Quantitative approaches of time-varying weight gain effects of antipsychotic drugs for Schizophrenia by meta-analysis.

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BACKGROUND AND PURPOSE

- Despite weight gain is one of the most important adverse drug effects (ADR) of antipsychotics, the quantitative approach was restricted because of a lack of methodology.
- In Recently, model-based meta-analysis (MBMA) is an approach that quantifies the integrated data along with internal studied data, which can perform a quantified benefit-risk assessment of the drug.
- We predicted the effect of time-varying weight gain effect of commonly used several atypical antipsychotics (aripiprazole, olanzapine, clozapine, quetiapine, and risperidone) on adult patients with schizophrenia and compared weight gains using model-based meta-analysis.

METHODS

- Data were collected using a systematic review of references released in PubMed.
- Structure model form ***(Equation 1)*** to address for weight gain effect of each drugs were consisted of baseline weight (Baseline WT) , Placebo term and Drug effect term were shown at below ***Table 1***.
- Time dependent exponential model as drug effect term was tested to predict time varying weight changes in aripiprazole, olanzapine, clozapine, quetiapine and risperidone.
- Placebo term was included as fixed weight change.
- Simulation were used to predict time varying weight change of each drug for 1 year, 1000 populations with various mean baseline weight were randomly created.
- Simulation compared the % weight change of each antipsychotics.
- Modeling and simulation were performed using a nonlinear mixed effects modeling methodology in the NONMEM (ver 7.5) assisted by PsN (ver 5.2.6) and R (ver 4.2.1)

Equation 1.

$$BW_{Drug_i} = Baseline\ BW + E_{Placebo} + E_{Drug}$$

Table 1. Terminology used in Equation 1

Terminology	Formation
Placebo term	$E_{Placebo} = median\ change\ (kg)\ of\ placebo$
Drug effect term	$E_{Drug} = drugeff\ * (1 - e^{-K_d * time})$ $drugeff = \frac{Emax * Dose}{ED50 + Dose}$
Residual term	$BW_{Drug_i} \sim N\ (\widehat{BW_{Drug_i}}, \frac{\sigma^2}{n})$.

Annotation :
Kd(/week) : The onset of drug ; drugeff(kg): Maximum drug effect on weight change; Emax (kg) *: maximum effect of dose on weight change ; ED50 (mg) : Dose for 50% of maximum effect ;* $\widehat{BW_{Drug_i}}$ *: Estimated body weight; n : sample size,* σ^2*: variance*

RESULTS

- We searched 930 references in PubMed with below MeSH Terms, 40 references were selected to perform MBMA. ; "Antipsychotic Agents"[MeSH Terms] OR "Clozapine"[MeSH Terms] OR "Olanzapine"[MeSH Terms] OR "Quetiapine Fumarate"[MeSH Terms] OR "Placebos"[MeSH Terms] AND "Body Weight"[MeSH Terms]
- Inclusion and Exclusion criteria for references were shown at ***Figure 1.***
- References that do have time-varying weight change data, same indication and meet purpose of our study were included.
- Baseline weight, changed weight in different time points, dose, number of subjects were collected from references to make data set and perform modeling.

