Examining side effect variability of antipsychotic treatment in schizophrenia spectrum disorders: A meta-analysis of variance

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Side effects of antipsychotic drugs play a key role in non-adherence of treatment in schizophrenia spectrum disorders (SSD). While clinical observations suggest that side effect variability between patients may be considerable, statistical evidence is required to confirm this. Here, we hypothesized to find larger side effect variability under treatment compared with control. We included double-blind, placebo-controlled, randomized controlled trials (RCTs) of adults with a diagnosis of SSD treated with 1 out of 14 antipsychotics. Standard deviations of the pre-post treatment differences of weight gain, prolactin levels, and corrected QT (QTc) times were extracted. The outcome measure was the variability ratio of treatment to control for individual antipsychotic drugs and the overall variability ratio of treatment to control across RCTs. Individual variability ratios were weighted by the inverse-variance method and entered into a random-effects model. We included N = 16578 patients for weight gain, N = 16633 patients for prolactin levels, and N = 10384 patients for QTc time. Variability ratios (VR) were significantly increased for weight gain (VR = 1.08; 95% CI: 1.02 - 1.14; P = 0.004) and prolactin levels (VR = 1.38; 95% CI: 1.17 - 1.62; P < 0.001) but did not reach significance for QTc time (VR = 1.05; 95% CI: 0.98 - 1.12; P = 0.135). We found marked differences between individual antipsychotics and increased variability in side effects in patients under treatment with antipsychotics suggesting that subgroups of patients or individual patients may benefit from treatment allocation through stratified or personalized medicine.

Introduction

Antipsychotics are a fundamental component in the treatment of schizophrenia spectrum disorders (SSD). Yet, a major problem are side effects which play a key role in non-adherence and discontinuation.[1–5] A common hypothesis among researchers and clinicians alike is that although side effects are pervasive, not all patients are equally susceptible, even when they are treated with the same drug.[6] However, empirical support for this hypothesis is lacking, as randomized controlled trials (RCTs) or conventional meta-analyses by design cannot answer whether such side effect variability does exist.[7,8]

While it is well-established that antipsychotics are associated with sides effects for the average patient, the approach we are taking with this study moves beyond comparing group averages but instead compares group variances. By comparing variances our study can for the first time test the hypothesis that there is indeed reason to believe that subgroups or even individual patients differ in their susceptibility to side effects – something that an analysis focused on group averages cannot do.

To date, studies have established the efficacy, safety, and side effect profiles of antipsychotic medications by averaging these indices across groups of patients. Such studies can provide us with average side effects for specific drugs, but they cannot tell us anything about individual patients or subgroups.[9,10] Nevertheless, before searching for potential biomarkers that might predict individual susceptibility, we should first quantify the extent to which such predictors are truly needed.

An approach to answering this question is to shift the focus from the means to the variances of side effects.[11] By comparing the variances between treatment and control groups of RCTs,[12] greater variability in treatment would mean that some patients are more susceptible to side effects than others.[11] Note that this method[13] has recently been applied for antipsychotics,[7] antidepressants,[8,14,15] and brain stimulation,[16] but in the context of treatment effect variability. It is worth noting that these studies found little evidence for treatment effect variability.[7,8,14,15] Importantly, in the case of pre-post differences used as input for a meta-analysis of variance it is crucial to think carefully about the way the variability ratio is expressed,[12,15,17] as the use of the coefficient of variation ratio (CVR) that has been proposed as an alternative of the variability ratio (VR)[12] may lead to unreliable results.[13,17]

A recently published study investigated the individual treatment response in antipsychotics and brought surprising results.[7,18] By comparing the variability between treatment and control groups, no evidence was found for an increase in variability in the treatment group. What might sound counter-intuitive at first raises the question of how big the need for precision medicine really is. However, that study evaluated the evidence for treatment effect variability. It is possible that although such variability in treatment effects is not as high as sometimes assumed,[19] it does exist in the susceptibility for side effects. In other words, even if there is little variability in response to treatment between patients, there may still be enough variability in side effects to justify a need for precision medicine. If true, then this would support optimization of treatment allocation with respect to side effect profiles.[20]

Side effects that are particularly relevant to antipsychotic treatment include weight gain,[5] hyperprolactinemia, and QTc prolongation.[20] Weight gain is a frequently observed side effect that can negatively impact one's physical health and thus may also influence treatment adherence. Every additional kilogram of weight gain can contribute to an increased risk of heart failure,[21] cardiovascular disease,[22] and diabetes.[23] In addition, treatment discontinuation is often seen in patients with increase of weight under treatment.[24] High prolactin levels can lead to symptoms like decreased bone mass, gallactorhea, and fertility problems in men and women. Further possible symptoms include menstrual disturbances in female patients and decreased libido and erectile dysfunction in male patients.[25] These symptoms are frequent, but often underreported by patients and unnoticed as well as untreated by clinicians.[26,27] They furthermore might lead to loss in quality of life and might be a reason for treatment discontinuation[1,28] and subsequent illness relapse, which together with persistent positive symptoms[29–32] may severely impact recovery and therapeutic alliance.[33] Prolongation of QTc was observed in 7 of 14 antipsychotics compared by placebo in the intergroup comparison by Huhn and colleagues.[6] Importantly, *torsade de pointes* tachycardia and sudden cardiac death are possible severe consequences of QTc prolongation.[34] Such cardiac events are one of the factors that lead to the loss of life expectancy observed in patients with SSD.[35–37]

In summary, antipsychotic side effects are highly relevant for long-term outcome and adherence in treatment of positive symptoms in SSD. The question remains whether variability in side effects is high enough to warrant efforts of treatment stratification or personalisation. If there is little or no evidence for variability in side effects there might not be a need for stratification or personalization and the already widely available data provided by intergroup comparisons might offer reasonable estimates for the individual patient. Thus, we compared the variances of side effects including weight gain, prolactin level and QTc-time between treatment and control groups to address this question and to evaluate the evidence for the presence of side effect variability. Based on the clinical impression that patients seem to vary in their susceptibility to side effects, we hypothesized that the variability in side effects would be higher in the treatment compared with the control groups across all published trials of antipsychotics in SSD.[6]

