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 nonadherence 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 $N = 16\,578$ patients for weight gain, $N = 16\,633$ patients for prolactin levels, and $N = 10\,384$ patients for QTc time. Variability ratios (VR) were significantly increased for weight gain (VR = 1.08; 95% CI: 1.02–1.14; $P = .004$) and prolactin levels (VR = 1.38; 95% CI: 1.17–1.62; $P < .001$) 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.

Key words: antipsychotics/adverse effects/variability/weight gain/prolactin/QTc prolongation/precision 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 nonadherence 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 inter-group 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:

$$\log \text{VR} = \log \left(\frac{\text{SD}_{\text{Tx}}}{\text{SD}_{\text{Ct}}} \right) + \frac{1}{2(n_{\text{Tx}} - 1)} - \frac{1}{2(n_{\text{Ct}} - 1)},$$

where SD_{Tx} was the reported sample SD for side effects under treatment, 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 ($s^2_{\log \text{VR}}$) for each comparison can be expressed as follows:

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

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/homanlab/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 $N = 16\ 578$ patients diagnosed with schizophrenia or schizoaffective disorder. There were 11 373 (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 = .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 = .004; supplementary figure S1).

Hyperprolactinemia

For hyperprolactinemia, we included 50 RCTs, with 71 comparisons of antipsychotic drugs with placebo. All together we included $N = 16\ 633$ patients diagnosed with schizophrenia or schizoaffective disorder. There were 11 409 (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 < .001; figure 2).
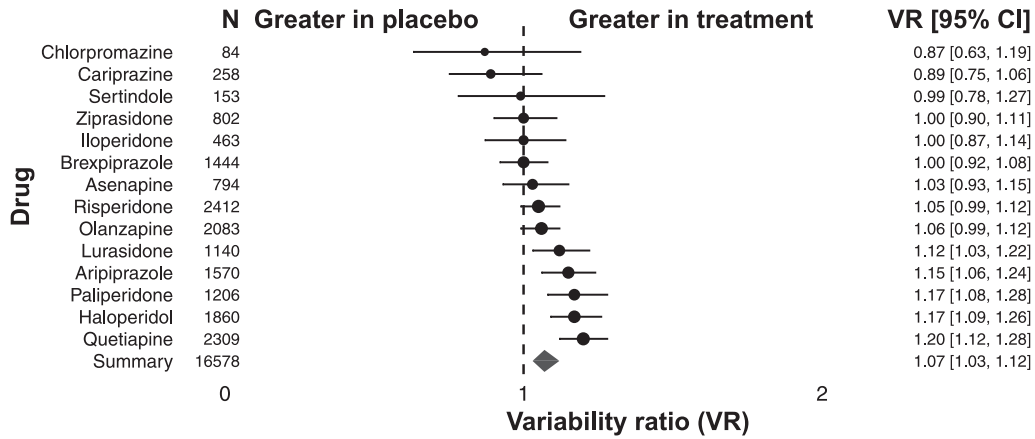
Fig. 1. Variability ratio for weight gain for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41–96] are also listed in supplementary table S1.
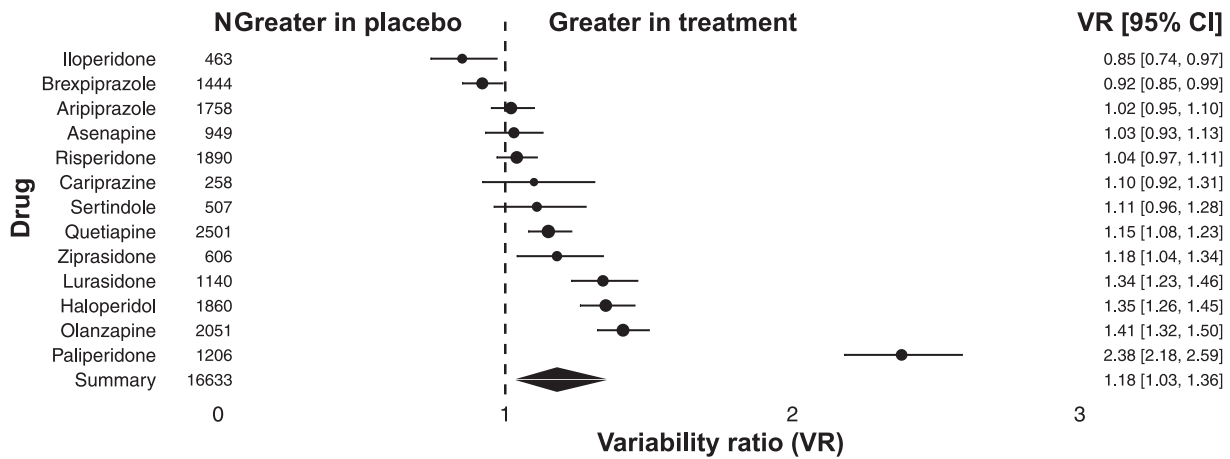