Figure1. Reference selection process

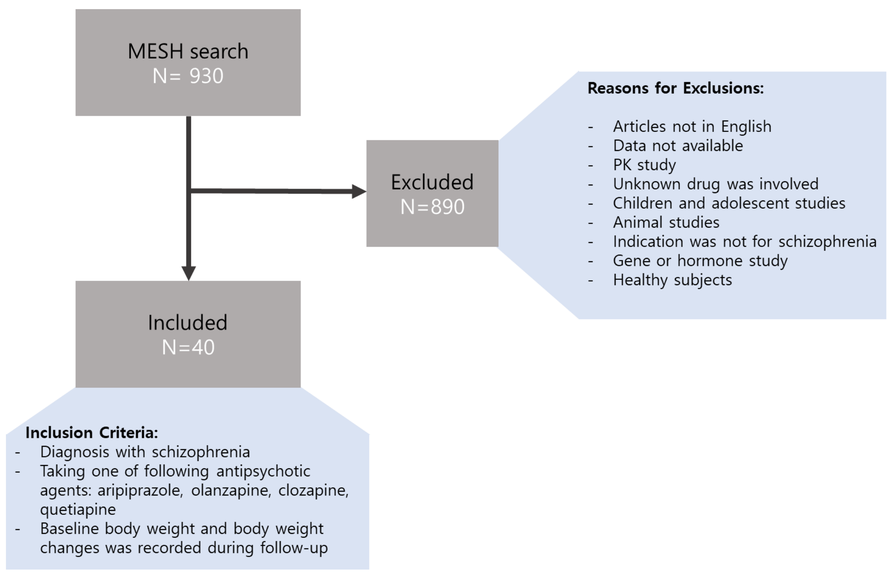


Table 2. Summary of baseline characteristics of selected references

	Aripiprazole	Clozapine	Lurasidone	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Total
# of groups	16	10	3	16	8	12	4	77
Body weight (kg) (Mean(SD))	75.67(9.85)	75.45(7.1)	74.43(1.65)	74.56(4.47)	72.3(5.16)	73.89(9.56)	72.22(10.32)	74.73(7.43)
Age (year) (min, max)	(22.9,42.1)	(24.5,46.2)	(36.2,41.4)	(22.8,54)	(31,56.5)	(22.8,64.5)	(32.1,40.8)	(22.8,64.5)
Dose (mg) (min, max)	(9.3,30)	(37.5,439.5)	(80,160)	(6.2,16.9)	(84.9,600)	(1.3,6)	(60,120)	

- During modeling, weight change due to placebo was fixed to 0.2463 (kg).
- The onset of drug, K_d(/week), and drug effects were estimated by fitting data into time-dependent exponential model.
- The K_d of aripiprazole, olanzapine, clozapine, quetiapine and risperidone were estimated by 0.001356, 0.0959, 0.00978, 0.103 and 0.0718, respectively.
- Estimated *drug effects (kg)* in collected dose range of aripiprazole, olanzapine, clozapine, quetiapine were 13.2, 4.62, 12.2, 2.88, respectively.
- Risperidone's drug effect was estimated using Emax (kg) model which describes change in drug effects by different dose, and estimated parameter Emax was 16.5 and ED50 (mg) was 9.52.
- The estimated parameter results were shown at ***Table 3.***