Methods

Search strategy and selection criteria

We used the data from the recent meta-analysis by Huhn and colleagues.[6] That study included placebo-controlled published and unpublished trials investigating orally administered atypical (second generation) antipsychotics and typical (first generation) antipsychotics in adults with schizophrenia spectrum disorders; and excluded patients with first episode psychosis, treatment resistance, mainly negative symptoms, comorbidity with other mental or physical illnesses and relapse-prevention studies. Long- and short-acting intramuscular injections were also excluded (as they are often used in relapse prevention or emergency treatment) and studies from mainland China were excluded because of data quality concerns.[38] Data sources were MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Biosis, PsycINFO, PubMed, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform and the US Food and Drug Administration until January 8 2019. Data quality and validity were ensured by following the PRISMA guidelines.[39] For missing data, we also contacted study authors.

We decided to investigate weight gain, prolactin elevation and QTc prolongation because these side effects are particularly relevant,[5,20] and quantifiable metric data were available in most studies. Other side effects such as extrapyramidal motor symptoms (EPS), sedation and diabetes can be equally burdensome and certainly pose a health risk to patients. However, those have often not been quantified in studies but rather assessed qualitatively (e.g. through categorical variables such as EPS: yes/no; sedation: yes/no; diabetes: treated/untreated). These types of variables did not allow us to estimate variability and so we had to restrain from including them in the analysis.

For the analysis, we used the standard deviations of pre-post differences in side effects. The primary outcome was the overall variability ratio of side effects in treatment versus control groups. Standard deviations (SD) and number of patients (N) were extracted for weight gain, prolactin level and QTc time. The units used were kg for weight gain, ng/mL for prolactin levels, and ms for QTc time. Some studies provided data for all of the three side effects, whereas the majority of the studies contained less data (see Results).

Statistical analysis

If patients or subgroups differ in their susceptibility to side effects, we would expect to observe increased variances in the treatment compared with the control group. To test this, we computed the log variability ratio (log VR) by comparing the relative variability of side effects under treatment versus control:

$$\log \mathrm{VR} = \log\left(\frac{\mathrm{SD_{Tx}}}{\mathrm{SD_{Ct}}}\right) + \frac{1}{2(n_{\mathrm{Tx}} - 1)} - \frac{1}{2(n_{\mathrm{Ct}} - 1)}$$

,

where $\mathrm{SD_{Tx}}$ was the reported sample SD for side effects under treatment, $\mathrm{SD_{Ct}}$ was the reported sample SD for side effects under control, n_{Tx} was the treatment sample size, and n_{Ct} the control sample size. The corresponding sampling variance ($s^2_{\log \mathrm{VR}}$) for each comparison can be expressed as follows:

$$s^2_{\log \mathrm{VR}} = \frac{1}{2(n_{\mathrm{Tx}} - 1)} + \frac{1}{2(n_{\mathrm{Ct}} - 1)}$$

.

The individual variability ratios were weighted with the inverse of this sampling variance[40] and entered into a random-effects model to quantify the overall variability ratio of side effects. For better interpretability, results were back-transformed from the logarithmic scale. Here, a variability ratio greater than one would indicate a higher side effect variability in treatment compared with control, whereas a variability ratio smaller than one would indicate less side effect variability under treatment compared with control.

Data and code availability

The analysis was performed from September 2019 to May 2020, using the R package metafor[40](version 2.4.0). The manuscript was produced with the R packages rmarkdown (version 2.6); represearch (version 0.0.0.9000; https://github.com/phoman/represearch/); knitr (version 1.30); and papaja (version 0.1.0.9997). All data and code are freely available online to ensure reproducibility at https://github.com/hom anlab/sideeffects/.

Results

Overall reporting details

Together, we screened N = 151 studies with 14 different antipsychotics from the original meta-analysis by Huhn and colleagues[6] as these studies reported data on at least one of the three side effects that we were interested in. Of these studies, N = 94 (62%) had missing variance measures despite reported means for at least one of the three side effects. We thus included the N = 60 (40%) studies that did report variance measures for at least one of the side effects of interest.

Weight gain

For weight gain, we included 51 RCTs, yielding 72 comparisons of antipsychotic drugs with placebo to investigate the individual occurrence of weight gain in patients. All together we included N = 16578 patients diagnosed with schizophrenia or schizoaffective disorder. There were 11373 (69%) patients randomly allocated to the treatment group, and 5205 (31%) to the placebo group. Patients in the treatment group received 1 out of 14 investigated antipsychotic drugs. Individual comparisons between drugs across studies indicated marked differences between individual antipsychotics. The VR for chlorpromazine, cariprazine, and sertindole was smaller than 1. The VR for ziprasidone, iloperidone, and brexpiprazole was 1. The VR for asenapine, risperidone, olanzapine, lurasidone, aripiprazol, paliperidone, haloperidol, and quetiapine was greater than 1 (VR = 1.08; 95% CI: 1.02 - 1.14; P = 0.004; Figure 1). Overall, the variability for weight gain was higher under treatment than under control (VR = 1.08; 95% CI: 1.02 - 1.14; P = 0.004; Figure S1).

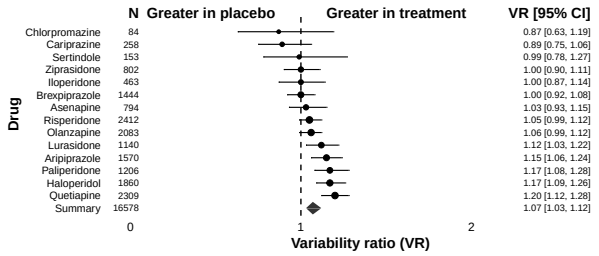

Figure 1. Variability ratio for weight gain for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41–95] are also listed in Table S1.

