Summary Description of Errors and Corrections

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Retrospective Analysis of Risk Factors in Patients with Treatment-Emergent Diabetes during Clinical Trials of Antipsychotic Medications

During further investigation of the data set post-publication, an error was observed in the treatment-emergent diabetes (TED) manuscript that led to a thorough data review. Additional errors were discovered. Despite these errors, conclusions from a reanalysis about the impact of pre-existing risk factors on TED are largely unchanged; however, the interpretation of the impact of weight gain on TED has been refined. Four errors had the most impact on the TED analyses.

First, for calculation of the categorical weight gain risk factor, three programming syntax errors were found. The syntax incorrectly used a >7% criterion as opposed to the appropriate ≥7% criterion for categorical weight gain, it incorrectly grouped patients with weight loss together with patients with weight gain as risk present, and it incorrectly set the value of the weight gain risk variable backwards (ie, if weight gain >7% then weight gain risk = 0 should have been = 1).

Second, for calculation of the overweight risk factor (body mass index [BMI] ≥27 kg/m^2), the programming syntax assigned patients to the risk-absent condition if their BMI was incalculable due to missing height data. Therefore, some patients who were overweight were categorized as risk absent. This error also affected the assessment of total number of risk factors, since being overweight was one of the included factors.

Third, a placebo-like 1-mg dose group was used in the analyses when only patients with standard olanzapine dosing (5-20 mg/day) were to be included.

Fourth, when serial glucose values were examined to identify confirmatory results for identification of TED cases, laboratory data were processed based upon highest glucose value across time between visits (from 1 to 8 weeks of time) rather than using each individual actual sample, resulting in a less sensitive process for identification of TED cases.

These errors were corrected in a reanalysis of the data following the approach described in the TED Manuscript. Patients without height data were excluded for analyses that included BMI.

The main findings in the original TED manuscript were incidence of TED and risk factor impact on the risk of developing TED (hazard ratios [HR]). These TED incidence and risk factor results for the “original analysis” and “reanalysis” are summarized below (Table 1 includes full summary of incidence rates). The original analysis included 5,013 patients. The reanalysis included 4,820 patients, largely due to exclusion of the 1-mg dose group (error 3, above). The crude TED incidence for olanzapine- versus placebo-treated patients in the original analysis (2.3% vs. 1.4%, p=0.626) was similar to the incidence of TED in the reanalysis (2.3% vs. 1.0%, p=0.321).

The incidence of TED after adjusting for exposure was not statistically significantly different for olanzapine-treated patients compared to haloperidol-, risperidone-, or placebo-treated patients

when these treatment groups were combined or when treated as separate treatment groups in either the original analysis or reanalysis. Patients treated with olanzapine had a statistically significantly lower rate of TED (after adjusting for exposure time) than clozapine-treated patients in both the original analysis (HR not reported in the original analysis, HR = 1.467, p=0.022) and in the reanalysis (HR = 1.387, p=0.018).

As reported in the original analysis, patients with baseline non-fasting glucose ≥6.7 mmol/L were at a greater risk of TED (HR = 11.85, p<0.001) than normoglycaemic patients. The reanalysis provided a similar result (HR = 12.70, p<0.0001). In patients with ≥2 baseline risk factors, the likelihood of TED was also similar between the original analysis (HR = 5.70, p<0.001) and reanalysis (HR = 7.35, p<0.0001). The risk of TED for olanzapine- vs. non-olanzapine-treated (risperidone, haloperidol, and placebo) patients was similar between the original analysis (HR = 1.46, p=0.186) and reanalysis (HR = 1.49, p=0.228), with the risk of TED for olanzapine-treated patients not statistically significantly greater than that of the non-olanzapine-treated patients.

As part of the original analyses, a multivariate analysis was performed, where the continuous variables baseline glucose, number of baseline risk factors, and weight change were included as covariates. As with the univariate analysis, the risk of TED was not statistically different between olanzapine- and non-olanzapine-treated patients (p=0.220). This finding was similar for the reanalysis (p=0.3956).

