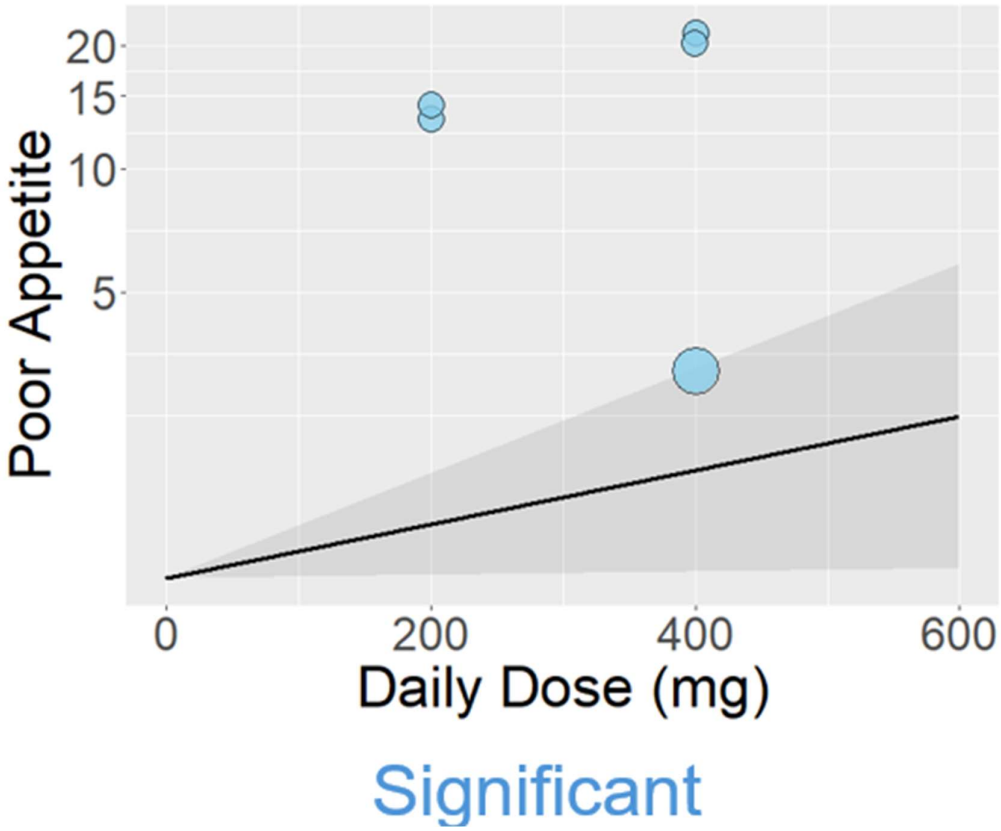
**eFigure 13.** Dose Response Meta-Analysis for Risk Ratio of Fatigue



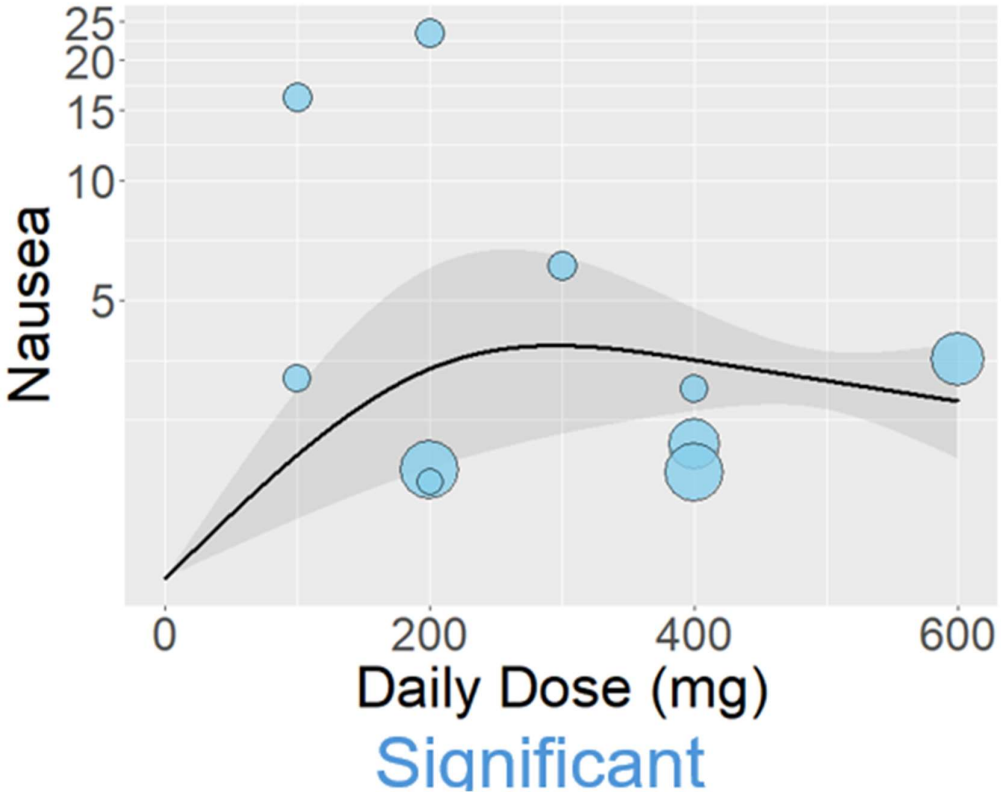
**eFigure 14.** Dose Response Meta-Analysis for Risk Ratio of Headache



**eFigure 15.** Dose Response Meta-Analysis for Risk Ratio of Poor Appetite



**eFigure 16.** Dose Response Meta-Analysis for Risk Ratio of Nausea



**eFigure 17.** Dose Response Meta-Analysis for Risk Ratio of Somnolence