Hyperprolactinemia

For hyperprolactinemia, we included 50 RCTs, with 71 comparisons of antipsychotic drugs with placebo. All together we included N = 16633 patients diagnosed with schizophrenia or schizoaffective disorder. There were 11409 (69%) patients randomly allocated to the treatment group, and 5224 (31%) to the placebo group. Patients in the treatment group received 1 out of 13 investigated antipsychotic drugs. Individual comparisons between drugs across studies indicated marked differences between individual antipsychotics. The VR for iloperidone and brexpiprazole was smaller than 1. The VR for aripiprazole, asenapine, risperidone, cariprazine, sertindole, quetiapine, ziprasidone, lurasidone, haloperidol, olanzapine, and paliperidone was greater than 1 (VR = 1.38; 95% CI: 1.17 - 1.62; P < 0.001; Figure 2). Overall, the variability for hyperprolactinemia was higher under treatment than under control (VR = 1.38; 95% CI: 1.17 - 1.62; P < 0.001; Figure S2).

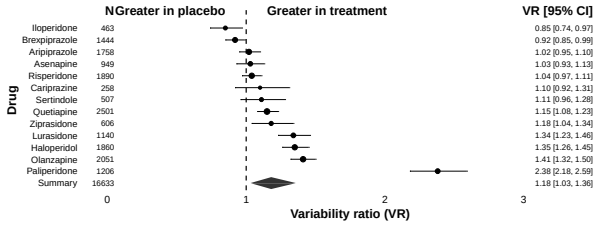

Figure 2. Variability ratio for hyperprolactinemia for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41,42,44–48,50–58,60,62,64,65,67–69,72,74–79,82–92,94–100] are also listed in Table S1.

QTc prolongation

For QTc prolongation, we included 29 RCTs, with 46 comparisons of antipsychotic drugs with placebo. All together we included N = 10384 patients diagnosed with schizophrenia or schizoaffective disorder. There were 7439 (72%) patients randomly allocated to the treatment group, and 2945 (28.00%) to the placebo group. Patients in the treatment group received 1 out of 11 investigated antipsychotic drugs. Individual comparisons between drugs across studies indicated marked differences between individual antipsychotics (VR = 1.05; 95% CI: 0.98 - 1.12; P = 0.135; Figure 3). The VR for ziprasidone, brexpiprazole, paliperidone, and olanzapine was smaller than 1. The VR for iloperidone was 1. The VR for risperidone, quetiapine, lurasidone, haloperidol, and sertindole was greater than 1. Even though the variability for QTc prolongation was higher under treatment than under control, the difference did not reach statistical significance (VR = 1.05; 95% CI: 0.98 - 1.12; P = 0.135; Figure S3).

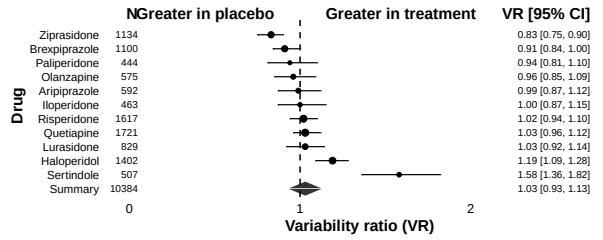

Figure 3. Variability ratio for QTC prolongation for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[42,45,51,52,54–60,62,68,70,74,76–80,85,86,88,91,95,96,100] are also listed in Table S1.

Discussion

Summary

This study assessed the variability in the three major side effects of antipsychotic treatment in schizophrenia spectrum disorders. We focused on side effects because their occurrence has a great impact on treatment adherence and physical health of patients, and clinical experience suggests a potential to improve treatment allocation by taking into account the variability in side effect occurrence. We also know from clinical trials and meta-analyses that some antipsychotics are more associated with specific side effects than others. For example, clozapine and olanzapine are strongly associated with weight gain,[6,20,101] QTc-time prolongation is most distinct in sertindole and amisulpride,[6] and prolactin level elevation in paliperidone and risperidone.[6] However, these data cannot address the question whether there is variability in subgroups or individual patients. Such side effect-by-subgroup or side effect-by-patient interaction would be a prime example for the need of a more stratified or personalized medicine, respectively, which allocates treatments according to side effect profiles of subgroups or individual patients. Overall, we found that the variability for weight gain and prolactin elevation was indeed significantly increased in patients who received treatment compared with those who received placebo. For QTc prolongation, the increase was not significant. Together, our results suggest that there is indeed marked variability in the occurrence of side effects in antipsychotic treatment. Variability also differed markedly between individual drugs.

Reporting

Altogether we included 43595 patients from 60 studies. The included studies provided data for treatment with 14 antipsychotic drugs for weight gain, 13 antipsychotic drugs for hyperprolactinemia, and 11 antipsychotic drugs for QTc prolongation compared to placebo. Only for about 40% of studies included in a previous meta-analysis[6] variance data for at least one of the side effects of interest (weight gain, prolactin levels, QTc prolongation) were available. In about 62% of the studies included[6] incomplete data existed such that means were reported without a measure of variance. Although we did contact authors for missing data whenever possible, we received missing data only for three studies. In summary, consistent reporting of antipsychotic side effects, specifically with respect to variability measures, is currently missing in the literature and should be improved in future studies.