Fig. 2. Variability ratio for hyperprolactinemia for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[41,42,44–48,50–58,60,62,64,65,67–69,72,74–79,82–92,94,95,97–104] are also listed in supplementary table S1.

Overall, the variability for hyperprolactinemia was higher under treatment than under control (VR = 1.38; 95% CI: 1.17–1.62; $P < .001$; figure S2).

QTc Prolongation

For QTc prolongation, we included 29 RCTs, with 46 comparisons of antipsychotic drugs with placebo. All together we included $N = 10\ 384$ 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; $P = .135$; 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; $P = .135$; supplementary figure S3).

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,[6,20,106] 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
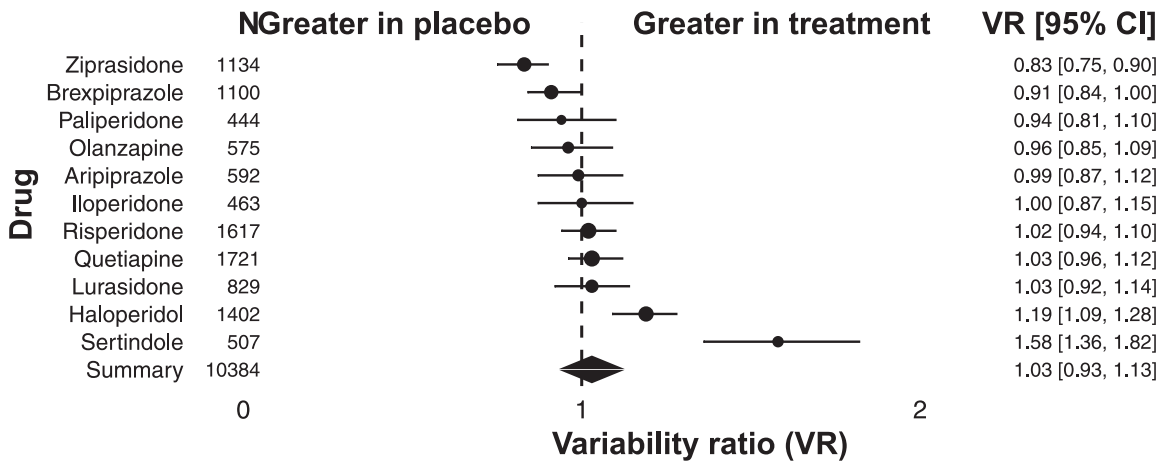
Fig. 3. Variability ratio for QTC prolongation for individual antipsychotics. The forest plot shows the VR together with its 95% confidence interval (CI) for treatment versus placebo. All included studies[42,45,51,52,54–60,62,68,70,74,76–80,85,86,88,91,95,97,101,104,105] are also listed in supplementary table S1.

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 43 595 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,[107] 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[108] and sex[109] 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,[110,111] 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.[5,112]

Hyperprolactinemia

Prolactin level elevations occur in up to 70% of patients[113] under the treatment with antipsychotics. By blocking dopamine D2 receptors on lacotroph cells a disinhibition of the synthesis and secretion of prolactin is observed.[114,115] 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,[116,117]

and a potentially increased risk in developing breast cancer in association with hyperprolactinemia.[118,119] 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.[6,120] 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.[121] 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.[121] Users of antipsychotic medication are reported to have higher rates of sudden cardiac death than nonusers.[123] Prolongation of QTc (longer than 450 ms in men and longer than 470 ms in women, respectively, when corrected with Bazetts Formula[124]) can contribute to this.[34] A prolongation of QTc can lead to *torsade de pointes* and subsequently to sudden death.[125,126] The molecular pathway of this side effect is not completely understood.[127] 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 predefined 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.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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