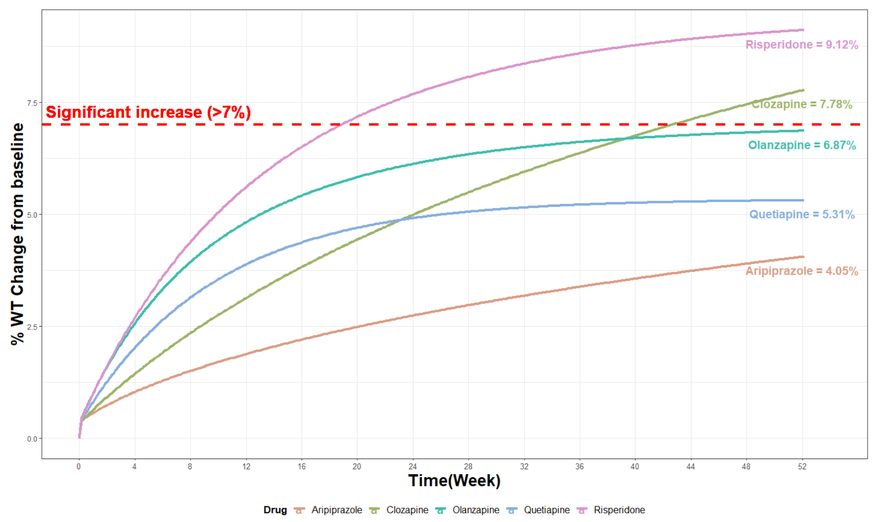
Table 3. Estimated parameter results

Parameter	Aripiprazole	Olanzapine	Clozapine	Quetiapine	Risperidone
$drug\ eff$ (kg) (RSE%)	13.2 (4%)	4.62 (11%)	12.2	2.88 (24%)	-
$\omega^2_{drug\ eff}$	-	0.149	-	0.506	-
$K_d\ (week^{-1})$ (RSE%)	0.001356 (154.2 %)	0.0959 (21%)	0.00978	0.103 (1%)	0.0718 (24%)
$\omega^2_{K_d}$	5.22	0.256	1.34		0.147
$Emax$ (kg) (RSE%)	-	-	-	-	16.5 (29%)
ω^2_{Emax}	-	-	-	-	0.376
$ED50$ (mg) (RSE%)	-	-	-	-	9.52 (45%)
$\omega^2_{ED_{50}}$	-	-	-	-	-
σ^2	1 (FIX)	1 (FIX)	1 (FIX)	1 (FIX)	1 (FIX)
$coefficient$ (theta(n) * eps(1))	8.69 (30%)	4.06 (35%)	1.64 (15%)	1.24 (26%)	4.37 (33%)

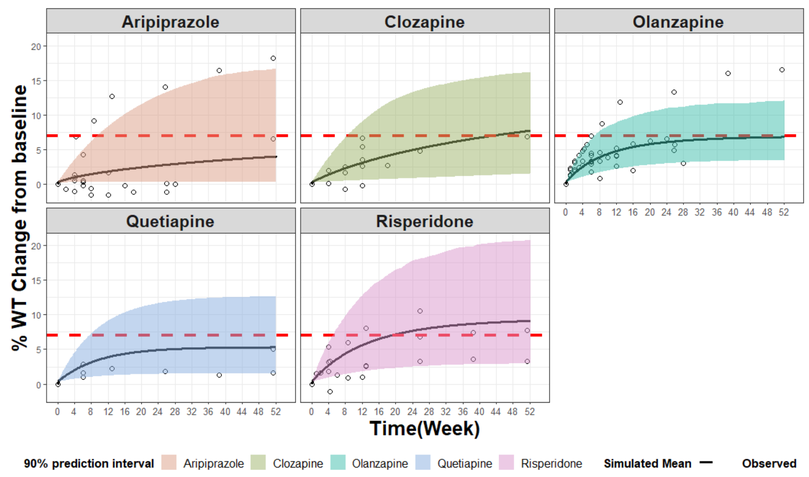
- To compare the weight change for each drug, simulation studies was conducted for 1 year simulation period and baseline weight of each population was assumed by distribution from Normal distribution (74.73, 7.43^2) and from 56.4 kg to 89.8kg range which was derived from collected baseline from 40 references.
- We confirmed that our model and simulation thoroughly reflect observed weight change over 1 year of each drugs. (***Figure 2-(2)***)
- Result showed the average percent weight change from baseline for each drug to be ***Figure 2 -(1)*** : Risperidone (9.12%), clozapine (7.78%), olanzapine (6.87%), quetiapine (5.31%) and aripiprazole (4.05%).
- Risperidone and clozapine showed significant weight increase (>7%) in this simulation.

Figure 2. Simulated mean percent change from baseline weight (%) of each drug with 90% predicted interval and observed data

(1)



(2)



CONCLUSION & DISCUSSION

- Although atypical antipsychotic's weight gain risk is well known adverse effect, it was restricted to conduct direct comparison between all available treatment options during clinical trial.
- In consequence, MBMA should be suggested as an alternative method to compare the treatment directly atypical antipsychotics.
- We confirmed the quantitative weight gain effect of commonly used antipsychotics(aripiprazole, olanzapine, clozapine, quetiapine, risperidone) using MBMA in this study.
- In the further study, we are planning to use model based meta-analysis to compare co-administration of drugs that can potentially inhibit weight gain due to antipsychotic use in patients with schizophrenia. Also, we want to see if weight-inhibition is correlated to reducing risk for metabolic syndrome.

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