Weight gain

Weight gain, especially for second generation antipsychotics,[102] is a severe side effect that can contribute to metabolic dysregulation. Importantly, every kg of weight gain leads to a linear increase in the risk of cardiovascular diseases,[22] heart failure,[21] and diabetes.[23] Clozapine, olanzapine, zotepine, and sertindole have the most severe impact in gaining weight. Some studies showed that a lower BMI at baseline[103] and sex[104] can lead to more weight gain, whereas other studies found that male sex

and higher BMI at baseline are related to a higher risk of metabolic disturbances.[20] Our findings provide evidence that some patients are indeed more susceptible to antipsychotic weight gain than others, and that this susceptibility varies also between medications. For example, for quetiapine we found that patients differed in their susceptibility for weight gain while we did not find such evidence for olanzapine and brexpiprazole, suggesting a potential for stratified or personalized medicine for quetiapine but not olanzapine and brexpiprazole. As antipsychotics in the treatment for schizophrenia and related diseases is often recommended to be taken as a relapse prevention for a longer period,[105,106] patients are likely to gain more weight during their treatment over months and years. Together, this suggests that there is a potential to improve long-term health and adherence by identifying the subgroups or individual patients that are particularly prone to weight gain. Preliminary evidence suggests that a dysregulated striatal reward circuit contributes to this weight gain susceptibility.[5,107]

Hyperprolactinemia

Prolactin level elevations occur in up to 70% of patients[108] under the treatment with antipsychotics. By blocking dopamine D2 receptors on lacotroph cells a disinhibition of the synthesis and secretion of prolactin is observed.[109,110] This can lead to both short- and long-term side effects with potentially severe impact on patients' health. Typical short-term effects include galactorrhea, gynecomastia, menstrual irregularities, and sexual dysfunction; a typical long-term result is osteoporosis,[111,112] and a potentially increased risk in developing breast cancer in association with hyperprolactinemia.[113,114] Our findings suggest that these risks may be particularly relevant for some patients but not others, and more relevant for some antipsychotic drugs than others. For example, a previous study found that prolactin level elevations are more pronounced and more frequent in women than in men.[115] In addition, some antipsychotics such as amisulpride, risperidone, and paliperidone are linked to a greater elevation of prolactin.[6,115] The striking difference between risperidone (for which we did not find evidence for significant variability in prolactin elevation) and paliperidone (for which we did find such evidence) is puzzling as paliperidone is an active metabolite of risperidone, and previous literature suggests that paliperidone and risperidone lead to similar elevations in serum prolactin concentrations.[116] A possible explanation is that the level of prolactin can be highly variable based on multiple biological and methodological factors such as stress, diurnal variation and type of assay performed. However, future studies should pay particular attention to differences in susceptibility to prolactinemia between these two antipsychotics. In summary, and in line with the weight gain findings, our findigns suggest that there is a potential to improve long-term health and antipsychotic adherence by identifying the subgroups or individual patients that are particularly likely to develop prolactin elevations under antipsychotic treatment.

QTc prolongation

Prolongation of QTc is another important antipsychotic side effect as cardiovascular diseases remain the most common cause of natural mortality in schizophrenia spectrum disorders.[117] Users of antipsychotic medication are reported to have higher rates of sudden cardiac death than nonusers.[118] Prolongation of QTc (longer than 450 ms in men and longer than 470 ms in women, respectively, when corrected with Bazetts Formula[119]) can contribute to this.[34] A prolongation of QTc can lead to *torsade de pointes* and subsequently to sudden death.[120,121] The molecular pathway of this side effect is not completely understood.[122] It is known, however, that some medications such as sertindole, amisulprid, and ziprasidone lead to more QTc prolongation than others.[6] Here, we found increased variability for some antipsychotics such as haloperidol in QTc prolongation. However, altogether we did not find a statistically significant increase in variability for QTc prolongation, potentially because a smaller number of studies were available which decreased statistical power.

Limitations and strengths

Our meta-analysis had some limitations. First, the occurrence of side effects might be a dose-dependent effect which could reflect a higher/different VR in some studies. Dose-dependent means and standard deviations are often missing but would be necessary to investigate dose-dependent effects. Second, for QTc, a reduced number of studies was available, potentially reducing statistical power to detect a significant variability increase. Third, our sample did not include pre-defined subgroups including patients with first-episode psychosis and treatment-resistant patients to create the most homogeneous sample possible. Finally, our method cannot determine whether the increased variability is due to variability differences in subgroups or individual patients.[11] The particular strength of our study is that we included all available studies of antipsychotic treatment in SSD reporting variability measures for side effects of interest. To our knowledge, this is the first comprehensive study that provides evidence for substantial variability in side effects.

Conclusion

While we did not find convincing evidence that patients differed in their susceptibility to QTc prolongation, we did find such evidence for weight gain and prolactin elevation: for half of all antipsychotics (7 out of 14) we can assume that subgroups of patients or even individual patients would

benefit from specific treatment allocation through stratified or personalized medicine, respectively. Such efforts in precision medicine might be crucial to improve adherence and long-term health under antipsychotic treatment.

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Conflict of interest

In the last 3 years Dr. Leucht has received honoraria for service as a consultant or adviser and/or for lectures from Angelini, Böhringer Ingelheim, Geodon&Richter, Janssen, Johnson&Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofiAventis, Sandoz, Sunovion, TEVA. Dr. Kane reported grants from Otsuka, Lundbeck and Janssen, as well as other from Alkermes, Allergan, Forum, Genentech, Lundbeck, Intracellular Therapies, Janssen, Johnson & Johnson, Merck, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda, Teva, Vanguard Research Group, and LB Pharmaceuticals outside of the submitted work. No other disclosures were reported.

Author contributions

MSN co-analyzed and interpreted the data, wrote the first draft of the manuscript and revised the final manuscript. SH conceptualized the study, wrote the primary analysis code and revised the final manuscript. SV helped initiate the study and revised the final manuscript. ES helped initiate the study and revised the final manuscript. JMK helped initiate the study and revised the final manuscript. MH collected the data and revised the final manuscript. SL conceptualized the study and revised the final manuscript. PH initiated, conceptualized and supervised the study, performed the statistical analysis, and revised the final manuscript. All authors approved the final version of the manuscript.