There was one analysis where the original results where not consistent with those of the reanalysis: impact of ≥7% weight gain on risk of TED. In the original analysis, ≥7% weight gain from baseline was a non-statistically significant risk factor (HR = 1.21, p=0.414). In contrast, in the reanalysis, a statistically significant temporal association was observed between >7% weight gain and a decreased risk of developing diabetes (HR = 0.538, p=0.0174). This finding does not intuitively make sense, given that being overweight is a known risk factor for diabetes.

Therefore, to further evaluate the potential contribution of treatment-emergent weight gain to the risk of TED, an alternative analysis was performed in which baseline weight was included as a fixed covariate and post-baseline weight change was utilized as a time-varying covariate. This methodology is considered to be more appropriate than the approach taken in the original analysis, which modeled weight change as a single post-baseline quantity measured up to the patient's last observation. In this alternative analysis, a multivariate model was used that incorporated baseline weight, each of the five key risk factors for TED (age ≥45 years, baseline nonfasting glucose ≥6.7 mmol/L (120 mg/dL), non-Caucasian origin, baseline hypertension, and female gender), treatment group assignment, and time-varying weight change. In this alternative analysis, weight gain was found to be a statistically significant risk factor (HR = 1.05, p=0.0117). Baseline weight, baseline nonfasting glucose ≥6.7 mmol/L, ≥45 years of age, and non-Caucasian origin were also statistically significant risk factors. Hazard ratio estimates for female gender and hypertension at baseline did not achieve statistical significance but the hazard ratio estimates did exceed 1 (estimate is in the direction of a risk). The risk of TED for patients treated with olanzapine was not statistically significantly different from the non-olanzapine

treatment cohort (risperidone, haloperidol, and placebo combined) when adjusted for all other factors included in the model (HR = 1.385, p=0.3455).

Overall, results from the reanalysis and alternative analysis are consistent with the main conclusion from the original TED manuscript: "The majority of patients who were identified as TED were likely to have pre-existing, unrecognized glycaemic abnormalities or to have had a greater burden of pre-existing risk factors for diabetes than patients who appeared to maintain normoglycaemia." and in addition, "…elevated baseline non-fasting glucose level and presence of multiple risk factors for diabetes appear to have a major impact on the risk of being identified with TED, whereas the impact of treatment-emergent weight gain on short-term [< 6-month median exposure] TED risk was relatively small." The risk of TED for patients treated with olanzapine was not statistically significantly different from a pooled cohort of patients receiving comparator treatments, including placebo. Similar to the original analysis, the baseline characteristics of patients identified as UGT were intermediate to those of patients identified as TED or NGT. There is only one substantial difference from the original manuscript that should be noted. The manuscript stated that weight gain "did not have a statistically significant effect on the risk of TED." When using a new, more appropriate characterization of weight gain as a time-varying covariate, weight gain was a statistically significant risk factor of TED.

Table 1 Post-randomisation glycaemic categories and median observation time by therapy assignment

		Post-randomization glycaemic category [1]				
Therapy	Patients Randomized (N)	NGT n (%)	UGT n (%)	TED n (%)	Median observation time days (max.)	Weight gain at end-point (kg) [2] means (s.d.)
Olanzapine	2899	2650 (91.4)	183 (6.3)	66 (2.3)	127 (1877)	3.90 (7.04)
Haloperidol	1147	1109 (96.7)	31 (2.7)	7 (0.6)	43 (893)	0.12 (4.50)
Risperidone	362	344 (95.0)	13 (3.6)	5 (1.4)	196 (866)	2.12 (5.61)
Clozapine	208	170 (81.7)	32 (15.4)	6 (2.9)	125 (213)	3.67 (5.64)
Placebo	204	198 (97.1)	4 (2.0)	2 (1.0)	22 (605)	-1.11 (3.75)
Total	4820	4471 (92.8)	263 (5.5)	86 (1.8)	92 (1877)	2.65 (6.49)

NA, not available; NGT, normal glucose tolerance; TED, treatment-emergent diabetes; UGT, uncertain glucose tolerance.

1. Results are shown as the number (n) and percentage (n/N x 100%) of patients within each treatment group where N=number of patients randomized.

2. Last observation carried forward.