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Supplementary Information

Supplementary Table

Table S1
All study arms with references

Study Arm	Year	Sample Size	Drug	Weight	Prolactin	QTc
Ishigooka 2018[53]	2018	116	Placebo	Yes	Yes	No
Ishigooka 2018[53]	2018	228	Brexpiprazole	Yes	Yes	No
Litman 2016[41]	2016	55	Placebo	Yes	Yes	No
Litman 2016[41]	2016	31	Risperidone	Yes	Yes	No
NCT01104766a[64]	2015	153	Placebo	Yes	Yes	No
NCT01104766a[64]	2015	152	Aripiprazole	Yes	Yes	No
NCT01104766b[64]	2015	312	Cariprazine	Yes	Yes	No
Lieberman 2015[75]	2015	85	Placebo	Yes	Yes	No
Lieberman 2015[75]	2015	82	Risperidone	Yes	Yes	No
Kane 2015[123]	2015	184	Placebo	Yes	Yes	Yes
Kane 2015[123]	2015	370	Brexpiprazole	Yes	Yes	Yes
Correll 2015[54]	2015	184	Placebo	Yes	Yes	Yes
Correll 2015[54]	2015	362	Brexpiprazole	Yes	Yes	Yes
NCT01098110[82]	2015	174	Placebo	Yes	Yes	No
NCT01098110[82]	2015	358	Asenapine	Yes	Yes	No
NCT01617187a[49]	2015	113	Asenapine	Yes	No	No
NCT01617187a[49]	2015	103	Placebo	Yes	No	No
NCT01617187b[49]	2015	46	Olanzapine	Yes	No	No
NCT00905307a[94]	2015	50	Aripiprazole	Yes	Yes	No
NCT00905307a[94]	2015	95	Placebo	Yes	Yes	No
NCT00905307b[94]	2015	90	Brexpiprazole	Yes	Yes	No
Loebel 2015a[92]	2015	199	Lurasidone	Yes	Yes	No
Loebel 2015a[92]	2015	112	Placebo	Yes	Yes	No
Litmann 2014[93]	2014	41	Placebo	Yes	No	No
Litmann 2014[93]	2014	22	Olanzapine	Yes	No	No
Schmidt 2014[98]	2014	93	Olanzapine	Yes	Yes	No
Shen 2014[81]	2014	78	Placebo	Yes	No	No
Shen 2014[81]	2014	77	Olanzapine	Yes	No	No
Durgam 2014a[77]	2014	151	Placebo	Yes	Yes	Yes
Durgam 2014a[77]	2014	140	Risperidone	Yes	Yes	Yes
Durgam 2014b[77]	2014	438	Cariprazine	Yes	Yes	Yes
Geffen 2012[99]	2012	91	Risperidone	No	Yes	No
Geffen 2012[99]	2012	93	Placebo	No	Yes	No
Kinon 2011[50]	2011	62	Olanzapine	Yes	Yes	No
Kinon 2011[50]	2011	122	Placebo	Yes	Yes	No
Kane 2010a[67]	2010	115	Haloperidol	Yes	Yes	No
Kane 2010a[67]	2010	123	Placebo	Yes	Yes	No
Kane 2010b[67]	2010	220	Asenapine	Yes	Yes	No
Study 006[45]	2010	99	Lurasidone	Yes	Yes	Yes
Study 006[45]	2010	50	Placebo	Yes	Yes	Yes
Study 049a[88]	2010	73	Haloperidol	Yes	Yes	Yes
Study 049a[88]	2010	72	Placebo	Yes	Yes	Yes
Study 049b[88]	2010	140	Lurasidone	Yes	Yes	Yes
Study 196[57]	2010	90	Placebo	Yes	Yes	Yes
Study 196[57]	2010	90	Lurasidone	Yes	Yes	Yes
Study 229[78]	2010	372	Lurasidone	Yes	Yes	Yes

Study Arm	Year	Sample Size	Drug	Weight	Prolactin	QTc
Study 229[78]	2010	128	Placebo	Yes	Yes	Yes
Study 231a[86]	2010	116	Placebo	Yes	Yes	Yes
Study 231a[86]	2010	123	Olanzapine	Yes	Yes	Yes
Study 231b[86]	2010	239	Lurasidone	Yes	Yes	Yes
Study 233a[85]	2010	122	Placebo	Yes	Yes	Yes
Study 233a[85]	2010	120	Quetiapine	Yes	Yes	Yes
Study 233b[85]	2010	246	Lurasidone	Yes	Yes	Yes
Garcia 2009[42]	2009	60	Haloperidol	Yes	Yes	Yes
Garcia 2009[42]	2009	64	Placebo	Yes	Yes	Yes
Hera 041-021a[124]	2009	208	Asenapine	No	Yes	No
Hera 041-021a[124]	2009	106	Placebo	No	Yes	No
Hera 041-021b[124]	2009	103	Olanzapine	No	Yes	No
Hera 041-022[125]	2009	93	Olanzapine	No	Yes	No
Hera 041-022[125]	2009	93	Placebo	No	Yes	No
Casey 2008[72]	2008	120	Risperidone	Yes	Yes	No
Casey 2008[72]	2008	119	Placebo	Yes	Yes	No
Cutler 2008a[60]	2008	151	Ziprasidone	Yes	Yes	Yes
Cutler 2008a[60]	2008	152	Placebo	Yes	Yes	Yes
Cutler 2008b[60]	2008	303	Iloperidone	Yes	Yes	Yes
Johnson NCT00397033[90]	2008	209	Paliperidone	Yes	Yes	No
Johnson NCT00397033[90]	2008	107	Placebo	Yes	Yes	No
Johnson NCT00412373[87]	2008	95	Placebo	Yes	Yes	No
Johnson NCT00412373[87]	2008	216	Paliperidone	Yes	Yes	No
Johnson NCT00524043[48]	2008	70	Paliperidone	Yes	Yes	No
Johnson NCT00524043[48]	2008	65	Placebo	Yes	Yes	No
Lindenmayer 2008[95]	2008	267	Quetiapine	Yes	Yes	Yes
Lindenmayer 2008[95]	2008	84	Placebo	Yes	Yes	Yes
Study 3000a[56]	2008	127	Placebo	Yes	Yes	Yes
Study 3000a[56]	2008	124	Haloperidol	Yes	Yes	Yes
Study 3000b[56]	2008	124	Iloperidone	Yes	Yes	Yes
Study 3004a[56]	2008	156	Placebo	Yes	Yes	Yes
Study 3004a[56]	2008	154	Iloperidone	Yes	Yes	Yes
Study 3004b[56]	2008	153	Risperidone	Yes	Yes	Yes
Study 3005a[56]	2008	157	Risperidone	Yes	No	Yes
Study 3005a[56]	2008	160	Placebo	Yes	No	Yes
Study 3005b[56]	2008	389	Iloperidone	Yes	No	Yes
Study RGH-MD-03[47]	2008	130	Placebo	Yes	Yes	No
Study RGH-MD-03[47]	2008	128	Cariprazine	Yes	Yes	No
Cutler 2008a[60]	2008	117	Placebo	Yes	Yes	Yes
Cutler 2008a[60]	2008	448	Quetiapine	Yes	Yes	Yes
Davidson 2007a[46]	2007	123	Placebo	Yes	Yes	No
Davidson 2007a[46]	2007	128	Olanzapine	Yes	Yes	No
Davidson 2007b[46]	2007	125	Paliperidone	Yes	Yes	No
Kahn 2007[44]	2007	118	Placebo	Yes	Yes	No
Kahn 2007[44]	2007	470	Quetiapine	Yes	Yes	No
McEvoy 2007b[83]	2007	206	Aripiprazole	Yes	Yes	No
McEvoy 2007b[83]	2007	108	Placebo	Yes	Yes	No
Meltzer 2007a[65]	2007	149	Placebo	Yes	Yes	No
Meltzer 2007a[65]	2007	154	Risperidone	Yes	Yes	No
Kane 2007b[84]	2007	127	Placebo	Yes	Yes	No
Kane 2007b[84]	2007	128	Olanzapine	Yes	Yes	No
Kane 2007c[84]	2007	375	Paliperidone	Yes	Yes	No

Study Arm	Year	Sample Size	Drug	Weight	Prolactin	QTc
Marder 2007c[79]	2007	110	Placebo	Yes	Yes	Yes
Marder 2007c[79]	2007	224	Paliperidone	Yes	Yes	Yes
Marder 2007d[79]	2007	110	Olanzapine	Yes	Yes	Yes
Patil 2007[74]	2007	34	Olanzapine	Yes	Yes	Yes
Patil 2007[74]	2007	63	Placebo	Yes	Yes	Yes
Potkin 2007d[58]	2007	62	Placebo	Yes	Yes	Yes
Potkin 2007d[58]	2007	60	Risperidone	Yes	Yes	Yes
Potkin 2007c[58]	2007	60	Asenapine	Yes	Yes	Yes
Potkin 2003a[76]	2003	202	Aripiprazole	Yes	Yes	Yes
Potkin 2003a[76]	2003	103	Placebo	Yes	Yes	Yes
Potkin 2003b[76]	2003	99	Risperidone	Yes	Yes	Yes
Kane 2002b[68]	2002	104	Haloperidol	Yes	Yes	Yes
Study 94202 2002a[126]	2002	61	Aripiprazole	No	Yes	Yes
Study 94202 2002a[126]	2002	64	Placebo	No	Yes	Yes
Study 94202 2002b[126]	2002	63	Haloperidol	No	Yes	Yes
Study 115 2000a[127]	2000	83	Placebo	No	No	Yes
Study 115 2000a[127]	2000	164	Ziprasidone	No	No	Yes
Study 115 2000b[127]	2000	85	Haloperidol	No	No	Yes
Daniel 1999[70]	1999	92	Placebo	Yes	No	Yes
Daniel 1999[70]	1999	104	Ziprasidone	Yes	No	Yes
Arvanitis 1997a[52]	1997	51	Placebo	Yes	Yes	Yes
Arvanitis 1997a[52]	1997	105	Quetiapine	Yes	Yes	Yes
Arvanitis 1997b[52]	1997	52	Haloperidol	Yes	Yes	Yes
Small 1997[97]	1997	96	Quetiapine	No	Yes	No
Small 1997[97]	1997	96	Placebo	No	Yes	No
Zimbroff 1997a[100]	1997	144	Sertindole	No	Yes	Yes
Zimbroff 1997a[100]	1997	73	Placebo	No	Yes	Yes
Zimbroff 1997b[100]	1997	137	Haloperidol	No	Yes	Yes
Beasley 1996a[89]	1996	50	Placebo	Yes	Yes	No
Beasley 1996a[89]	1996	50	Olanzapine	Yes	Yes	No
Beasley 1996b[91]	1996	69	Haloperidol	Yes	Yes	Yes
Beasley 1996b[91]	1996	68	Placebo	Yes	Yes	Yes
Beasley 1996c[91]	1996	133	Olanzapine	Yes	Yes	Yes
Borison 1996[62]	1996	55	Placebo	Yes	Yes	Yes
Borison 1996[62]	1996	54	Quetiapine	Yes	Yes	Yes
van Kammen 1996[51]	1996	105	Sertindole	Yes	Yes	Yes
van Kammen 1996[51]	1996	48	Placebo	Yes	Yes	Yes
Zborowski 1995a[55]	1995	116	Placebo	Yes	Yes	Yes
Zborowski 1995a[55]	1995	115	Haloperidol	Yes	Yes	Yes
Zborowski 1995b[55]	1995	117	Sertindole	Yes	Yes	Yes
Clark 1972a[43]	1972	19	Chlorpromazine	Yes	No	No
Clark 1972a[43]	1972	18	Placebo	Yes	No	No
Clark 1972b[43]	1972	18	Loxapine	Yes	No	No
Clark 1970a[61]	1970	15	Chlorpromazine	Yes	No	No
Clark 1970a[61]	1970	14	Placebo	Yes	No	No

Supplementary Figures

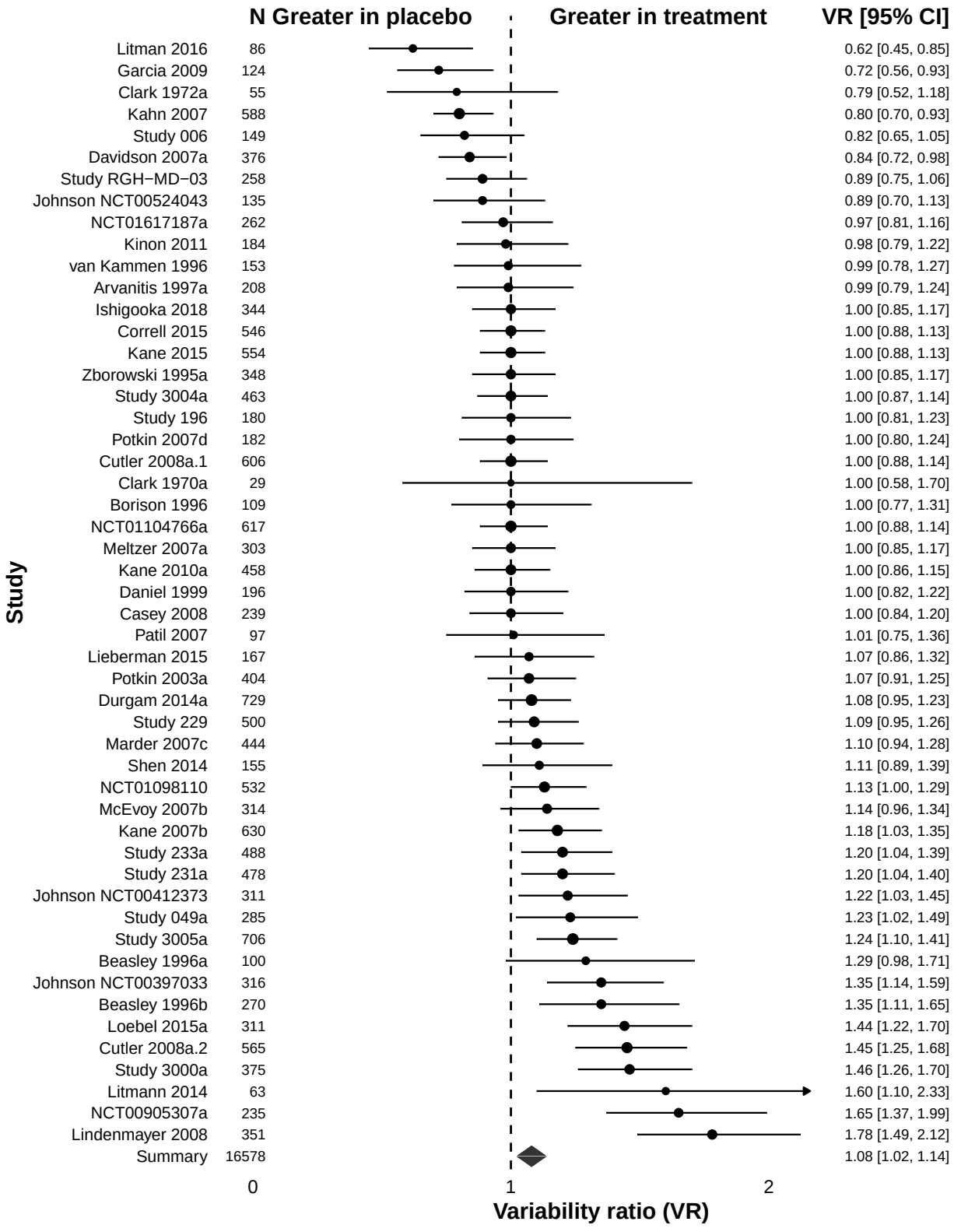

Figure S1. Variability ratio for weight gain. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41–95] are also listed in Table S1.

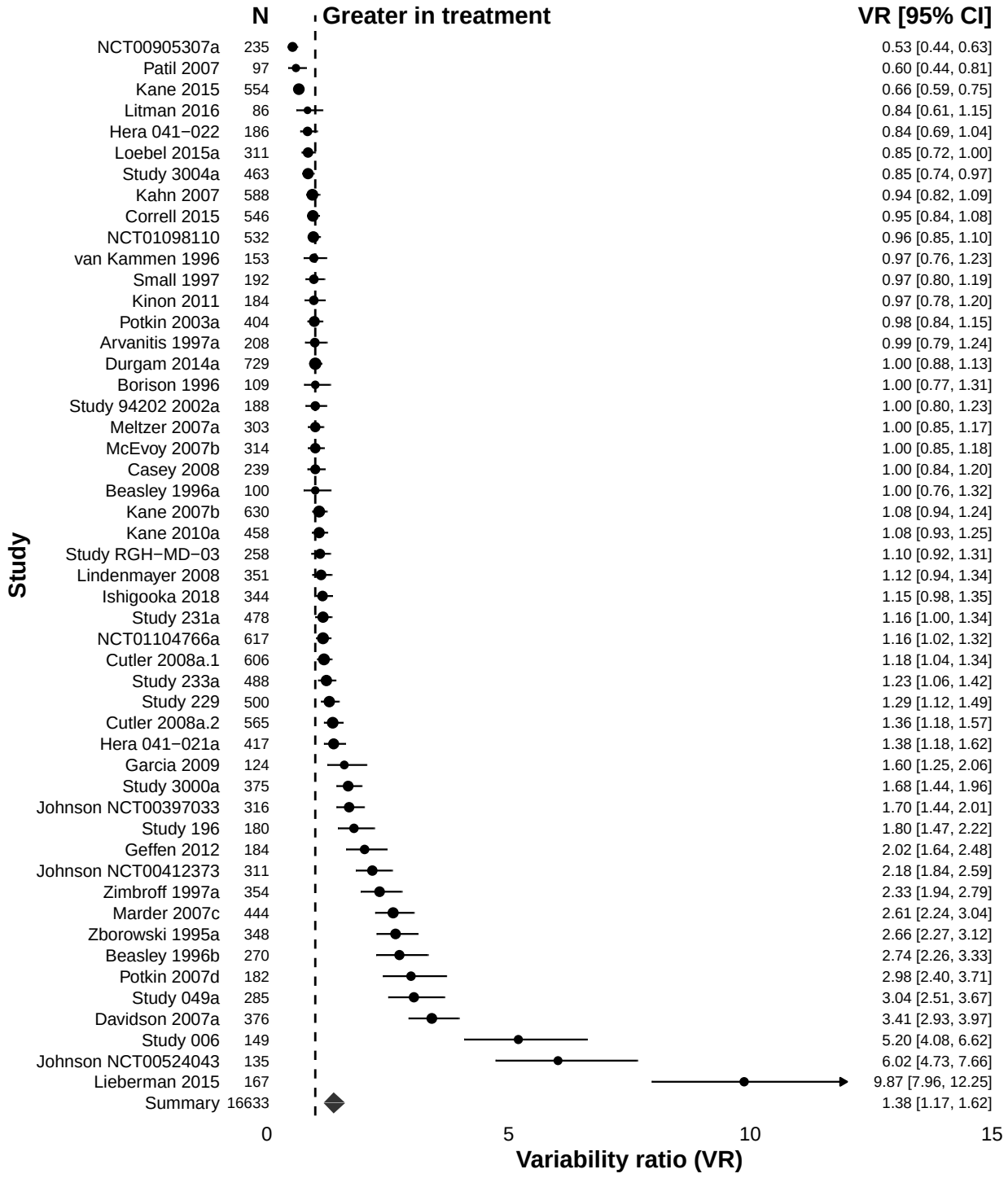

Figure S2. Variability ratio for hyperprolactinemia. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41,42,44–48,50–58,60,62,64,65,67–69,72,74–79,82–92,94–100] are also listed in Table S1.

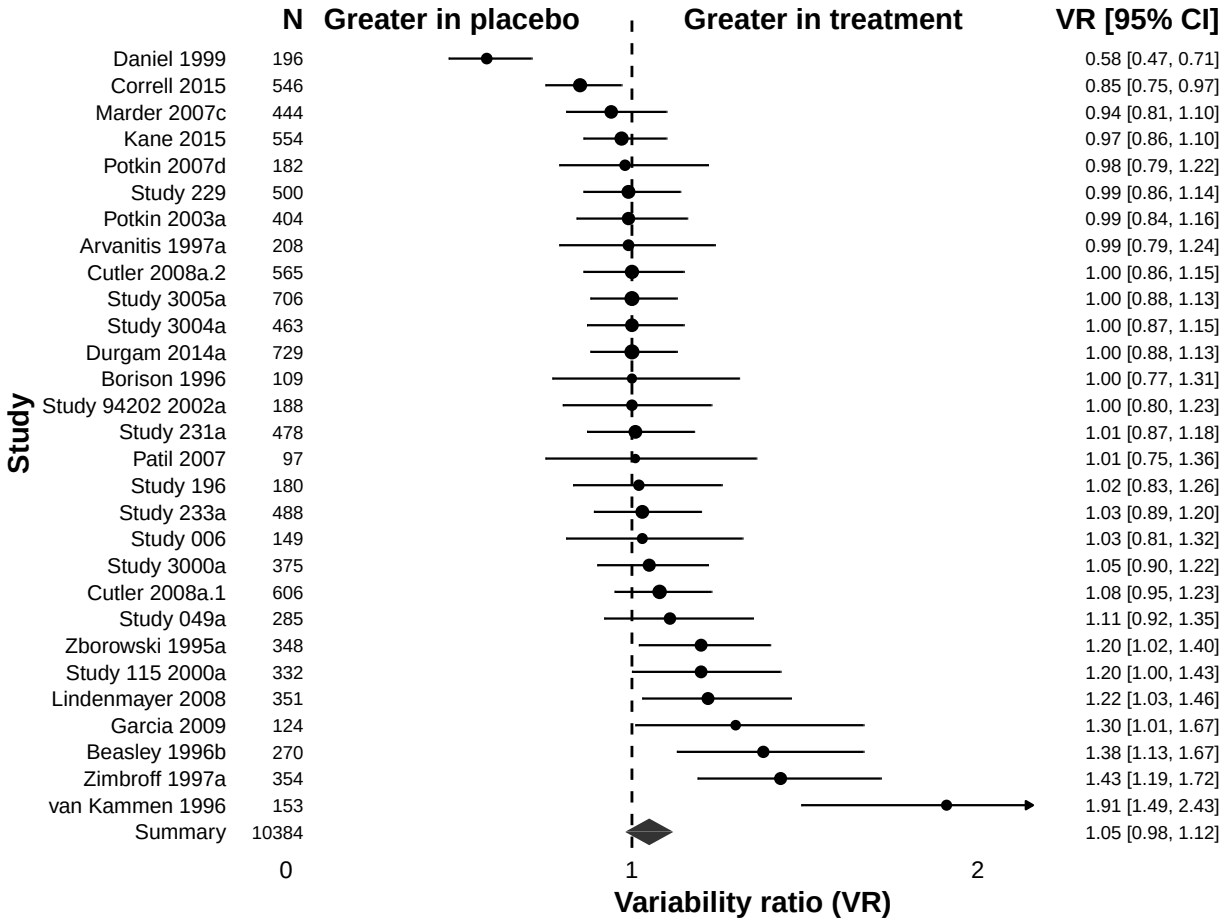

Figure S3. Variability ratio for QTc prolongation. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[42,45,51,52,54–60,62,68,70,74,76–80,85,86,88,91,95,96,100] are also listed in Table S1.